EXHIBIT A

Initial Shared System REMS approval: 04/2019
Most Recent Modification: 03/2023

Mifepristone Tablets, 200 mg
Progestin Antagonist

RISK EVALUATION AND MITIGATION STRATEGY (REMS)
SINGLE SHARED SYSTEM FOR MIFEPRISTONE 200 MG

I. GOAL

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.

b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.

c) Informing patients about the risk of serious complications associated with mifepristone.

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe mifepristone must be specially certified.
    a. To become specially certified to prescribe mifepristone, healthcare providers must:
        i. Review the Prescribing Information for mifepristone.
        ii. Complete a *Prescriber Agreement Form*. By signing[1] a *Prescriber Agreement Form*, prescribers agree that:
            1) They have the following qualifications:
                a) Ability to assess the duration of pregnancy accurately
                b) Ability to diagnose ectopic pregnancies
                c) Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
            2) They will follow the guidelines for use of mifepristone (see b.i-vii below).
    b. As a condition of certification, prescribers must follow the guidelines for use of mifepristone described below:
        i. Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
        ii. Ensure that the healthcare provider and patient sign the *Patient Agreement Form.*

[1] In this REMS, the terms “sign” and “signature” include electronic signatures.

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iii. Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.

iv. Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.

v. Ensure that any deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

vi. If mifepristone will be dispensed by a certified pharmacy:

1) Provide the certified pharmacy a signed *Prescriber Agreement Form*.

2) Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.

3) Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of the patient.

vii. The certified prescriber who dispenses mifepristone or who supervises the dispensing of mifepristone must:

1) Provide an authorized distributor with a signed *Prescriber Agreement Form*.

2) Ensure that the NDC and lot number from each package of mifepristone dispensed are recorded in the patient's record.

3) Ensure that healthcare providers under their supervision follow guidelines i.-v.

c. Mifepristone Sponsors must:

i. Ensure that healthcare providers who prescribe their mifepristone are specially certified in accordance with the requirements described above and de-certify healthcare providers who do not maintain compliance with certification requirements.

ii. Ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*:

1) Within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies.

2) Within one year after approval of this modification, if previously certified and ordering from an authorized distributor.

iii. Ensure that healthcare providers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy.

iv. Provide the Prescribing Information and their *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.

v. Ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date.

The following materials are part of the Mifepristone REMS Program:

- *Prescriber Agreement Form for Danco Laboratories, LLC*
- *Prescriber Agreement Form for GenBioPro, Inc.*
- *Patient Agreement Form*

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2. Pharmacies that dispense mifepristone must be specially certified

   a. To become specially certified to dispense mifepristone, pharmacies must:

      i. Be able to receive *Prescriber Agreement Forms* by email and fax.

      ii. Be able to ship mifepristone using a shipping service that provides tracking information.

      iii. Designate an authorized representative to carry out the certification process on behalf of the pharmacy.

      iv. Ensure the authorized representative oversees implementation and compliance with the Mifepristone REMS Program by doing the following:

         1) Review the Prescribing Information for mifepristone.

         2) Complete a *Pharmacy Agreement Form*. By signing a *Pharmacy Agreement Form*, the authorized representative agrees that the pharmacy will put processes and procedures in place to ensure the following requirements are completed:

            a) Verify that the prescriber is certified by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with the pharmacy.

            b) Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in c) below.

            c) Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.

            d) Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.

            e) Track and verify receipt of each shipment of mifepristone.

            f) Dispense mifepristone in its package as supplied by the Mifepristone Sponsor.

            g) Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to the Mifepristone Sponsor that provided the mifepristone. Notify the Mifepristone Sponsor that provided the dispensed mifepristone that the pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.

            h) Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.

            i) Maintain records of *Prescriber Agreement Forms*.

            j) Maintain records of dispensing and shipping.

            k) Maintain records of all processes and procedures including compliance with those processes and procedures.

            l) Maintain the identity of the patient and prescriber as confidential, including limiting access to patient and prescriber identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes..

            m) Train all relevant staff on the Mifepristone REMS Program requirements.

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n) Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

b. Mifepristone Sponsors must:

i. Ensure that pharmacies are specially certified in accordance with the requirements described above and de-certify pharmacies that do not maintain compliance with certification requirements.

ii. Ensure that pharmacies can complete the certification process by email and fax to an authorized distributor.

i. Verify annually that the name and contact information for the pharmacy's authorized representative corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, require the pharmacy to recertify with the new authorized representative.

The following materials are part of the Mifepristone REMS Program:

- *Pharmacy Agreement Form for Danco Laboratories, LLC*
- *Pharmacy Agreement Form for GenBioPro, Inc.*

3. Mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions as ensured by the certified prescriber in signing the *Prescriber Agreement Form.*

a. The patient must sign a *Patient Agreement Form* indicating that the patient has:

i. Received, read and been provided a copy of the *Patient Agreement Form*.

ii. Received counseling from the healthcare provider regarding the risk of serious complications associated with mifepristone.

B. Implementation System

1. Mifepristone Sponsors must ensure that their mifepristone is only distributed to certified prescribers and certified pharmacies by:

a. Ensuring that distributors who distribute their mifepristone comply with the program requirements for distributors.

i. The distributors must put processes and procedures in place to:

1) Complete the certification process upon receipt of a *Prescriber Agreement Form* or *Pharmacy Agreement Form*.

2) Notify healthcare providers and pharmacies when they have been certified by the Mifepristone REMS Program.

3) Ship mifepristone only to certified pharmacies or locations identified by certified prescribers.

4) Not ship mifepristone to pharmacies or prescribers who become de-certified from the Mifepristone REMS Program.

5) Provide the Prescribing Information and their Prescriber Agreement Form to healthcare providers who (1) attempt to order mifepristone and are not yet certified, or (2) inquire about how to become certified.

ii. Put processes and procedures in place to maintain a distribution system that is secure,

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confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, NDC and lot numbers, proof of delivery and controlled returns of mifepristone.

iii. Train all relevant staff on the Mifepristone REMS Program requirements.

iv. Comply with audits by Mifepristone Sponsors or a third party acting on behalf of Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed for the Mifepristone REMS Program. In addition, distributors must maintain appropriate documentation and make it available for audits.

b. Ensuring that distributors maintain secure and confidential distribution records of all shipments of mifepristone.

2. Mifepristone Sponsors must monitor their distribution data to ensure compliance with the Mifepristone REMS Program.

3. Mifepristone Sponsors must ensure that adequate records are maintained to demonstrate that the Mifepristone REMS Program requirements have been met, including, but not limited to records of mifepristone distribution; certification of prescribers and pharmacies; and audits of pharmacies and distributors. These records must be readily available for FDA inspections.

4. Mifepristone Sponsors must audit their new distributors within 90 calendar days and annually thereafter after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their distributor compliance if noncompliance is identified.

5. Mifepristone Sponsors must audit their certified pharmacies within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter audit certified pharmacies that have ordered mifepristone in the previous 12 months, to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their pharmacy compliance if noncompliance is identified.

6. Mifepristone Sponsors must take reasonable steps to improve implementation of and compliance with the requirements of the Mifepristone REMS Program based on monitoring and assessment of the Mifepristone REMS Program.

7. Mifepristone Sponsors must report to FDA any death associated with mifepristone whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the Mifepristone Sponsor. This requirement does not affect the sponsors' other reporting and follow-up requirements under FDA regulations.

C. Timetable for Submission of Assessments

The NDA Sponsor must submit REMS assessments to FDA one year from the date of the approval of the modified REMS (01/03/2023) and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 90 calendar days before the submission date for that assessment. The NDA Sponsor must submit each assessment so that it will be received by the FDA on or before the due date.

MIFEPREX® (Mifepristone) Tablets, 200 mg

PRESCRIBER AGREEMENT FORM

Mifeprex* (Mifepristone) Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To ***become a certified prescriber***, you must:

- **If you submit Mifeprex prescriptions for dispensing from certified pharmacies**:
  - Submit this form to each certified pharmacy to which you intend to submit Mifeprex prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order Mifeprex for dispensing by you or healthcare providers under your supervision:**
  - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
  - Healthcare settings, such as medical offices, clinics, and hospitals, where Mifeprex will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free), or by visiting www.earlyoptionpill.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received Mifeprex are reported to Danco Laboratories, LLC, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of Mifeprex that was dispensed to the patient.

Ensure that healthcare providers under your supervision follow the guidelines listed above.

- If Mifeprex will be dispensed through a certified pharmacy:
  - Assess appropriateness of dispensing Mifeprex when contacted by a certified pharmacy about patients who will receive Mifeprex more than 4 calendar days after the prescription was received by the certified pharmacy.
  - Obtain the NDC and lot number of the package of Mifeprex the patient received in the event the prescriber becomes aware of the death of a patient.
- If Mifeprex will be dispensed by you or by healthcare providers under your supervision:
  - Ensure the NDC and lot number from each package of Mifeprex are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Name(s): _____

Practice Setting Address: _____

_____

Email: _____ Phone: _____ Preferred __ email __ phone

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.

Approved 03/2023

PRESCRIBER AGREEMENT FORM Mifepristone Tablets, 200 mg

Mifepristone Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To ***become a certified prescriber***, you must:

- **If you submit mifepristone prescriptions for dispensing from certified pharmacies**:
  - Submit this form to each certified pharmacy to which you intend to submit mifepristone prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order mifepristone for dispensing by you or healthcare providers under your supervision:**
  - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
  - Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855—643-3463 toll-free), or by visiting www.MifeInfo.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received mifepristone are reported to GenBioPro, Inc., identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

Ensure that healthcare providers under your supervision follow the guidelines listed above.

- If mifepristone will be dispensed through a certified pharmacy:
  - Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.
  - Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of a patient.
- If mifepristone will be dispensed by you or by healthcare providers under your supervision:
  - Ensure the NDC and lot number from each package of mifepristone are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Name(s): _____

Practice Setting Address: _____

_____

Email: _____ Phone: _____ Preferred __ email __ phone

Return completed form to **RxAgreements@GenBioPro.com** or fax to 1-877-239-8036

Approved 03/2023 GBP-PA-01

PATIENT AGREEMENT FORM Mifepristone Tablets, 200 mg

Healthcare Providers: *Counsel the patient on the risks of mifepristone. Both you and the patient must provide a written or electronic signature on this form.*

Patient Agreement:

1. I have decided to take mifepristone and misoprostol to end my pregnancy and will follow my healthcare provider's advice about when to take each drug and what to do in an emergency.
2. I understand:
   a. I will take mifepristone on Day 1.
   b. I will take the misoprostol tablets 24 to 48 hours after I take mifepristone.
3. My healthcare provider has talked with me about the risks, including:
   - heavy bleeding
   - infection
4. I will contact the clinic/office/provider right away if in the days after treatment I have:
   - a fever of 100.4°F or higher that lasts for more than four hours
   - heavy bleeding (soaking through two thick full-size sanitary pads per hour for two hours in a row)
   - severe stomach area (abdominal) pain or discomfort, or I am “feeling sick,” including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol
     — these symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

   My healthcare provider has told me that these symptoms listed above could require emergency care. If I cannot reach the clinic/office/provider right away, my healthcare provider has told me who to call and what to do.
5. I should follow up with my healthcare provider about 7 to 14 days after I take mifepristone to be sure that my pregnancy has ended and that I am well.
6. I know that, in some cases, the treatment will not work. This happens in about 2 to 7 out of 100 women who use this treatment. If my pregnancy continues after treatment with mifepristone and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy.
7. If I need a surgical procedure because the medicines did not end my pregnancy or to stop heavy bleeding, my healthcare provider has told me whether they will do the procedure or refer me to another healthcare provider who will.
8. I have the MEDICATION GUIDE for mifepristone.
9. My healthcare provider has answered all my questions.

Patient Signature: _____ **Patient Name** (print): _____ **Date**: _____

Provider Signature: _____ **Provider Name** (print): _____ **Date**: _____

Patient Agreement Forms may be provided, completed, signed, and transmitted in paper or electronically.

01/2023

MIFEPREX®(Mifepristone) Tablets, 200mg

PHARMACY AGREEMENT FORM

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense Mifeprex is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense Mifeprex is able to ship Mifeprex using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for Mifeprex. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free) or online at www.earlyoptionpill.com; and
- Each location of my pharmacy that will dispense Mifeprex will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting Mifeprex orders.
    - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
    - Dispense Mifeprex such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
    - Confirm with the prescriber the appropriateness of dispensing Mifeprex for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
    - Record in the patient's record the NDC and lot number from each package of Mifeprex dispensed.
    - Track and verify receipt of each shipment of Mifeprex.
    - Dispense mifepristone in its package as supplied by Danco Laboratories, LLC.
    - Report any patient deaths to the prescriber, including the NDC and lot number from the package of Mifeprex dispensed to the patient, and remind the prescriber of their obligation to report the deaths to Danco Laboratories, LLC. Notify Danco that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
    - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
    - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, and all processes and procedures including compliance with those processes and procedures.
    - Maintain the identity of Mifeprex patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance.
    - Train all relevant staff on the Mifepristone REMS Program requirements.
    - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____

DANCO
Support • Progress • Options

*MIFEPREX is a registered trademark of Danco Laboratories, LLC

P.O. Box 4816-New York, NY 10185
1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred __ email __ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.

PHARMACY AGREEMENT FORM **Mifepristone Tablets, 200 mg**

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense mifepristone is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense mifepristone is able to ship mifepristone using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855-643-3463 toll-free) or online at www.MifeInfo.com; and
- Each location of my pharmacy that will dispense mifepristone will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting mifepristone orders.
    - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
    - Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
    - Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
    - Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.
    - Track and verify receipt of each shipment of mifepristone.
    - Dispense mifepristone in its package as supplied by GenBioPro, Inc.
    - Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to GenBioPro, Inc. Notify GenBioPro that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
    - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
    - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, all processes and procedures including compliance with those processes and procedures.
    - Maintain the identity of mifepristone patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance purposes.
    - Train all relevant staff on the Mifepristone REMS Program requirements.
    - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred __ email __ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to **RxAgreements@GenBioPro.com** or fax to **1-877-239-8036.**

EXHIBIT B

GenBioPro

July 3, 2025

VIA ELECTRONIC SUBMISSION (WWW.REGULATIONS.GOV)

Division of Dockets Management
U.S. Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

CITIZEN PETITION

The undersigned submits this petition under Section 505 of the Federal Food, Drug, and Cosmetic Act ("FDCA") and 21 C.F.R. § 10.30 to request the Commissioner of Food and Drugs to: (1) refrain from taking any action that would reduce patient access to the drug mifepristone and/or increase the burdens associated with prescribing or dispensing mifepristone, absent new robust scientific or clinical evidence that meets applicable statutory standards warranting such a change; and (2) confirm that any steps that may be taken to modify, suspend, or withdraw FDA approval for mifepristone, including in response to any court order, will follow all applicable rules and procedures for any withdrawal or suspension required under the Administrative Procedure Act ("APA"), the FDCA, and implementing regulations, and that Petitioner will be permitted to continue to market and sell mifepristone in the United States until all such procedures have been completed.[1]

GenBioPro, Inc. ("Petitioner") markets a generic version of mifepristone, which provides patients with a safe, effective, and non-invasive medication option for terminating a pregnancy. Mifepristone was first approved by the Agency as safe and effective for medically terminating early pregnancies over two decades ago, when FDA approved a New Drug Application ("NDA") for mifepristone tablets marketed under the brand name Mifeprex®.[2] Petitioner has held an FDA-approved Abbreviated New Drug Application ("ANDA") to market generic mifepristone since 2019.[3] In the twenty-five years since the medication's approval, mifepristone's safety and efficacy have been confirmed time and again through FDA's repeated and rigorous review of the underlying scientific data and literature, as well as real-world clinical experience of the millions of American women who have safely terminated their pregnancies with the mifepristone regimen. The robust scientific and clinical record demonstrates that mifepristone is safely used under the mifepristone Risk Evaluation and Mitigation Strategy ("REMS") with Elements to Assure Safe Use ("ETASU") as currently framed. And, as FDA has repeatedly recognized, there is no scientific

[1] All articles, references, and sources cited herein are provided in an attached Appendix, in accordance with 21 C.F.R. § 10.20(c).

[2] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., NDA Approval Letter, NDA 020687 (Sept. 28, 2000), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.pdf.

[3] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., ANDA Approval Letter, ANDA 091178 (Apr. 11, 2019), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/091178Orig1s000ltr.pdf.



basis for allegations that administration of mifepristone causes harm to the environment. In light of mifepristone's longstanding safety and effectiveness profile, Petitioner respectfully requests that FDA take no action that would reduce or inhibit patient access to this important medication.[4]

Furthermore, as FDA is well aware, FDA's approvals regarding mifepristone have come under legal challenge, and efforts are underway to seek withdrawal of, or limitations on, Petitioner's ANDA approval. These unfounded attacks on FDA's well-reasoned and appropriate decisions pursuant to its congressional mandate are of grave concern to Petitioner, which has invested considerable effort and resources in reliance on FDA's prior regulatory actions with respect to mifepristone, with the understanding that any possible attempt to withdraw or take other actions with respect to an FDA approval are subject to well-established and legally required FDA processes. Accordingly, Petitioner respectfully requests confirmation that any steps to withdraw or limit FDA's approval of Petitioner's ANDA for mifepristone—whether in effectuation of a court order or otherwise—will follow all applicable procedures afforded by law and regulation to Petitioner as the ANDA holder and that FDA will permit Petitioner to continue marketing and selling mifepristone until those procedures have been completed, as required by law.

Petitioner is aware of recent statements by Department of Health and Human Services ("HHS") Secretary Robert F. Kennedy, Jr. that the Commissioner will undertake a "complete review" of mifepristone and will provide a recommendation to President Trump regarding the mifepristone label and REMS.[5] Petitioner requests that it be provided an opportunity to comment and provide input with respect to any such review, in accordance with Petitioner's rights as the ANDA holder for mifepristone. Additionally, Petitioner requests that, in the course of any such review, FDA ensure that all data reviewed are made public; that the Agency consider the entire body of evidence supporting mifepristone's safety and effectiveness, which reflects over two decades of robust scientific research and the experience of millions of patients; and that FDA consider the content of and attachments to this Petition as part of its review. As the expert agency charged by Congress with evaluating the safety and efficacy of drugs, FDA must adhere to its longstanding scientific and legal standards requiring objective safety data and transparent study methodologies, such that the Agency can continue to engage in scientifically sound, evidence-based decision-making on important matters affecting public health.

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[4] If anything, the current scientific and medical record may support expanding patient access by revising aspects of the current REMS and ETASU.

[5] *Hearing on Fiscal Year 2026 Department of Health and Human Services Budget: Hearing Before the S. Comm. On Health, Educ., Labor & Pensions*, 119th Cong. (May 4, 2025) (statement of Robert F. Kennedy, Jr., Secretary, Health and Human Services), https://www.help.senate.gov/hearings/hearing-on-fiscal-year-2026-department-of-health-and-human-services-budget (Secretary Kennedy expressing that "at very least the [mifepristone] label should be changed"); *see also* Amna Nawaz, *What the new FDA commissioner says about possible restrictions on abortion medication*, PBS News (Apr 24, 2025), https://www.pbs.org/newshour/show/what-the-new-fda-commissioner-says-about-possible-restrictions-on-abortion-medication (reporting that the Commissioner stated he has "no plans to take action on mifepristone"); Letter from Martin A. Makary, Comm'r of Food & Drugs, U.S. Food & Drug Admin., to Senator Josh Hawley (June 2, 2025) (stating that the Commissioner is "committed to conducting a review of mifepristone").

GenBioPro

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A. ACTION REQUESTED

Petitioner requests that, absent new peer-reviewed studies or otherwise robust scientific or clinical evidence warranting such action, FDA take no action that would reduce patient access to mifepristone and/or increase the burdens associated with prescribing or dispensing mifepristone, including but not limited to any of the following actions:

(1) revoking or suspending the 2000 approval of Mifeprex (NDA 020687) or the 2019 approval of generic mifepristone (ANDA 091178);

(2) adding new ETASU to the current REMS for mifepristone;

(3) reinstating former ETASU that are not part of the current REMS;

(4) making the existing ETASU more onerous;



(5) modifying the REMS or labeling for mifepristone in a manner that is not supported by robust scientific or clinical evidence;

(6) modifying the REMS or labeling for mifepristone based on any scientific or clinical evidence that has not been provided to Petitioner with sufficient time to comment on its validity, relevance, and application to any REMS or labeling modification; or

(7) otherwise restricting healthcare practitioner or patient access to mifepristone without adherence to statutory processes and standards.

Additionally, Petitioner requests that FDA confirm that:

(1) any withdrawal or other adverse action by FDA on the approval of Petitioner's ANDA for mifepristone—whether in effectuation of a court order or otherwise—will follow all applicable procedures and meet all standards afforded by law and regulation to Petitioner as the ANDA holder; and

(2) FDA will permit Petitioner to continue marketing and shipping mifepristone until such procedures have been completed.

B. STATEMENT OF GROUNDS

1. As FDA Has Repeatedly Found, The Safety and Efficacy of Mifepristone is Well-Established and Supported by Robust Scientific Data

As FDA is aware, mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.[6] Under the FDA-approved dosing regimen, mifepristone is administered in a single oral dose, followed by buccal administration of misoprostol 24 to 48 hours after taking mifepristone. The label provides that patients should follow up with their healthcare provider approximately 7 to 14 days after taking mifepristone to confirm that complete termination of pregnancy has occurred. Since the medication's approval nearly twenty-five years ago, mifepristone has continued to exhibit a robust safety and efficacy profile, as demonstrated by its FDA approval history and countless peer-reviewed medical studies.

a. FDA Has Repeatedly Concluded Mifepristone is Supported by Substantial Evidence of Safety and Efficacy

For over two decades, FDA has consistently affirmed mifepristone's safety and effectiveness, grounded in rigorous scientific review and real-world data from millions of uses. As the body of evidence supporting its safety and efficacy has grown over time, FDA has appropriately updated mifepristone's conditions of use to remove unduly burdensome restrictions on patient access and the health care delivery system. At every stage, FDA's decisions have been

[6] MIFEPREX Prescribing Information (Mar. 23, 2023), https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s026lbl.pdf.



based on a comprehensive review of the entire body of scientific evidence, including peer-reviewed clinical studies and robust scientific data, as further outlined below.

(i) NDA Approval and REMS

Mifepristone was first approved by FDA under the brand name Mifeprex in 2000.[7] This approval was based on an extensive body of scientific data substantiating its safety and effectiveness, including three clinical studies involving approximately 2,500 patients.[8] The approval was granted under FDA regulations at 21 C.F.R Part 314 Subpart H, which allowed FDA to impose conditions it deemed necessary to ensure the product's safe use.

In 2008, at the request of several members of Congress, the U.S. Government Accountability Office ("GAO") reviewed FDA's approval of mifepristone and the Agency's oversight of the drug since approval.[9] GAO found that the mifepristone NDA was supported by a four-year analysis by FDA of three clinical studies involving mifepristone, other substantial scientific and medical data, and additional safety data from the prior extensive use of the drug overseas. GAO concluded that FDA's approval process and postmarket oversight of mifepristone was consistent with its processes and postmarket oversight for other Subpart H drugs.

When Congress adopted the REMS framework in 2007, it deemed each drug with existing Subpart H restrictions to have an approved REMS imposing the same restrictions.[10] Congress directed that ETASU imposed under REMS must "not be unduly burdensome on patient access to the drug," and, "to the extent practicable," must "minimize the burden on the health care delivery system."[11] In 2008, FDA reviewed the distribution restrictions set forth in the first FDA-approved label for mifepristone and concluded they were sufficient to constitute an acceptable REMS for

[7] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., NDA Approval Letter, NDA 020687 (Sept. 28, 2000), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.pdf. *See also* U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., Medical Review (Sept. 28, 2000), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P1.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P2.pdf.

[8] MIFEPREX Prescribing Information (Sept. 28, 2000), https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.pdf (describing three clinical trials underlying MIFEPREX 2000 approval). *See also* Irving M. Spitz et al., *Early Pregnancy Termination with Mifepristone and Misoprostol in the United States*, 338 New England J. Med. 1241 (1998).

[9] U.S. Gov't Accountability Off., GAO-08-751, *Food and Drug Administration: Approval and Oversight of the Drug Mifeprex* 15 (2008), https://www.gao.gov/assets/gao-08-751.pdf.

[10] 21 U.S.C. § 331 note.

[11] 21 U.S.C. § 355-1(f)(2).



the drug.[12] In 2011, FDA approved a REMS for mifepristone providing for essentially the same requirements previously imposed under Subpart H.[13]

(ii) 2016 Changes

Fifteen years after FDA's initial approval of Mifeprex, Danco Laboratories, LLC ("Danco"), the NDA holder, submitted a supplemental NDA ("sNDA") to revise Mifeprex's label and REMS in light of the further development of extensive data from dozens of clinical studies.[14] FDA approved most of the proposed modifications in 2016,[15] including: (1) increasing the gestational age limit in the labeling from 49 days to 70 days;[16] (2) reducing the number of required

[12] 73 Fed. Reg. 16313 (Mar. 27, 2008).

[13] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., Supplement Approval Letter, NDA 020687/S-014 (June 8, 2011), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/020687s014ltr.pdf.

[14] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., Supplement Approval Letter, NDA 020687/S-020 (Mar. 29, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/020687Orig1s020ltr.pdf.

[15] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., Medical Review, Application No. 020687Orig1s020 (Mar. 29, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf (hereinafter "2016 FDA Medical Review").

[16] *Id.* at 32-38, 53-57 & tbls. 6 & 7 (citing Beverly Winikoff et al., *Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion: A Randomized Controlled Trial*, 112 Obstetrics & Gynecology 1303 (2008), https://pubmed.ncbi.nlm.nih.gov/19037040/; Beverly Winikoff et al., *Extending Outpatient Medical Abortion Services Through 70 Days of Gestational Age*, 120 Obstetrics & Gynecology 1070 (2012), https://pubmed.ncbi.nlm.nih.gov/23090524/; Mary Gatter et al., *Efficacy and Safety of Medical Abortion Using Mifepristone and Buccal Misoprostol Through 63 Days*, 91 Contraception 269 (2015), https://pmc.ncbi.nlm.nih.gov/articles/PMC4373977/; Patricio Sanhueza Smith et al., *Safety, Efficacy and Acceptability of Outpatient Mifepristone-Misoprostol Medical Abortion Through 70 Days Since Last Menstrual Period in Public Sector Facilities in Mexico City*, 22 Reprod. Health Matters 75 (2015), https://pubmed.ncbi.nlm.nih.gov/25702071/; Adriana A. Boersma et al., *Mifepristone Followed by Home Administration of Buccal Misoprostol for Medical Abortion Up to 70 Days of Amenorrhoea in a General Practice in Curacao*, 16 Eur. J. Contraception & Reprod. Health Care 61 (2011), https://pubmed.ncbi.nlm.nih.gov/21303309/; Melanie Peña et al., *Efficacy and Acceptability of a Mifepristone-misoprostol Combined Regimen for Early Induced Abortion Among Women in Mexico City*, 127 Int'l J. Gynecology & Obstetrics 82 (2014), https://pubmed.ncbi.nlm.nih.gov/24957534/; Erica Chong et al., *A Randomized Controlled Trial of Different Buccal Misoprostol Doses in Mifepristone Medical Abortion*, 86 Contraception 251 (2012), https://pubmed.ncbi.nlm.nih.gov/22305917/; Hillary Bracken et al., *A Two-pill Sublingual Misoprostol Outpatient Regimen Following Mifepristone for Medical Abortion Through 70 days' LMP: A Prospective Comparative Open-label Trial*, 89 Contraception 181 (2014), https://pubmed.ncbi.nlm.nih.gov/24332431/; Elaine V. Gouk et al., *Medical Termination of Pregnancy at 63-83 Days Gestation*, 106 Brit. J. Obstetrics & Gynaecology 535 (1999), https://pubmed.ncbi.nlm.nih.gov/10426609/; Daniel Grossman et al., *Effectiveness and Acceptability of Medical Abortion Provided Through Telemedicine*, 118 Obstetrics & Gynecology 296 (2011), https://pubmed.ncbi.nlm.nih.gov/21775845/; Mitchell D. Creinin et al., *Mifepristone and Misoprostol Administered Simultaneously Versus 24 Hours Apart for Abortion: A Randomized Controlled Trial,* 109 Obstetrics & Gynecology 885 (2007), https://pubmed.ncbi.nlm.nih.gov/17400850/; Luu Doan Ireland et



in-person visits in the labeling from 3 to 1 (allowing for home administration of misoprostol and remote follow-up);[17] and (3) allowing mifepristone to be prescribed by non-physicians licensed to

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al., *Medical Compared with Surgical Abortion for Effective Pregnancy Termination in the First Trimester*, 126 Obstetrics & Gynecology 22 (2015), https://pubmed.ncbi.nlm.nih.gov/26241252/).

[17] 2016 FDA Medical Review at 38-41, 44, 65-66 & tbl. 8, (Mar. 29, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf (citing Mary Gatter et al., *Efficacy and Safety of Medical Abortion Using Mifepristone and Buccal Misoprostol Through 63 Days*, 91 Contraception 269 (2015), https://pmc.ncbi.nlm.nih.gov/articles/PMC4373977/; Beverly Winikoff et al., *Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion: A Randomized Controlled Trial*, 112 Obstetrics & Gynecology 1303 (2008), https://pubmed.ncbi.nlm.nih.gov/19037040/; Beverly Winikoff et al., *Extending Outpatient Medical Abortion Services Through 70 Days of Gestational Age*, 120 Obstetrics & Gynecology 1070 (2012), https://pubmed.ncbi.nlm.nih.gov/23090524/; Yael Swica et al., *Acceptability of Home Use of Mifepristone for Medical Abortion*, 88 Contraception 122 (2013), https://pubmed.ncbi.nlm.nih.gov/23177917; Karmen S. Louie et al., *Acceptability and Feasibility of Mifepristone Medical Abortion in the Early First Trimester in Azerbaijan*, 19 Eur. J. Contraception & Reprod. Health Care 457 (2014), https://pubmed.ncbi.nlm.nih.gov/25047120/; Melanie Peña et al., *Efficacy and Acceptability of a Mifepristone-misoprostol Combined Regimen for Early Induced Abortion Among Women in Mexico City*, 127 Int'l J. Gynecology & Obstetrics 82 (2014), https://pubmed.ncbi.nlm.nih.gov/24957534/; Hillary Bracken et al., *A Two-pill Sublingual Misoprostol Outpatient Regimen Following Mifepristone for Medical Abortion Through 70 days' LMP: A Prospective Comparative Open-label Trial*, 89 Contraception 181 (2014), https://pubmed.ncbi.nlm.nih.gov/24332431/; Adriana Boersma et al., *Mifepristone Followed by Home Administration of Buccal Misoprostol for Medical Abortion Up to 70 Days of Amenorrhoea in a General Practice in Curacao*, 16 Eur. J. Contraception & Reprod. Health Care 61 (2011), https://pubmed.ncbi.nlm.nih.gov/21303309/; Erica Chong et al., *A Randomized Controlled Trial of Different Buccal Misoprostol Doses in Mifepristone Medical Abortion*, 86 Contraception 251 (2012), https://pubmed.ncbi.nlm.nih.gov/22305917/; Nguyen Thi Nhu Ngoc et al., *Acceptability and Feasibility of Phone Follow-up After Early Medical Abortion in Vietnam: A Randomized Controlled Trial*, 123 Obstetrics & Gynecology 88 (2014), https://pubmed.ncbi.nlm.nih.gov/24463668/; Phillip Goldstone et al., *Early Medical Abortion Using Low-dose Mifepristone Followed by Buccal Misoprostol: A Large Australian Observational Study*, 197 Med. J Austral. 282 (2012), https://pubmed.ncbi.nlm.nih.gov/22938126/; Patricio Sanhueza Smith et al., *Safety, Efficacy and Acceptability of Outpatient Mifepristone-Misoprostol Medical Abortion Through 70 Days Since Last Menstrual Period in Public Sector Facilities in Mexico City*, 22 Reprod. Health Matters 75 (2015), https://pubmed.ncbi.nlm.nih.gov/25702071/; Elizabeth G. Raymond et al., *First-trimester Medical Abortion with Mifepristone 200 mg and Misoprostol: A Systematic Review*, 87 Contraception 26 (2013), https://pubmed.ncbi.nlm.nih.gov/22898359/; Daniel Grossman & Kate Grindlay, *Alternatives to Ultrasound for Follow-up After Medication Abortion: A Systematic Review*, 83 Contraception 504 (2011), https://pubmed.ncbi.nlm.nih.gov/21570546/; Lisa K. Perriera et al., *Feasibility of Telephone Follow-Up After Medical Abortion*, 81 Contraception 143 (2010), https://www.contraceptionjournal.org/article/S0010-7824(09)00387-4/abstract; Christian Fiala et al., *Verifying the Effectiveness of Medical Abortion; Ultrasound Versus hCG Testing*, 109 Eur. J. Obstetrics & Gynecology & Reprod. Biology 190 (2003), https://pubmed.ncbi.nlm.nih.gov/12860340/; Kelsey Lynd et al., *Simplified Medical Abortion Using a Semi-quantitative Pregnancy Test for Home-Based Follow-up*, 121 Int'l J Gynecology & Obstetrics 144 (2013), https://pubmed.ncbi.nlm.nih.gov/23477704/; S.T. Cameron et al., *Can Women Determine the Success of Early Medical Termination of Pregnancy*



prescribe drugs (e.g., nurse practitioners).[18] Before granting the sNDA and REMS modification, FDA undertook a full review of all elements of the mifepristone REMS, finding that "[t]he safety profile of [mifepristone] is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance."[19] FDA found that medication abortion "has been increasingly used as its efficacy and safety have become well-established by both research and experience, and serious complications have proven to be extremely rare."[20] FDA also found that the rates of serious adverse events associated with the new regimen, including home administration of misoprostol, are "exceedingly low."[21]

In 2018, responding to another request from members of Congress, GAO reviewed FDA's approval of the 2016 changes. It found that FDA had reviewed numerous peer-reviewed published studies, articles and data that supported the efficacy and safety of the proposed changes and had

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Themselves? 91 Contraception 6 (2015), https://www.sciencedirect.com/science/article/abs/pii/S0010782414006908).

[18] 2016 FDA Medical Review at 43-44, 78-79 (Mar. 29, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf (citing R. Renner et al., *Who Can Provide Effective and Safe Termination of Pregnancy Care: A Systematic Review*, 10 BJOG 23 (2013), https://pubmed.ncbi.nlm.nih.gov/22900974/; Claudia Diaz Olavarrieta et al., *Nurse Versus Physician-Provision of Early Medical Abortion in Mexico: A Randomized Controlled Non-Inferiority Trial*, 93 Bull. World Health Org. 249 (2015), https://pmc.ncbi.nlm.nih.gov/articles/PMC4431559/; H. Kopp Kallner et al., *The Efficacy, Safety and Acceptability of Medical Termination of Pregnancy Provided by Standard Care by Doctors or by Nurse-Midwives: A Randomized Controlled Equivalence Trial*, 122 BJOG 510 (2015), https://pubmed.ncbi.nlm.nih.gov/25040643/; I.K. Warriner et al., *Can Midlevel Health-Care Providers Administer Early Medical Abortion as Safely and Effectively as Doctors? A Randomized Controlled Equivalence Trial in Nepal*, 377 Lancet 1155 (2011), https://pubmed.ncbi.nlm.nih.gov/21458058/; Mahesh Puri et al., *The Role of Auxiliary Nurse-Midwives and Community Health Volunteers in Expanding Access to Medical Abortion in Rural Nepal*, 22 Reprod. Health Matters 94 (2015), https://pubmed.ncbi.nlm.nih.gov/25702073/). Since FDA's 2016 review, additional studies have confirmed FDA's finding that mifepristone remains safe and effective when prescribed and dispensed by qualified nonphysicians. *See, e.g.*, L. Porsch et al., *Advanced Practice Clinicians and Medication Abortion Safety: A 10-Year Retrospective Review*, 101 Contraception 357 (2020), https://www.contraceptionjournal.org/article/S0010-7824(20)30119-0/abstract; Lydia Mainey et al., *The Role of Nurses and Midwives in the Provision of Abortion Care: A Scoping Review*, 29 J. Clinical Nursing 1513 (2020), https://pubmed.ncbi.nlm.nih.gov/32045070/.

[19] 2016 FDA Medical Review at 88 (Mar. 29, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf.

[20] *Id.* at 12 (citing Kelly Cleland & Nicole Smith, *Aligning Mifepristone Regulation with Evidence: Driving Policy Change Using 15 Years of Excellent Safety Data*, 92 Contraception 179 (2015), https://www.contraceptionjournal.org/article/S0010-7824(15)00254-1/fulltext).

[21] 2016 FDA Medical Review at 62 (Mar. 29, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf.



also evaluated adverse event data associated with Mifeprex.[22] Specifically, GAO found that FDA had reviewed 19 studies that evaluated increasing the gestational age limit, which demonstrated efficacy rates of greater than 90% through 70 days gestation.[23] FDA also reviewed 15 studies that evaluated home administration of misoprostol, including a large literature review of 87 studies that included over 45,000 women. GAO noted that FDA found no evidence that home use of misoprostol increased rates of treatment failure or serious complications.[24] After reviewing 11 studies that evaluated different methods for follow-up care after mifepristone administration, FDA determined that various methods of follow-up, including home pregnancy testing and telephone visits, were acceptable alternatives to an in-clinic follow up.[25] Finally, FDA reviewed four studies addressing the ability of nonphysician health care providers to provide abortion care, finding that efficacy rates were at least 96% across all studies, regardless of gestational age or provider type.[26]

Petitioner is not aware of any peer-reviewed study or other robust evidence (clinical or epidemiological) that casts any doubt on these findings of either the FDA or GAO. Nor has FDA ever provided any contrary studies or evidence to Petitioner or asked Petitioner for comments on any such studies or evidence.

(iii) ANDA Approval

On April 11, 2019, FDA approved Petitioner's ANDA to manufacture and market generic mifepristone.[27] FDA's approval of Petitioner's ANDA reflects the Agency's consistent finding that mifepristone is safe and effective and was based on a robust review of vast amounts of data and hundreds of medical studies over more than two decades, including data submitted by Petitioner to support the approval of its ANDA. As required by the FDCA, Petitioner's generic mifepristone and Danco's Mifeprex must have substantively identical labels, in recognition of the fact that they are "bioequivalent" and have "the same therapeutic effect" and thus have the same benefits and risks.[28] FDA accordingly determined that the branded and generic mifepristone should share a single, shared REMS pursuant to 21 U.S.C. § 355-1(i). Petitioner is the sole supplier of generic mifepristone in the United States and currently supplies the majority of the mifepristone used domestically for medication abortions.

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[22] U.S. Gov't Accountability Off., GAO-18-292, Food and Drug Administration: Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts 11 (2018), https://www.gao.gov/assets/gao-18-292.pdf.

[23] *Id.* at 12-13.

[24] *Id.* at 13-14.

[25] *Id.* at 15.

[26] *Id.*

[27] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., ANDA Approval Letter, ANDA 091178 (Apr. 11, 2019), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/091178Orig1s000ltr.pdf.

[28] 21 U.S.C. § 355(j)(2)(A)(iv)-(v), (j)(4)(F)-(G).



(iv) 2023 Changes

FDA more recently concluded that in-person dispensing of mifepristone is not necessary to ensure its safe use, following a comprehensive review of published scientific literature and adverse event data. From July 13, 2020 through January 2021, a court injunction barred FDA from enforcing the in-person dispensing requirement during the COVID-19 Public Health Emergency ("PHE").[29] In April 2021, as the COVID-19 PHE continued, FDA further stated it intended to exercise enforcement discretion with respect to the in-person dispensing requirement, finding that requiring a patient to visit a clinic to receive mifepristone could pose COVID-related safety risks to those patients and healthcare personnel.[30] FDA reached this decision following "a thorough scientific review" by experts within FDA's Center for Drug Evaluation and Research ("CDER"), who "evaluated relevant information, including available clinical outcomes data and adverse event reports."[31]

Throughout the remainder of 2021, FDA "undertook a full review" of the mifepristone REMS, evaluating published literature, safety information submitted to FDA during the COVID-19 PHE, adverse event data, the one-year assessment report for the mifepristone REMS, and information provided by advocacy groups, individuals, and the sponsors of the NDA and the ANDA.[32] In December 2021, FDA determined that the in-person dispensing requirement was not necessary and directed sponsors to initiate the process to modify REMS.[33] In particular, after reviewing adverse event data, FDA found no difference in adverse event rates between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced, suggesting that "mifepristone may be safely used without an in-person dispensing requirement."[34] FDA further concluded, based on published studies, that dispensing by mail does not jeopardize efficacy of medical abortion, finding that the

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[29] *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183, 233 (D. Md. July 13, 2020), *order clarified*, 2020 WL 8167535 (D. Md. Aug. 19, 2020) (preliminarily enjoining FDA from enforcing the in-person dispensing requirement and any other in-person requirements of the mifepristone REMS); *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (Jan. 12, 2021) (staying the preliminary injunction imposed by the District Court).

[30] Letter from Janet Woodcock, Acting Comm'r of Food & Drugs, to Maureen Phipps, Chief Exec. Off., Am. Coll. of Obstetricians & Gynecologists, and William Grobman, President, Soc'y for Maternal Fetal Med. (Apr. 12, 2021), available at https://www.aclu.org/sites/default/files/field_document/fda_acting_commissioner_letter_to_acog_april_12_2021.pdf.

[31] Response Letter from FDA CDER to Am. Ass'n of Pro-Life Obstetricians & Gynecologists and Am. Coll. of Pediatricians, No. FDA-2019-P-1534, at 5 (Dec. 16, 2021), https://www.regulations.gov/document/FDA-2019-P-1534-0016.

[32] *Id.* at 6.

[33] U.S. Food & Drug Admin., REMS Modification Rationale Review (Dec. 16, 2021), available at https://www.accessdata.fda.gov/drugsatfda_docs/summary_review/2023/020687Orig1s025SumR.pdf#page=41 (hereinafter "2021 REMS Modification Rationale Review").

[34] *Id.* at 23.



safety and efficacy outcomes reported in these studies were "within the ranges described in mifepristone labeling."[35]

Based on this comprehensive review of the evidence, FDA concluded that mifepristone "will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met, and pharmacy certification is

[35] *Id.* at 39; *id.* at 24-36 (citing Daniel Grossman et al., *Mail-order Pharmacy Dispensing of Mifepristone for Medication Abortion After In-person Clinical Assessment*, 107 Contraception 36 (2021), https://pubmed.ncbi.nlm.nih.gov/34555420/; Daniel Grossman et al., *Medication Abortion with Pharmacist Dispensing of Mifepristone*, 137 Obstetrics & Gynecology 613 (2021), https://pubmed.ncbi.nlm.nih.gov/33706339/; Erica Chong et al., *Expansion of a Direct-to-Patient Telemedicine Abortion Service in the United States and Experience During the COVID-19 Pandemic,* 104 Contraception 43 (2021), https://pubmed.ncbi.nlm.nih.gov/33781762/; Courtney Kerestes et al., *Provision of Medication Abortion in Hawai'i During COVID-19: Practical Experience with Multiple Care Delivery Models*, 104 Contraception 49 (2021), https://pmc.ncbi.nlm.nih.gov/articles/PMC8005318/; Abigail R.A. Aiken et al., *Effectiveness, Safety and Acceptability of No-test Medical Abortion (Termination of Pregnancy) Provided via Telemedicine: A National Cohort Study*, 128 BJOG 1464 (2021), https://pubmed.ncbi.nlm.nih.gov/33605016/; Corinne H. Rocca et al., *Effectiveness and Safety of Early Medication Abortion Provided in Pharmacies by Auxiliary Nurse-Midwives: A Non-inferiority Study in Nepal*, 13 PLoS ONE 1 (2018), https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0191174; Ellen R. Wiebe et al., *Comparing Telemedicine to In-Clinic Medication Abortions Induced with Mifepristone and Misoprostol*, 2 Contracept X 1 (2020), https://pubmed.ncbi.nlm.nih.gov/32550538/; Ushma D. Upadhyay et al., *Safety and Efficacy of Telehealth Medication Abortion in the US During the COVID-19 Pandemic*, 4 JAMA Network Open 1 (2021), https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2783451; Paul Hyland et al., *A Direct-to-Patient Telemedicine Abortion Service in Australia: Retrospective Analysis of the First 18 Months*, 58 Austl. & N.Z. J. Obstetricians & Gynaecologists 335 (2018), https://pubmed.ncbi.nlm.nih.gov/29603139/; Elizabeth G. Raymond et al., *TelAbortion: Evaluation of a Direct to Patient Telemedicine Abortion Service in the United States*, 100 Contraception 173 (2019), https://www.sciencedirect.com/science/article/abs/pii/S0010782419301763; Holly A. Anger et al., *Clinical and Service Delivery Implications of Omitting Ultrasound Before Medication Abortion Provided Via Direct-to-Patient Telemedicine and Mail in the U.S.*, 104 Contraception 659 (2021), https://pubmed.ncbi.nlm.nih.gov/34329607/; John Joseph Reynolds-Wright et al., *Telemedicine Medical Abortion at Home Under 12 Weeks' Gestation: A Prospective Observational Cohort Study During the COVID-19 Pandemic*, 47 BMJ Sex Reprod. Health 246 (2021), https://pubmed.ncbi.nlm.nih.gov/33542062/; Abigail R.A. Aiken et al., *Self Reported Outcomes and Adverse Events After Medical Abortion Through Online Telemedicine: Population Based Study in the Republic of Ireland and Northern Ireland*, 357 BMJ 1 (2017), https://www.bmj.com/content/357/bmj.j2011; Hanna Nortén et al., *10-year Evaluation of the Use of Medical Abortion Through Telemedicine: A Retrospective Cohort Study*, 129 BJOG 151 (2022), https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1111/1471-0528.16765; M. Endler et al. *Safety and Acceptability of Medical Abortion Through Telemedicine After 9 Weeks of Gestation: A Population-Based Cohort Study*, 126 BJOG 609 (2019), https://pubmed.ncbi.nlm.nih.gov/30456778/; Elizabeth G. Raymond et al., *Commentary: No-test Medication Abortion: A Sample Protocol for Increasing Access During a Pandemic and Beyond*, 101 Contraception 361 (2020), https://pubmed.ncbi.nlm.nih.gov/32305289/).



added."[36] FDA determined that this modification would "render the REMS less burdensome to healthcare providers and patients" and that the modified REMS will "continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks."[37] FDA further recognized that removing the in-person dispensing requirement would allow "dispensing of mifepristone by mail via certified prescribers or pharmacies."[38] In January 2023, FDA approved the sponsors' applications to remove the in-person dispensing requirement from the REMS.[39]

Again, Petitioner is not aware of any peer-reviewed study or other robust scientific evidence (clinical or epidemiological) that casts any doubt on these findings. Nor has FDA ever provided any contrary studies or evidence to Petitioner or asked Petitioner for comments on any such studies or evidence. On the contrary, as discussed below, since December 2023, additional research has further confirmed that the dispensing of mifepristone via telehealth is safe and effective.

b. Mifepristone Remains Safe and Effective Under the Current REMS

Mifepristone's safety and efficacy profile has remained strongly supported across multiple iterations of the mifepristone REMS, including after removing the in-person dispensing requirement. As detailed above, the safety and efficacy of mifepristone is supported by a robust body of scientific evidence, reflecting vast amounts of data and hundreds of medical studies evaluating thousands of patients.[40] Moreover, mifepristone is recognized as a safe and effective option for abortion care by numerous clinical practice guidelines and best practices issued by professional groups and other reproductive health experts.[41]

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[36] 2021 REMS Modification Rationale Review at 39 (Dec. 16, 2021), available at https://www.accessdata.fda.gov/drugsatfda_docs/summary_review/2023/020687Orig1s025SumR.pdf#page=41.

[37] *Id.* at 39-40.

[38] *Id.* at 40.

[39] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., Supplement Approval Letter, NDA 020687/S-025 (Jan. 3, 2023), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/020687Orig1s025ltr.pdf; U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., Prior Approval Supplement Approval Letter, ANDA 091178/S-004 (Jan. 3, 2023), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/091178Orig1s004ltr.pdf. *See also* U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., Approval Package, Application No. 020687Orig1s025 (Jan. 3, 2023), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/020687Orig1s025.pdf.

[40] *See* Nat'l Acad. of Sci., Eng'g & Med., *The Safety and Quality of Current Abortion Methods* in *The Safety & Quality of Abortion Care in the U.S.* (2018), https://nap.nationalacademies.org/read/24950/chapter/1.

[41] *See, e.g.*, Am. Coll. of Obstetricians & Gynecologists, *Prac. Bull. No. 225: Medication Abortion Up to 70 Days of Gestation* (Oct. 2020), https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2020/10/medication-abortion-up-to-70-days-of-gestation; Nat'l Abortion Fed., 2024



Adverse events with mifepristone are extremely rare, as demonstrated by FDA's summary report of post-marketing adverse events through December 31, 2024.[42] In that report, FDA estimates that approximately 7.5 million women have used mifepristone in the U.S. for medical termination of pregnancy from its approval through December 2024. Among those millions of patients, there have been 36 reported deaths (which are included regardless of any causal attribution to mifepristone), corresponding to an approximate mortality rate of 0.00048%.[43] Moreover, as FDA has recognized, even that small percentage of deaths cannot be causally attributed to mifepristone because of concurrent use of other drugs, other medical or surgical treatments, co-existing medical conditions, and/or information gaps about patient health status and clinical management of the patient.[44]

Other adverse events also remain rare: from November 2012 through December 2024, adverse events were reported in 1,512 cases of mifepristone users in the entire nation, of which 288 required hospitalization (excluding deaths).[45] As the FDA-approved label recognizes, infections and bleeding can occur "very rarely following *spontaneous, surgical, and medical abortions*," and "[n]o causal relationship between the use of [mifepristone] and misoprostol and these events has been established."[46] Evidence suggests that the "critical risk factor" in the reported

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Clinical Policy Guidelines for Abortion Care (2024), https://prochoice.org/wp-content/uploads/2024-CPGs-FINAL-1.pdf; World Health Organization, *Abortion Care Guideline* 95 (Mar. 8, 2022), https://www.who.int/publications/i/item/9789240039483; Royal Coll. of Obstetricians & Gynaecologists, *Best Practice in Abortion Care* (Mar. 2022), https://www.rcog.org.uk/media/geify5bx/abortion-care-best-practice-paper-april-2022.pdf; Nathalie Kapp & Patricia A. Lohr, *Modern Methods to Induce Abortion: Safety, Efficacy and Choice*, 63 Best Prac. & Rsch. Clinical Obstetrics & Gynaecology 37 (2020), https://pubmed.ncbi.nlm.nih.gov/32029379/.

[42] U.S. Food & Drug Admin., Mifepristone U.S. Post-Marketing Adverse Events Summary through 12/31/2024, https://www.fda.gov/media/185245/download?attachment.

[43] *Id.* The 36 total number of reported deaths includes 13 cases associated with sepsis; 2 cases of homicide, 2 cases of combined drug intoxication/overdose, 2 cases of ruptured ectopic pregnancy, 2 cases of drug intoxication, 2 cases of suicide, and 1 case each of the following: substance abuse/drug overdose; methadone overdose; suspected homicide; delayed onset toxic shock-like syndrome; hemorrhage; bilateral pulmonary thromboemboli; unintentional overdose resulting in liver failure; probable anaphylactic medication reaction; septic shock due to necrotizing fasciitis; sepsis with multiple complications possibly secondary to toxic shock syndrome 82 days after mifepristone; sudden death of undetermined etiology despite performance of an autopsy; and a case of natural death due to severe pulmonary emphysema.

[44] U.S. Food & Drug Admin., *Questions and Answers on Mifepristone for Medical Termination of Pregnancy Through Ten Weeks Gestation* (Feb. 11, 2025), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/questions-and-answers-mifepristone-medical-termination-pregnancy-through-ten-weeks-gestation.

[45] U.S. Food & Drug Admin., Mifepristone U.S. Post-Marketing Adverse Events Summary through 12/31/2024, https://www.fda.gov/media/185245/download?attachment.

[46] MIFEPREX Prescribing Information (Mar. 23, 2023), https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s026lbl.pdf (emphasis added).



cases of infection "is pregnancy itself."[47] Importantly, mifepristone is associated with significantly fewer, and less severe, complications than full-term pregnancy. Approximately 1.6% of women giving birth in U.S. hospitals experience severe maternal morbidity—including hemorrhage, eclampsia, sepsis, and organ failure—which can have significant short- and long-term health consequences.[48] In 2023, the maternal mortality rate was 18.6 deaths per 100,000 live births (0.0186%).[49]

As discussed above, FDA's decision to eliminate the in-person dispensing requirement was fully supported by the scientific evidence available as of December 2021. Since December 2021, further research has demonstrated that the dispensing of mifepristone via telehealth is safe and effective.[50] Again, Petitioner is not aware of any peer-reviewed study or other robust data (clinical

[47] Citizen Petition Denial Response from FDA CDER to the Am. Ass'n of Pro Life Obstetricians & Gynecologists 25-26 n.69, No. FDA-2002-P-0364 (Mar. 29, 2016), https://www.regulations.gov/document/FDA-2002-P-0364-0002.

[48] Dorothy A. Fink et al., *Trends in Maternal Mortality and Severe Maternal Morbidity During Delivery-Related Hospitalizations in the United States, 2008 to 2021*, 6 JAMA Network Open 1 (2023), https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2806478.

[49] Donna L. Hoyert, Ctrs. for Disease Control & Prevention, *Health E-Stat 100: Maternal Mortality Rates in the United States, 2023* (Feb. 2025), https://www.cdc.gov/nchs/data/hestat/maternal-mortality/2023/Estat-maternal-mortality.pdf; *see also* Elizabeth G. Raymond & David Grimes, *The Comparative Safety of Legal Induced Abortion and Childbirth in the United States*, 119 Obstetrics & Gynecology 215 (2012), https://journals.lww.com/greenjournal/abstract/2012/02000/the_comparative_safety_of_legal_induced_abortion.3.aspx.

[50] *See, e.g.*, Ushma D. Upadhyay et al., *Effectiveness and Safety of Telehealth Medication Abortion in the USA*, 30 Nature Med. 1191 (2024), https://www.nature.com/articles/s41591-024-02834-w; Lauren J. Ralph et al., *Comparison of No-Test Telehealth and In-Person Medication Abortion*, 332 JAMA 898 (2024), https://jamanetwork.com/journals/jama/article-abstract/2820321; Silpa Srinivasulu et al., *Telehealth Medication Abortion in Primary Care: A Comparison to Usual in-Clinic Care*, 37 J. Am. Bd. Fam. Med. 295 (2024), https://pubmed.ncbi.nlm.nih.gov/38740468/; Caitlin Hunter et al., *Test or No-Test: Comparison of Medication Abortion Outcomes and Adverse Events When Forgoing Ultrasound, Laboratory Testing, and Physical Examination*, 47 J. Obstetrics & Gynaecology Can. 1, 7 (2025), https://pubmed.ncbi.nlm.nih.gov/39615625/; Holly Anger & Elizabeth G. Raymond, *Clinical and Service Delivery Outcomes Following Medication Abortion Provided With or Without Pretreatment Ultrasound or Pelvic Examination: An Updated Comparative Analysis*, 140 Contraception 1 (2024), https://pubmed.ncbi.nlm.nih.gov/39059683/; Leonardo Cely-Andrade et al., *Telemedicine for the Provision of Medication Abortion to Pregnant People at up to Twelve Weeks of Pregnancy: A Systematic Literature Review and Meta-Analysis*, 21 Reprod. Health 136, 155 (2024), https://pubmed.ncbi.nlm.nih.gov/39300581/; Martha K. Smith et al., *The Safety and Efficacy of a "No Touch" Abortion Program Implemented in the Greater Toronto Area During the COVID-19 Pandemic*, 46 J. Obstetrics & Gynaecology Can. 1 (2024), https://pubmed.ncbi.nlm.nih.gov/38458271/; Ushma D. Upadhyay et al., *Outcomes and Safety of History-Based Screening for Medication Abortion: A Retrospective Multicenter Cohort Study*, 182 JAMA Internal Med. 482 (2022), https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2790319; Marit Pearlman Shapiro et al., No-Test Medication Abortion: A Systemic Review, 141 Obstetrics & Gynecology 23 (2023), https://pubmed.ncbi.nlm.nih.gov/36701607/. *See also* Karin Brandell et al., *Randomized Trial of Very Early Medication Abortion*, 391 New England J. Med. 1685 (2024),



or epidemiological) that contradicts FDA's decision to remove the in-person dispensing requirement.

c. Unsubstantiated Claims by Abortion Opponents Do Not Justify Imposing Restrictions on Mifepristone Access

Despite mifepristone's well-established safety and efficacy profile—which has been borne out in hundreds of medical studies over more than two decades as well as use by millions of women—some ideological opponents of abortion have alleged that mifepristone carries unacceptable safety risks. Such opponents have urged FDA either to revoke its approval of mifepristone or to impose burdensome restrictions on patient access. As discussed further below, there is no scientifically robust evidence to support these spurious claims, which fall far short of the evidentiary standard required by the FDCA.

First, to withdraw the mifepristone approval, FDA would need to find that: (1) "*clinical or other experience, tests, or other scientific data* show that such drug is *unsafe for use* under the conditions of use upon the basis of which the application was approved," (2) "new evidence of *clinical experience*" or "*tests by new methods*" show that a drug is "*not shown to be safe for use* under the conditions of use upon the basis of which the application was approved," or (3) "new information" demonstrates a "*lack of substantial evidence* that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof."[51] No such evidence exists with respect to mifepristone. Petitioner is not aware of any scientifically robust evidence—including clinical experience, tests, or data—showing that mifepristone is unsafe for use under its conditions of use. Nor is Petitioner aware of any new information that demonstrates a lack of substantial evidence of effectiveness. To the contrary, the overwhelming weight of scientific research and peer-reviewed studies demonstrate that mifepristone is safe and effective for the medical termination of intrauterine pregnancy through 70 days gestation.

Second, when evaluating a REMS for potential modification, FDA considers "new safety information."[52] The statute provides explicit instruction on the type of evidence that FDA may consider, defining "new safety information" to mean "information derived from a *clinical trial*, an *adverse event report*, a *postapproval study* . . . , or *peer-reviewed biomedical literature*; data derived from the *postmarket risk identification and analysis system* . . . ; or other *scientific data*

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https://www.nejm.org/doi/10.1056/NEJMoa2401646; Vera Kelesidou et al., *Combination of Mifepristone and Misoprostol for First-Trimester Medical Abortion: A Comprehensive Review of the Literature*, 79 Obstetrical & Gynecological Survey 54 (2024), https://pubmed.ncbi.nlm.nih.gov/38306292/; Abigail R.A. Aiken et al., *Safety and Effectiveness of Self-Managed Medication Abortion Provided Using Online Telemedicine in the United States: A Population Based Study*, 10 Lancet Reg'l Health – Ams. 1 (2022), https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(22)00017-5/fulltext; Ushma D. Upadhyay et al., *Safety and Effectiveness of Synchronous and Asynchronous Telehealth Medication Abortion Provided by US Virtual Clinics*, 116 Contraception 69 (2022), https://www.contraceptionjournal.org/article/S0010-7824(22)00263-3/abstract.

[51] 21 U.S.C. § 355(e) (emphasis added).

[52] 21 U.S.C. § 355-1(b)(3).



deemed appropriate by the Secretary."[53] Such information must address: (1) "a serious risk or an unexpected serious risk associated with the use of the drug that the Secretary has become aware of (that may be based on a new analysis of existing information) . . . *since the last assessment of the approved [REMS]* for the drug"; or (2) "the effectiveness of the approved [REMS] for the drug obtained *since the last assessment of such strategy*."[54] Petitioner is not aware of any such new clinical trial, adverse event report, postapproval study, peer-reviewed biomedical literature, or other scientific data that merits a modification to the mifepristone label or REMS to make them more restrictive or to reinstate previously removed requirements.[55]

Petitioner is aware that, in late April 2025 and early May 2025, the Ethics and Public Policy Center ("EPPC") issued two documents arguing that FDA should reverse its findings with respect to the mifepristone REMS and label and "reconsider its approval altogether."[56] Secretary Kennedy was expressly questioned about the April 2025 document at a recent congressional hearing where Senator Josh Hawley (a strong opponent of abortion) demanded that FDA undertake a complete review of mifepristone.

At the outset, it is important to note that EPPC is not a medical or scientific organization: EPPC describes its mission as "working to apply the riches of the Jewish and Christian traditions to contemporary questions of law, culture, and politics, in pursuit of America's continued civic and cultural renewal."[57] The EPPC documents on mifepristone were issued as part of the organization's "Life and Family Initiative," which "works nationwide to advance pro-life policies that protect unborn children by restricting abortion at the state and federal levels, via legislation,

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[53] *Id.* (emphasis added)

[54] *Id.* (emphasis added).

[55] Some abortion opponents have advocated that FDA should re-impose the in-person dispensing requirement or otherwise modify the REMS to mitigate a purported risk that a pregnant individual could be forced or coerced to ingest mifepristone in order to induce an abortion. Any forced or coerced use of mifepristone would be inconsistent with the *existing* FDA-approved label and REMS, as well as both unethical and illegal. Petitioner is unaware of *any* study or data analyzing whether or to what extent such conduct has occurred in the United States, let alone linking such conduct to the recent REMS modification. Petitioner also is unaware of any evidence of such alleged activity indicated in the FDA Adverse Event Reporting System ("FAERS") database. In the absence of any such scientific evidence evaluating this purported risk, FDA cannot reinstate the in-person dispensing requirement or otherwise modify the REMS on the basis of this unfounded allegation. Moreover, if FDA believed such evidence existed, it would be incumbent on FDA to accord Petitioner, who worked with FDA to develop and finalize the current REMS, notice and an opportunity to comment on such material.

[56] Jamie Bryan Hall & Ryan T. Anderson, Ethics & Pub. Pol'y Ctr., *The Abortion Pill Harms Women: Insurance Data Reveals One in Ten Patients Experiences a Serious Adverse Event* (Apr. 28, 2025), https://eppc.org/wp-content/uploads/2025/04/25-04-The-Abortion-Pill-Harms-Women.pdf; Jamie Bryan Hall & Ryan T. Anderson, Ethics & Pub. Pol'y Ctr., *The Abortion Pill Harms Women: Insurance Data Reveals Repeated Abortion Attempts Due to High Failure Rate* (May 12, 2025), https://eppc.org/wp-content/uploads/2025/05/25-05-SHW-Insurance-Data-Reveals-Repeated-Abortion-Attempts-Due-to-High-Failure-Rate.pdf.

[57] Ethics & Pub. Pol'y Ctr., *About Us*, https://eppc.org/about/.



regulation, and litigation."[58] Similarly, the authors of the documents at issue, Jamie Bryan Hall and Ryan T. Anderson, are neither physicians nor medical scientists. Hall and Anderson state that the project was conducted by an unnamed "team" of data scientists, analysts, and engineers, with assistance from a group of unnamed physicians. Most critically, the documents were self-published on EPPC's website and not subject to peer review, meaning Hall and Anderson's methodology, data, and conclusions were never scrutinized by experts in the field for accuracy or reliability.

The EPPC documents are, in fact, deeply flawed and present no legitimate basis for FDA to revise the mifepristone REMS or to revoke its approval of the drug. We outline some (but not all) of those flaws below.

In the first document, Hall and Anderson claim that the unnamed team used an unnamed dataset to identify patients whose medical records contained a code for a medication abortion, a prescription for mifepristone, or a code for an abortion or unwanted pregnancy alongside coding consistent with a medication abortion. Among those patients, Hall and Anderson claim that10.93% allegedly also had some mention of some other purported adverse event within 45 days of the prior entry.[59] Hall and Anderson state that they identified "serious adverse events" using an undefined list of "relevant" diagnosis codes and procedure codes. They then grouped those codes into 10 categories, which include, among other categories: (1) emergency room visits (with abortion-related diagnosis and procedure codes); (2) other events that a group of unnamed doctors "judge to be life-threatening" (including ectopic pregnancy); (3) subsequent surgical abortion procedures; or (4) unspecified "other abortion complications," including "life-threatening mental health diagnoses."[60] These categories present several critical and likely fatal issues.

To begin, it is clear that Hall and Anderson did not follow accepted scientific practices in conducting their result-oriented analysis, including, but not limited to, use of a validated algorithm for probing the data. For example, counting abortion-related emergency room visits by themselves as serious adverse events is contrary to the FDCA and FDA guidance.[61] It is also inconsistent with real world evidence: studies have repeatedly demonstrated that the majority of patients with abortion-related emergency room visits receive observation care only.[62] Patients often visit

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[58] Ethics & Pub. Pol'y Ctr., *Life and Family Initiative*, https://eppc.org/program/life-and-family-initiative/.

[59] Jamie Bryan Hall & Ryan T. Anderson, Ethics & Pub. Pol'y Ctr., *The Abortion Pill Harms Women: Insurance Data Reveals One in Ten Patients Experiences a Serious Adverse Event* (Apr. 28, 2025), https://eppc.org/wp-content/uploads/2025/04/25-04-The-Abortion-Pill-Harms-Women.pdf.

[60] *Id.*

[61] 21 U.S.C. § 355-1(b)(4); U.S. Food & Drug Admin., *What is a Serious Adverse Event?* (May 18, 2023), https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event ("Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).").

[62] Ushma D. Upadhyay et al., *Incidence of Emergency Department Visits and Complications After Abortion*, 125 Obstetrics & Gynecology 175 (2015), https://pubmed.ncbi.nlm.nih.gov/25560122/; Ushma D. Upadhyay et al., *Abortion-Related Emergency Department Visits in the United States: An Analysis of a*



emergency rooms to receive care for normal uterine cramping and bleeding, to ask questions, or simply to confirm they are no longer pregnant. None of those scenarios would qualify as a serious adverse event under FDA's definition. In any event, it is well established in the scientific literature (and reflected in the mifepristone label) that a small number of patients will visit an emergency room following administration of mifepristone and misoprostol, and this evidence was available to, and considered by, FDA when it approved changes to mifepristone's labeling and REMS. Yet, emergency room visits constitute over 40% of the purported serious adverse events identified by Hall and Anderson.

Hall and Anderson also count any subsequent procedure to *complete* the abortion as a serious adverse event. But, again, it is well-known and expected that approximately 2-7% of patients will need a surgical procedure following mifepristone administration, and this possibility is already included in the FDA-approved mifepristone labeling.[63] Yet again, surgical abortion procedures account for over 25% of the purported serious adverse events identified by EPPC.

Hall and Anderson also include ectopic pregnancy as a serious adverse event, even though ectopic pregnancies are not caused by mifepristone. As already made clear in its labeling, mifepristone is contraindicated in patients with ectopic pregnancy because it is not effective for terminating such pregnancies; however, there is no evidence that mifepristone leads to unusual complications for women with ectopic pregnancies.[64] Yet Hall and Anderson claim, without support, that use of mifepristone in the case of ectopic pregnancy "poses extraordinary, heightened risk" to the patient's health.[65]

The largest category of alleged adverse events in the EPPC's findings—over half—is made up of unspecified "other abortion-specific complications." Hall and Anderson do not list the diagnosis or procedure codes used for this category, and hence it is impossible to determine the codes' relevance (if any) to mifepristone treatment.

National Emergency Department Sample, 16 BMC Med. (2018), https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-018-1072-0.

[63] MIFEPREX Prescribing Information (Mar. 23, 2023), https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s026lbl.pdf; *see also* Ushma D. Upadhyay et al., *Incidence of Emergency Department Visits and Complications After Abortion*, 125 Obstetrics & Gynecology 175 (2015), https://pubmed.ncbi.nlm.nih.gov/25560122/; Elizabeth G. Raymond et al., *First-trimester Medical Abortion with Mifepristone 200 mg and Misoprostol: A Systematic Review*, 87 Contraception 26 (2013); Kelly Cleland et al., *Significant Adverse Events and Outcomes After Medical Abortion*, 121 Obstetrics & Gynecology 166 (2013), https://pubmed.ncbi.nlm.nih.gov/23262942/.

[64] Caitlin Shannon et al., *Ectopic Pregnancy and Medical Abortion*, 104 Obstetrics & Gynecology 161 (2004), https://pubmed.ncbi.nlm.nih.gov/15229016/.

[65] Jamie Bryan Hall & Ryan T. Anderson, Ethics & Pub. Pol'y Ctr., *Frequently Asked Questions About the Largest Study on Chemical Abortion* (May 7, 2025), https://eppc.org/wp-content/uploads/2025/05/Frequently-Asked-Questions-About-the-Largest-Study-on-Chemical-Abortion.pdf.



In the second document, Hall and Anderson claim that, among those patients identified as having received a medication abortion based on claims data, within a 45-day window, 3.22% had some entry suggesting repeated mifepristone administration, and 2.84% had some entry suggesting a subsequent procedure to complete the abortion. Hall and Anderson use these "findings" to assert that mifepristone has a "real-world failure rate" of 5.26%.[66] Again, there are several seriously problematic issues with this document. We highlight just two. First, as discussed above, it is known and expected that a small percentage of patients will need a surgical procedure following mifepristone administration to complete the abortion, and this possibility is already included in the mifepristone labeling. Second, Hall and Anderson do not explain how they identified the purported repeated use of mifepristone, or the steps taken (if any) to ensure such entries in the unnamed dataset did not merely reflect duplicate claims. Such entries may also reflect instances in which a patient received two mifepristone prescriptions but only ingested a single dose.

The failure of Hall and Anderson to disclose the "commercially available all-payer health insurance claims database"[67] underlying their "findings;" the methodology (if any) used to address misclassified or missing information; any steps taken to preserve data quality or remove duplicate claims; or the diagnosis and procedure codes used to identify adverse events make it impossible to independently verify or replicate the results. More specifically, EPPC's decision to withhold the identity of the claims database also makes it impossible for FDA, the mifepristone NDA and ANDA holders, the scientific and medical community at large, or anyone else to assess either the reliability or relevance of that dataset with respect to any decision on the approval or REMS requirements for the drug.

As FDA recognized in its guidance regarding the use of electronic health records and medical claims data ("EHR Guidance"), "existing electronic health care data were not developed for research purposes or to support regulatory submissions to FDA, [so] it is important to understand their potential limitations when they are used for that purpose."[68] One potential limitation recognized by FDA is that the purpose of medical claims data is to "support payment for care."[69] Accordingly, as FDA has stated, claims data "may not accurately reflect" the presence, characteristics, severity, or clinical management of a particular condition or event.[70]

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[66] Jamie Bryan Hall & Ryan T. Anderson, Ethics & Pub. Pol'y Ctr., *The Abortion Pill Harms Women: Insurance Data Reveals Repeated Abortion Attempts Due to High Failure Rate* (May 12, 2025), https://eppc.org/wp-content/uploads/2025/05/25-05-SHW-Insurance-Data-Reveals-Repeated-Abortion-Attempts-Due-to-High-Failure-Rate.pdf.

[67] Jamie Bryan Hall & Ryan T. Anderson, Ethics & Pub. Pol'y Ctr., *The Abortion Pill Harms Women: Insurance Data Reveals One in Ten Patients Experiences a Serious Adverse Event* (Apr. 28, 2025), https://eppc.org/wp-content/uploads/2025/04/25-04-The-Abortion-Pill-Harms-Women.pdf.

[68] U.S. Food & Drug Admin., *Guidance for Industry: Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products* 4 (2024), https://www.fda.gov/media/152503/download.

[69] *Id.*

[70] *Id.*



FDA has likewise cautioned that investigators should "identify whether the data sources cover all populations relevant to the study" and that "[d]ifferences in terminology and coding systems used in different health care systems" may affect the relevance of the data source.[71] There is no evidence suggesting Hall and Anderson gave any consideration to these issues or other potential limitations of their dataset. Until EPPC discloses the identity of the dataset it claims to have analyzed—and independent reviewers at FDA and the medical community are able to assess its relevance, reliability and integrity (or any of the more detailed data issues FDA has also specified in its EHR Guidance)—any use of (much less reliance on) EPPC's purported "findings" from that unidentified data would violate FDA's own standards and procedures.

In sum, the EPPC documents utterly fail to provide robust scientific evidence regarding the safety and effectiveness of mifepristone. The documents do not constitute "new safety information" for purposes of REMS modification assessments, which the FDCA requires to be derived from a clinical trial, adverse event reports, a postapproval study, peer-reviewed biomedical literature, FAERS data, or other scientific data.[72] To the extent that FDA considers these documents at all, FDA must also consider the overwhelming weight of scientific research and peer-reviewed studies that support mifepristone's safety and efficacy. In light of its many obvious scientific flaws—which are apparent even upon a facial review—the EPPC documents cannot provide a legitimate basis to restrict access to mifepristone—a drug which has been repeatedly verified as safe and effective for terminating early pregnancies through vast amounts of data, hundreds of medical studies, and use by millions of women over more than two decades.

d. FDA Must Avoid Undue Burdens on Patient Access to Mifepristone

The FDCA requires FDA to balance safety *and access* in adopting and revising a REMS.[73] Specifically, ETASU imposed under a REMS must "not be unduly burdensome on patient access to the drug," and, "to the extent practicable," must "minimize the burden on the health care delivery system."[74]

In its 2021 review of the mifepristone REMS, FDA correctly determined that removing the in-person dispensing requirement would "render the REMS less burdensome to healthcare providers and patients" and that the modified REMS would "continue to ensure that the benefits

[71] *Id.* at 5.

[72] 21 U.S.C. § 355-1(b)(3).

[73] 21 U.S.C. § 355-1(g)(4)(B) (authorizing FDA to require a sponsor to modify a REMS to "ensure benefits of the drug outweigh the risks of the drug" or "minimize the burden on the health care delivery system"); 21 U.S.C. § 355-1(f)(5) (requiring FDA to periodically evaluate whether ETASU "are not unduly burdensome on patient access to the drug" and "to the extent practicable, minimize the burden on the health care delivery system"). Congress was particularly concerned about access to REMS drugs for "patients who have difficulty accessing health care (such as patients in rural or medically underserved areas)." 21 U.S.C. § 355-1(f)(2).

[74] 21 U.S.C. § 355-1(f)(2).



of mifepristone for medical abortion outweigh the risks."[75] Since then, numerous peer-reviewed studies have confirmed that the availability of medication abortion through telehealth improves patient access to care.[76] In particular, studies have shown that telehealth provides an important care option for patients living in rural and medically underserved areas, who would otherwise have to travel long distances to receive in-person care. Telehealth also provides a particular benefit for patients who may find it difficult to take time off work or arrange for childcare in order to travel for abortion care.

FDA appropriately balanced patient safety and access when it determined that the mifepristone REMS should be modified in 2021. Reinstating the prior ETASU, such as the in-person dispensing requirement, would unduly restrict patient access to mifepristone without a legitimate patient safety rationale. Doing so would also violate the FDCA's mandate that REMS requirements be firmly rooted in scientific evidence and clinical data and no more burdensome than necessary to ensure safe use.

2. There is No Scientific Evidence Suggesting that Mifepristone Causes Harm to the Environment

FDA has previously and correctly rejected claims that mifepristone somehow causes harm to the environment, and there continues to be no evidence that would support restricting access to

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[75] 2021 REMS Modification Rationale Review at 39-40, (Dec. 16, 2021), available at https://www.accessdata.fda.gov/drugsatfda_docs/summary_review/2023/020687Orig1s025SumR.pdf#page=41.

[76] Leah R. Koenig et al., *The Role of Telehealth in Promoting Equitable Abortion Access in the United States: Spatial Analysis*, 9 JMIR Pub. Health Surveillance e45671 (2023), https://publichealth.jmir.org/2023/1/e45671; Amy Tressan et al., *Telemedicine Abortion in Primary Care: An Exploration of Patient Experiences*, 22 Annals of Fam. Med. 19 (2024), https://pubmed.ncbi.nlm.nih.gov/38253506/; Leah R. Koenig et al., *Patient Acceptability of Telehealth Medication Abortion Care in the United States, 2021-2022: A Cohort Study*, 114 Am. J. Pub. Health 241, 247-48 (2024), https://pubmed.ncbi.nlm.nih.gov/38237103/; Emily M. Godfrey et al., *Patient Perspectives Regarding Clinician Communication During Telemedicine Compared With In-Clinic Abortion*, 141 Obstetrics & Gynecology 1139, 1143 (2023), https://pubmed.ncbi.nlm.nih.gov/37141602/; Andréa Becker et al., *"It Was So Easy in a Situation That's So Hard": Structural Stigma and Telehealth Abortion*, J. Health & Soc. Behav. (2025), https://journals.sagepub.com/doi/epub/10.1177/00221465241303873; Samantha P. Ruggiero et al., *Patient and Provider Experiences Using a Site-to-Site Telehealth Model for Medication Abortion*, 30 mHealth 1 (2022), https://mhealth.amegroups.org/article/view/100653/html; Courtney Kerestes et al., *Person-Centered, High-Quality Care From a Distance: A Qualitative Study of Patient Experiences of TelAbortion, a Model for Direct-to-Patient Medication Abortion by Mail in the United States,* 54 Perspectives Sexual & Reprod. Health 177 (2022), https://pubmed.ncbi.nlm.nih.gov/36229416/; Leah R. Koenig et al., *Mailing Abortion Pills Does Not Delay Care: A Cohort Study Comparing Mailed to In-Person Dispensing of Abortion Medications in the United States*, 121 Contraception 1 (2023), https://www.contraceptionjournal.org/article/S0010-7824(23)00015-X/fulltext; Kathleen Marie Beardsworth et al., *Miles and Days until Medical Abortion via TelAbortion versus Clinic in Oregon and Washington, USA*, 48 BMJ Sex Reprod Health, e38 (2021), https://srh.bmj.com/content/48/e1/e38.long; Anna E. Fiastro et al., *Telehealth vs In-Clinic Medication Abortion Services,* 6 JAMA Network Open 1-5, 4 (Sept. 1, 2023), https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2809068.



mifepristone on this basis. Further, when granting the mifepristone NDA and ANDA, FDA complied with all applicable law and regulations regarding environmental reviews and consultations, including environmental assessment requirements.

As FDA is aware, opponents of medical abortion have alleged that mifepristone or its metabolites cause harm to the environment, despite the lack of any scientific evidence, including by filing the below citizen petitions:

(1) *Students for Life of America ("SFLA") Citizen Petition (Nov. 2022)*: This petition requested that FDA modify the REMS to require prescribers to include a medical waste bag and catch-kit with all mifepristone prescriptions to "alleviate some amount of human remains (this includes fetal remains) and Mifepristone contaminants in the nation's water supply."[77] SFLA's petition claimed that exposure to mifepristone in the nation's water can cause "teratologic repercussions or congenital anomalies."[78]

(2) *SFLA Citizen Petition (Apr. 2023)*: This petition requested that FDA revoke approval of the NDA, ANDA, and modifications to the REMS, on the basis that FDA failed to comply with the Endangered Species Act ("ESA") by not consulting with the United States Fish and Wildlife Service ("FWS") and National Marine Fisheries Service ("NMFS").[79] SFLA claimed that mifepristone in the water supply can have "detrimental effects on the fertility of animals, as well as having unknown detrimental effects on plant life and ecosystems."[80]

(3) *SFLA Citizen Petition (Aug. 2023)*: This petition requested that FDA revoke approval of the mifepristone NDA, ANDA, and modifications to the REMS, on the basis that FDA failed to comply with certain requirements of the Clean Water Act ("CWA").[81]

(4) *SFLA Citizen Petition (Dec. 2024)*: This petition requested that FDA "refrain from modifying the approved use of [m]ifepristone to include miscarriage care" until the Agency requires the provision of a medical waste bag and catch-kit and determines compliance with the CWA and ESA.[82]

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[77] Citizen Petition from Students for Life of America, No. FDA-2022-P-2872, at 2 (Nov. 15, 2022), https://www.regulations.gov/document/FDA-2022-P-2872-0001.

[78] *Id.* at 7.

[79] Citizen Petition from Students for Life of America, No. FDA-2023-P-1528, at 1 (Apr. 19, 2023), https://www.regulations.gov/document/FDA-2023-P-1528-0001.

[80] *Id.* at 15.

[81] Citizen Petition from Students for Life of America, No. FDA-2023-P-3328, at 1 (Aug. 1, 2023), https://www.regulations.gov/document/FDA-2023-P-3328-0001.

[82] Citizen Petition from Students for Life of America, No. FDA-2024-P-5967 (Dec. 18, 2024), https://www.regulations.gov/document/FDA-2024-P-5967-0001.



FDA correctly rejected these requests.[83] There is no scientific evidence whatsoever that suggests mifepristone or the products of conception have any effect, let alone an adverse one, on the environment (including protected species, habitats, or water quality).

As FDA has recognized, the 2000 approval of Mifeprex and the 2019 approval of generic mifepristone complied with all environmental assessment requirements and demonstrated that mifepristone would have no adverse environmental effects.[84] FDA is required under the National Environmental Policy Act ("NEPA") to assess the environmental impacts of qualifying actions and ensure that the public is informed of these analyses.[85] When assessing "environmental effects and feasible alternatives for NEPA," an agency is accorded "substantial deference" as to the "depth and breadth of its inquiry."[86] Under FDA regulations, the approval of an NDA, ANDA, and certain supplements to these applications require at least the preparation of an environmental assessment ("EA"), unless the action qualifies for a categorical exclusion.[87] Action on an ANDA qualifies for a categorical exclusion from the requirement to prepare an EA "if the action does not increase the use of the active moiety."[88]

FDA's approval of the mifepristone NDA complied with all applicable EA requirements, and Petitioner properly claimed a categorical exclusion on its ANDA, meaning no additional EA was required. In 1996, the applicant for the mifepristone NDA submitted an EA in accordance with NEPA and applicable FDA regulations, which was reviewed by FDA to determine whether approval of mifepristone would have a significant environmental impact.[89] The EA evaluated the potential environmental impacts of the manufacture of the drug product, use of the drug product by patients (i.e., excretion by patients), and disposal of pharmaceutical waste. In accordance with FDA guidance, the EA calculated a projected environmental introduction concentration into the

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[83] Response from FDA CDER to Students for Life of America, No. FDA-2022-P-2872 (Jan. 15, 2025), https://www.regulations.gov/document/FDA-2022-P-2872-0004; Final Response from FDA CDER to Students for Life of America, No. FDA-2023-P-1528 (Jan. 15, 2025), https://www.regulations.gov/document/FDA-2023-P-1528-0005; Response Letter from FDA CDER to Students for Life of America, No. FDA-2023-P-3328 (Jan. 15, 2025), https://www.regulations.gov/document/FDA-2023-P-3328-0004; Response Letter from FDA CDER to Students for Life of America, No. FDA-2024-P-5967 (May 21, 2025), https://www.regulations.gov/document/FDA-2024-P-5967-0003.

[84] Response from FDA CDER to Students for Life of America, No. FDA-2022-P-2872, at 17 (Jan. 15, 2025), https://www.regulations.gov/document/FDA-2022-P-2872-0004.

[85] 42 U.S.C. § 4321 et seq.

[86] *Seven Cnty. Infrastructure Coal. v. Eagle Cnty., Colorado*, 145 S. Ct. 1497, 1513 (2025); *see id.* (according "substantial deference" to the agency's decision as to "*whether and to what extent* to prepare an [environmental impact statement]" (quoting *Dep't of Transp. v. Pub. Citizen*, 541 U.S. 752, 767 (2004)).

[87] 21 C.F.R. § 25.20(l).

[88] 21 C.F.R. § 25.31(a).

[89] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., *Environmental Assessment and Finding of No Significant Impact for NDA 20-687 Mifepristone Tablets* (1996), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.



aquatic environment from use of *much less than 1 part per billion* using default, conservative screening-level assumptions that all drug substance produced is used, there is even distribution throughout the United States per day, and there are no metabolism or depletion mechanisms.[90] The Material Safety Data Sheet also noted that mifepristone is "[b]iodegradable in natural media," meaning that mifepristone is not expected to accumulate in the environment because it will break down through the action of microorganisms.[91] Based on these materials, FDA made a finding of no significant impact, concluding that mifepristone "can be manufactured, used and disposed of *without any expected adverse environmental effects*," that "[a]dverse effects are not anticipated upon endangered or threatened species," and that approval of the NDA "will not have a significant effect on the quality of the human environment."[92] In support of its ANDA, Petitioner appropriately claimed a categorical exclusion under 21 C.F.R. § 25.31(a) because action on its ANDA would not increase use of the active moiety.

In rejecting the aforementioned citizen petitions, in January 2025, FDA reaffirmed that the 1996 EA complied with NEPA and FDA's regulations, concluding that "FDA appropriately assessed the potential impact on the human environment from excretion by patients who use mifepristone and determined that there would be no significant effects on the quality of the human environment."[93] FDA concluded that the 1996 EA and FDA's finding of no significant impact "show that 'remnants of mifepristone' are not causing harm to the environment and to people through environmental pathways**,** and also show, by extension, that metabolites from patients using mifepristone have not been 'causing teratologic repercussions or congenital anomalies in animals like birth defects.'"[94]

The findings from the 1996 EA were also reaffirmed by a new environmental analysis conducted by FDA. In January 2025, FDA conducted its own environmental analysis, using publicly available data on current usage rates of mifepristone and applying the default

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[90] Response from FDA CDER to Students for Life of America, No. FDA-2022-P-2872, at 3, 12-14 (Jan. 15, 2025), https://www.regulations.gov/document/FDA-2022-P-2872-0004; *see also* U.S. Food & Drug Admin., *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements* (1995) (hereinafter "1995 EA Guidance"); U.S. Food & Drug Admin., *Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications* (1998), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/environmental-assessment-human-drug-and-biologics-applications (hereinafter "1998 EA Guidance"). The 1995 EA Guidance was replaced in July 1998 by the 1998 EA Guidance.

[91] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., *Environmental Assessment and Finding of No Significant Impact for NDA 20-687 Mifepristone Tablets*, Appendix D, Material Safety Data Sheet (1996), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[92] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., *Environmental Assessment and Finding of No Significant Impact for NDA 20-687 Mifepristone Tablets* 1-2 (1996), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf (emphasis added).

[93] Response from FDA CDER to Students for Life of America, No. FDA-2022-P-2872, at 19 (Jan. 15, 2025), https://www.regulations.gov/document/FDA-2022-P-2872-0004.

[94] *Id.* at 12 (citing Citizen Petition from Students for Life of America, No. FDA-2022-P-2872, at 2, 9 (Nov. 15, 2022), https://www.regulations.gov/document/FDA-2022-P-2872-0001)).



environmental calculations described in FDA's current environmental guidance. This analysis reaffirmed the findings from the 1996 EA: FDA concluded that its "conservative calculations" using estimates of current use rates of mifepristone "show an exposure level that is *so low that is it predicted to have no effect on the environment*, including threatened and endangered species."[95] As FDA recognized, the SFLA petitions "provide[d] *no evidence* showing that bodily fluid from patients who have used mifepristone (a one-time, single-dose drug product) is causing harm to the nation's aquatic environment."[96] FDA further stated that the Agency is not aware of any evidence "suggesting that products of conception pose an environmental hazard to the water supply" or that "products of conception from induced abortions differ from the naturally occurring products of conception from spontaneous abortions."[97] No new evidence contradicts FDA's conclusions. And, if FDA now believes such evidence exists, it must accord Petitioner notice and an opportunity to comment on such material.

Separately, FDA also correctly concluded that the ESA and CWA do not impose requirements on FDA's approval of drug applications. In rejecting the April 2023 SFLA citizen petition, FDA correctly explained that it does not have "discretionary Federal involvement or control" over approvals of the type that would trigger obligations under ESA Section 7; accordingly, it is not required to consult with FWS or NMFS before approving an NDA or ANDA.[98] Additionally, in rejecting the August 2023 SFLA citizen petition, FDA explained that the CWA does not apply to FDA's approval of mifepristone, because excretion of mifepristone, its metabolites, or any products of conception into wastewater would not be considered a "discharge" or nonpoint "runoff" under the CWA.[99] It remains the case today that the ESA and CWA are inapplicable to FDA's approval of drug applications. If FDA adopts the position that these regimes somehow impact the approval of mifepristone, Petitioner must be accorded notice and opportunity to comment on and challenge such an unfounded interpretation.

* * *

In summary, FDA's approval of mifepristone and the current REMS reflects its judgment that the drug is safe and effective and has a favorable benefit-risk balance under the current conditions of use. FDA's decisions regarding mifepristone have been based on the agency's review of vast amounts of data and hundreds of medical studies over more than two decades. Further, FDA's decisions regarding mifepristone have twice been found to be legally and factually valid by the GAO.

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[95] *Id.* at 16-17 (emphasis added).

[96] *Id.* at 8-9 (emphasis added).

[97] *Id.* at 13.

[98] Final Response from FDA CDER to Students for Life of America 8, No. FDA-2023-P-1528 (Jan. 15, 2025), https://www.regulations.gov/document/FDA-2023-P-1528-0005.

[99] Response Letter from FDA CDER to Students for Life of America 8-10, No. FDA-2023-P-3328 (Jan. 15, 2025), https://www.regulations.gov/document/FDA-2023-P-3328-0004.



Accordingly, FDA should take no action that would reduce patient access to mifepristone and/or increase the burdens associated with prescribing or dispensing mifepristone, as such actions are not scientifically or medically warranted, or consistent with applicable law.

3. Any FDA Withdrawal of Petitioner's ANDA Approval Must Follow All Applicable Procedures Afforded by Law and Regulation

As FDA is well aware, FDA's longstanding approvals regarding mifepristone have come under legal challenge. These ill-advised and unfounded attacks on FDA's decisions pursuant to its congressional mandate are of grave concern to Petitioner, which has invested considerable effort and expense in reliance on FDA's past regulatory actions with respect to mifepristone, and with the understanding that any withdrawal of an FDA approval is subject to a well-established FDA regulatory process. Petitioner therefore must respectfully insist that any steps to withdraw or otherwise restrict FDA's approval of Petitioner's ANDA for mifepristone as currently labeled—whether in effectuation of a court order or otherwise—follow all applicable procedures afforded by law and regulation, and that FDA permit Petitioner to continue marketing and selling mifepristone under current conditions of use until those procedures have been completed.

a. FDA's Approval of Petitioner's ANDA is Facing a Legal Challenge

On November 18, 2022, the Alliance for Hippocratic Medicine filed a complaint in the U.S. District Court for the Northern District of Texas challenging FDA's approvals of Danco's NDA for Mifeprex and Petitioner's ANDA for mifepristone, as well as other FDA actions related to mifepristone. On April 7, 2023, the district court granted in part the plaintiffs' preliminary injunction motion, purporting to "stay[] the effective date of FDA's September 28, 2000, [a]pproval of mifepristone" and subsequent actions on mifepristone that the plaintiffs challenged, including the REMS modifications in 2016 and 2021 and the approval of Petitioner's ANDA in 2019.[100] That order, however, was stayed pending appeal; on June 13, 2024, the Supreme Court ultimately held that the plaintiffs lacked Article III standing to challenge FDA's actions relating to mifepristone.[101] The case was subsequently remanded to the district court.[102]

But that was not the end of the legal threat to Petitioner's ANDA. On remand, intervenor-plaintiff States in the lawsuit, now captioned *Missouri v. FDA*, have alleged that FDA "lacked legal authority" when approving Petitioner's ANDA.[103] Intervenor-plaintiffs have asserted that Petitioner's ANDA approval "must be held unlawful, stayed, set aside, vacated, and preliminarily and permanently enjoined."[104] Because Petitioner's ANDA for generic mifepristone remains under

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[100] *All. for Hippocratic Med. v. FDA*, 668 F. Supp. 3d 507, 560 (N.D. Tex. 2023).

[101] *FDA v. All. for Hippocratic Med.*, 602 U.S. 367 (2024).

[102] *All. for Hippocratic Med. v. FDA*, 117 F.4th 336, 340 (5th Cir. 2024).

[103] Amended Complaint ¶ 764, *Missouri v. FDA*, No. 2:22-cv-223-Z (N.D. Tex. Jan. 16, 2025), ECF No. 217.

[104] *Id.* ¶ 787.



attack, Petitioner is acutely interested in FDA's adherence to all applicable procedures governing any potential withdrawal of approved drug applications.[105]

As a result of this legal threat, Petitioner has previously and repeatedly insisted that FDA confirm that any withdrawal of approval for Petitioner's ANDA for mifepristone would follow all applicable procedures afforded by law to Petitioner as the ANDA holder, and that FDA would permit Petitioner to continue marketing and selling mifepristone until those procedures have been completed. Petitioner communicated these requests in letters to FDA in March and April 2023, as it considered the potential impact of the district court's order in *Alliance for Hippocratic Medicine v. FDA*.[106] FDA responded to one such letter by declining to provide the assurances sought by Petitioner, instead stating that FDA would "need to review the Court's opinion and order before determining what steps may be necessary to comply with it."[107] FDA did not respond to Petitioner's other communications on this topic.

b. Statute and Regulations Require FDA to Follow Specific Procedures to Withdraw an ANDA

Petitioner believes that FDA should confirm that any steps to withdraw the approval of Petitioner's ANDA for mifepristone—whether in purported effectuation of a court order or otherwise—will follow all applicable procedures afforded by law and regulation to Petitioner as the ANDA holder, and that Petitioner may continue marketing and selling mifepristone until those procedures have been completed.

(i) *Statutory Withdrawal Procedures*

Any withdrawal of Petitioner's ANDA must comport with the statutory provisions governing the withdrawal of an approved drug application. Congress granted FDA, and FDA alone, the authority to oversee the withdrawal of an approved drug application.[108] Withdrawal requires a finding by FDA that one of the relevant statutory criteria has been met, as well as "due notice and opportunity for hearing to the applicant."[109] As discussed above, under the FDCA, and

[105] Petitioner has intervened in the *Missouri v. FDA* lawsuit to defend against the Intervenor-plaintiff States' unfounded attacks on the ANDA approval and other FDA regulatory actions, including on the basis that the lawsuit is procedurally improper for multiple reasons. As Petitioner has made clear in its filings in the case, Intervenor-plaintiffs' legal challenges should be dismissed.

[106] *See* Letter from Evan Masingill, Chief Exec. Officer, GenBioPro, Inc., to the Honorable Robert M. Califf, M.D., Comm'r, FDA (Mar. 1, 2023); Letter from Evan Masingill, Chief Exec. Officer, GenBioPro, Inc., to the Honorable Robert M. Califf, M.D., Comm'r, FDA (Apr. 9, 2023); Letter from Evan Masingill, Chief Exec. Officer, GenBioPro, Inc., to the Honorable Robert M. Califf, M.D., Comm'r, FDA (Apr. 13, 2023).

[107] Letter from Patrizia Cavazzoni, MD, Dir., Ctr. for Drug Evaluation and Rsch., FDA, to Evan Masingill, Chief Exec. Officer, GenBioPro, Inc. (Mar. 24, 2023).

[108] 21 U.S.C. § 355(e).

[109] *Id.*



as relevant here, the Secretary of HHS may withdraw approval of an application *only* if the Secretary finds that:

> [C]linical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved . . . [or] on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.[110]

The Secretary, in turn, has delegated the responsibility for making the requisite finding to the FDA Commissioner.[111] Any withdrawal of a drug approval on safety or efficacy grounds therefore requires a finding that the evidence demonstrates that the drug's benefit-risk balance requires withdrawal. As the Supreme Court has emphasized, the FDCA does "not provide any mechanism other than the Commissioner's suspension authority under [section 355(e)], whereby an NDA once effective could cease to be effective."[112]

(ii) FDA Regulations on Withdrawal Procedures

The regulations that implement 21 U.S.C. § 355(e)'s requirements of notice and opportunity to be heard set out the specific and detailed procedures FDA must follow when withdrawing a drug approval. In addition to notice and the opportunity for a hearing on a proposal to withdraw a drug, FDA regulations also expressly permit the applicant to submit studies, data, and other information.[113] Specifically with regard to the holder of an ANDA such as Petitioner, the regulations require an opportunity to submit written comments and, if a hearing is granted, the opportunity to participate and to submit written objections to an initial decision.[114]

The participation of the manufacturer in withdrawal proceedings is crucial to upholding the legitimacy of (and public confidence in) FDA's decision-making. Moreover, manufacturers such as Petitioner are often the most knowledgeable party regarding the drug's use, safety profile, and the related health care delivery systems. The due process protections embodied within these statutory and regulatory procedures are also constitutionally necessary for the protection of Petitioner's property interest in its mifepristone ANDA.

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[110] *Id.*

[111] FDA Staff Medical Guides, Staff Manual Guides 1410.10, Delegations of Authority to the Commissioner of Food and Drugs 1.A(1) (Nov. 29, 2022), https://www.fda.gov/media/81983/download.

[112] *Weinberger v. Hynson, Wescott & Dunning, Inc.*, 412 U.S. 609, 633 (1973).

[113] 21 C.F.R. §§ 314.150, 314.200, 314.530.

[114] 21 C.F.R. § 314.151.



(iii) Authority to Suspend Approval Without Pre-Deprivation Process

While the FDCA permits the suspension of an ANDA without pre-deprivation process, this power may be used only in exceptional circumstances.[115] Such suspension requires a finding of "an imminent hazard to the public health."[116] FDA regulations, in turn, provide that an "imminent hazard to the public health" is considered to exist only when "the evidence is sufficient to show that a product or practice, posing a *significant threat* of danger to health, creates a public health situation: (1) that should be corrected immediately to *prevent injury* and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held."[117]

The legislative history of the suspension statute makes clear that this authority is to be used only in extraordinary situations. Congress believed that the suspension authority, "which could have grave effects upon a manufacturer and upon the confidence of the public in a drug which might later be found appropriate for continued availability to physicians, should only be exercised under the most extreme conditions and with the utmost care."[118] In the event that FDA finds an "imminent hazard" and orders the immediate suspension of an application approval, the approval holder is entitled to immediate procedural protections, including "prompt notice," and "an expedited hearing."[119] The holders of any ANDAs whose approval rests on a suspended NDA must be allowed to participate in the post-suspension proceeding for the NDA.[120]

c. Suspension of Mifepristone Outside FDA Procedure Would Be Unlawful

To date, there has been no finding of imminent hazard made with respect to mifepristone—nor could there be given the mountain of replicated scientific data establishing the drug is safe and effective as used by millions of women for over twenty years in the United States. Therefore, without the requisite "imminent hazard" finding—and the procedural protections that accompany such a finding—FDA may not deprive Petitioner of its protected property interests in marketing its ANDA for mifepristone.

HHS and FDA's procedures for withdrawing or suspending drug approvals are far more than regulatory formalities. In addition to harming the constitutional rights of NDA and ANDA holders, suspension of approvals outside FDA and HHS's express procedures disrupts the evidence-based mandate of FDA. It undermines public confidence in FDA's approval of drugs by incorrectly suggesting that FDA approval is not grounded in scientific principles or by implying

[115] 21 U.S.C. § 355(e)

[116] *Id.*

[117] 21 C.F.R. § 2.5 (emphasis added).

[118] 108 Cong. Rec. 17366 (Aug. 23, 1962).

[119] 21 U.S.C. § 355(e); *see* 21 C.F.R. § 314.150(a)(1).

[120] 21 C.F.R. § 314.150(a)(1).



that FDA misinterpreted those scientific principles in such a way that a drug must be immediately pulled from the market.

Crucially, since FDA's approval of Petitioner's ANDA in 2019, FDA has never presented Petitioner with any scientific evidence that would justify withdrawal or suspension of its approval. Petitioner must be afforded an opportunity to be heard on any such evidence prior to any withdrawal or suspension.

In sum, the statutory and regulatory procedures governing the withdrawal and suspension of an application approval are necessary to protect Petitioner's property interests in its mifepristone ANDA, as well as the patient desire for medication access. Accordingly, Petitioner requests that FDA confirm that any withdrawal of the approval of Petitioner's ANDA for mifepristone, or any other action that would impair the approval or labeling—whether in effectuation of a court order or otherwise—must follow all applicable procedures afforded by law and regulation to Petitioner as the ANDA holder, and that Petitioner may continue marketing and selling mifepristone until those procedures have been completed.

4. Conclusion

For the foregoing reasons, Petitioner respectfully requests that FDA:

(1) refrain from taking any action that would reduce patient access to mifepristone and/or increase the burdens associated with prescribing or dispensing mifepristone; and

(2) confirm that any FDA withdrawal of approval for mifepristone, including in response to any court order, will follow all applicable rules and procedures for any withdrawal, suspension or other action under the APA, the FDCA, and implementing regulations, and that Petitioner will be permitted to continue to market and sell mifepristone in the United States until those procedures have been completed.

C. ENVIRONMENTAL IMPACT

We claim categorical exclusion under 21 C.F.R. § 25.31. Therefore, an environmental impact analysis is not required.

D. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted upon request of the Commissioner.

E. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

GenBioPro

Respectfully submitted,



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EXHIBIT B-1

APPENDIX TO PETITIONER GENBIOPRO, INC.'S CITIZEN PETITION DATED JULY 3, 2025[1]

Source	Appendix Starting Page
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108 Cong. Rec. 17366 (Aug. 23, 1962)	GBP-PET00001
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[1] This Appendix includes all documents cited in the accompanying July 3, 2025 Citizen Petition with the exception of certain documents not required by 21 C.F.R. § 10.20(c). Volumes I, II, III, IV, V, and IX contain copyright restricted materials.

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the Executive Calendar, I ask unanimous consent that they be ordered to lie on the Secretary's desk, for the information of any Senator.

The PRESIDING OFFICER. The nominations will lie on the desk, as requested by the Senator from Maine.

The nominations are as follows:

Howard F. Stevenson, and sundry other officers of the Marine Corps, for temporary appointment to the grade of colonel;

Willard F. Angen, and sundry other officers, for promotion in the Regular Army of the United States;

Jacquard H. Rothschild, for reappointment as a temporary brigadier general in the Army of the United States and for reappointment as colonel in the Regular Army of the United States;

Edward J. Osborne, and sundry other persons, for appointment in the Regular Army;

Franklin H. Andrew, Jr., and sundry other distinguished military students, for appointment in the Regular Army of the United States; and

Lawrence A. Adams, Jr., and sundry other officers for promotion in the Regular Air Force.

The PRESIDING OFFICER. If there be no further reports of committees, the clerk will state the nominations placed on the Secretary's desk.

COAST AND GEODETIC SURVEY

The Chief Clerk proceeded to read sundry nominations in the Coast and Geodetic Survey.

The PRESIDING OFFICER. Without objection, the nominations will be considered en bloc; and, without objection, they are confirmed en bloc.

U.S. COAST GUARD

The Chief Clerk proceeded to read sundry nominations in the U.S. Coast Guard.

The PRESIDING OFFICER. Without objection, the nominations will be considered en bloc; and, without objection, they are confirmed en bloc.

Without objection, the President will be immediately notified of the confirmation of all nominations confirmed today.

LEGISLATIVE SESSION

Mr. MANSFIELD. Mr. President, I move that the Senate resume the consideration of legislative business.

The motion was agreed to; and the Senate resumed the consideration of legislative business.

Mr. MANSFIELD. Mr. President, is there further morning business?

The PRESIDING OFFICER. Is there further business in the morning hour? If there is no further business, morning business is concluded.

DRUG INDUSTRY ACT OF 1962

Mr. MANSFIELD. Mr. President, I ask unanimous consent that the unfinished business be laid before the Senate.

The PRESIDING OFFICER. The bill will be stated by title for the information of the Senate.

The CHIEF CLERK. A bill (S. 1552) to amend and supplement the antitrust laws with respect to the manufacture and distribution of drugs, and for other purposes.

The PRESIDING OFFICER. Is there objection to the request by the Senator from Montana?

There being no objection, the Senate resumed the consideration of the bill.

PRIVILEGE OF THE FLOOR

Mr. EASTLAND. Mr. President, I ask unanimous consent that during the consideration of the drug bill, Mr. Jerome N. Sonosky, special assistant to the Assistant Secretary for Legislation of the Department of Health, Education, and Welfare, be allowed the privilege of the Senate floor.

The PRESIDING OFFICER. Without objection, it is so ordered.

Mr. MANSFIELD. Mr. President, I ask unanimous consent that Mr. Clarence M. Dinkins, chief counsel of the Patents Subcommittee, be authorized to be present on the floor of the Senate during the discussion of the bill today.

The PRESIDING OFFICER. Without objection, it is so ordered.

Mr. MANSFIELD. Mr. President, I suggest the absence of a quorum.

The PRESIDING OFFICER. The clerk will call the roll.

The Chief Clerk proceeded to call the roll.

Mr. MANSFIELD. Mr. President, I ask unanimous consent that the order for the quorum call be rescinded.

The PRESIDING OFFICER (Mr. BURDICK in the chair). Without objection, it is so ordered.

Mr. MANSFIELD. Mr. President, I ask unanimous consent that the time used for the call of the roll not be charged to the time on either side under the unanimous-consent agreement.

The PRESIDING OFFICER. Is there objection to the request by the Senator from Montana? The Chair hears none, and it is so ordered.

Mr. EASTLAND. Mr. President, on behalf of the Committee on the Judiciary, I ask unanimous consent to withdraw the substitute amendment contained in the bill as reported to the Senate on July 19 last, and that the additional substitute amendment reported on the 21st of August be considered in lieu thereof. Under the Senate precedents, this latter substitute amendment would be deemed to be the original text for the purpose of amendment.

The PRESIDING OFFICER. Is there objection to the request by the Senator from Mississippi? The Chair hears none, and it is so ordered.

Mr. MANSFIELD. Mr. President, will the Senator yield?

Mr. EASTLAND. I yield.

Mr. MANSFIELD. Mr. President, I ask unanimous consent that the time under the control of the majority leader be allotted to the chairman of the committee which reported the bill.

The PRESIDING OFFICER. Is there objection to the request by the Senator from Montana? The Chair hears none, and it is so ordered.

Mr. EASTLAND. Mr. President, S. 1552 as reported by the Committee on the Judiciary to the Senate on July 19, 1962, together with the additional amendments voted by the committee on August 20, 1962, is the result of long and intensive study. Under the chairmanship of the senior Senator from Tennessee [Mr. KEFAUVER], beginning in 1959, the Antitrust and Monopoly Subcommittee studied the drug industry for many months, with particular emphasis on prices, profits, and patent matters. The Senator from Tennessee [Mr. KEFAUVER] then introduced S. 1552, in April 1961, and the subcommittee held additional hearings from July 1961 to February 1962 on this bill. On March 8, 1962, the subcommittee reported out a revised bill. The full committee then referred the bill to the Patent Subcommittee for study of the patent provisions. In reporting the bill back to the full committee, the Patent Subcommittee withheld for further consideration two of the patent provisions and suggested amendments of the third provision.

The Judiciary Committee then spent many weeks in executive sessions going over the bill line by line, sentence by sentence, and section by section. In addition to the suggestions from the two subcommittees, the committee was guided by the recommendations of the President in his consumer message of March 14, 1962, and in his letter dated April 10, 1962, to the chairman of the Judiciary Committee.

After this intensive study, the committee approved a bill which in its opinion struck a reasonable and workable balance among the conflicting views of the Department of Health, Education, and Welfare, the majority and minority of the Antitrust Subcommittee, the pharmaceutical industry, and the medical profession. The committee felt that it covered the recommendations of the President in his letter of April 10 in every respect except one, the recommendation for legislation to establish special controls for habit-forming barbiturates and amphetamines, a matter on which the committee took no action because a bill on this subject is now pending before the Committee on Labor and Public Welfare.

The bill was reported to the Senate on July 19, 1962. Thereafter, as a result of the tragic thalidomide episode, the committee undertook a further review of the Food, Drug, and Cosmetic Act and the text of the pending bill on the calendar to determine whether additional amendments were necessary and appropriate. On August 4 the President submitted seven amendments to the bill. Beginning on August 6 the committee held a number of meetings at which these amendments were carefully reviewed. As a result the committee voted unanimously, on August 20, to recommend a number of amendments to the bill previously reported.

In general, the principal features of the bill as it would be amended by the committee amendments would accomplish the following:

First. Provide for cooperation between the Patent Office and the Department of Health, Education, and Welfare on questions relating to drug patents.

Second. Insure greater Government supervision of drug manufacturers by

(a) requiring every plant to be registered; (b) strengthening the inspection authority and requiring inspection of each plant at least once in every 2 years; and (c) authorizing the seizure of a drug if, regardless of its quality, it is made under inadequate methods, facilities or controls.

Third. Require that a new drug be shown to be effective, as well as safe, before it is cleared for the market, and authorize withdrawal of such a drug from the market if new evidence shows it to be ineffective.

Fourth. Strenghen the authority to withdraw a new drug from the market on safety grounds, and include a provision, in the event of an imminent hazard to the public health, for immediate suspension from the market pending a hearing.

Fifth. Add to the Secretary's existing authority to issue regulations to control the testing of new drugs before they are placed on the general market, by giving him specific authority to require records and reports as to data obtained as the result of investigational use of, and clinical experience with, both new drugs and antibiotics.

The committee drafted a drug bill responsive to the recommendations of the administration and to the needs of the American people. It will provide a framework under which industry and Government, working together, can continue to make available improved medicines and new medicines that are safe and useful. It will preserve the system of incentives which has made U.S. industry the most inventive and the most productive and will guarantee continued American prominence in this field.

SUMMARY OF THE PROVISIONS OF S. 1552 AS AMENDED BY THE COMMITTEE AMENDMENTS OF AUGUST 20, 1962

On the desk of each Senator appears Senate Report No. 1744 of July 19, the further amendments adopted by the Judiciary Committee on August 20, and a supplementary report explaining the committee amendments of August 20. I believe it would be helpful if I summarized the provisions of the bill, together with the committee amendments of August 20, 1962.

INFORMATION OF PATENTS FOR DRUGS

Section 2, which is not affected by the August 20 amendments, would amend the Federal Food, Drug, and Cosmetic Act to establish the basis for assistance from the Department of Health, Education, and Welfare to the Patent Office on questions relating to drug patents submitted by the Commissioner of Patents. It is designed to achieve the kind of collaboration that is in effect between the Patent Office and the Agriculture Department in connection with patents on plants. Any information on drugs furnished by the Secretary of Health, Education, and Welfare would be advisory. The final decision as to patentability would be left to the Commissioner of Patents, as has been the practice in the past. With such help from the Department of Health, Education, and Welfare, the Commissioner of Patents will be better equipped to make the decision as to whether a new drug represents the kind of genuine technical advance and new-product competition that should continue to be stimulated by patent rights.

This section of the bill is in lieu of three proposals in the bill as reported by the Antitrust Subcommittee to the full committee. One of such provisions would have imposed compulsory licensing on every drug patent; the committee did not feel that this proposal, which would drastically affect patent rights, should be included in legislation at this time, particularly in view of the testimony that it would seriously reduce the incentives to incur the risks of conducting research and developing new products for the market. Another would have created a new test of patentability for certain drug products; the committee felt that this provision raised so many technical questions that it should not be included in the bill as reported out. The third patent provision would have required all agreements relating to drug patents to be filed in the Patent Office; the committee felt that such proposals should be considered in the light of proposals with respect to patent agreements in general, not limited to drugs, and should therefore not be a part of S. 1552. Indeed, a bill on the subject of filing patent settlement agreements has been passed by the House and has been referred to the Senate Judiciary Committee.

REGISTRATION OF PRODUCERS OF DRUGS

Section 3, which was affected in only minor and technical respects by the August 20 amendments, calls upon every person who owns or operates any establishment for the manufacture, preparation, propagation, compounding, or processing of a drug or drugs to register each year with the Secretary of Health, Education, and Welfare. The Secretary is directed to inspect each such establishment at least once every 2 years. The purpose of this section is to enable the Secretary of Health, Education, and Welfare to be able to identify every manufacturer of prescription and nonprescription drugs and facilitate the inspection of each establishment. It is not a licensing system. The committee decided that it was not necessary, and would be inadvisable, to establish a system of licensing drug plants and operators. The committee felt that this registration provision, coupled with the added inspection authority in section 4 of the bill and the quality manufacturing controls in section 5 of the bill, were preferable to the provisions recommended by the subcommittee which would have set up a complete per-drug-per-plant licensing system.

FACTORY INSPECTION

Section 4, as it would read under the August 20 amendments, broadens the authority of the Food and Drug Administration to inspect establishments in which prescription drugs are made or held. The basic new authority is stated in such sweeping terms that it is necessary to set forth certain limitations necessary to exclude access to data that should be allowed to be held in confidence. Thus, it is provided that financial data, sales data other than shipment records, and pricing data shall be protected from inspection. There would also be a protection for personnel data other than data as to qualifications of technical and professional personnel performing functions subject to the act. Also protected from inspection would be a company's research data, other than records and reports of the type required by the regulations issued under the new drug and antibiotic sections of the act. The object of these limitations is to give the Government adequate power to insure high standards of manufacture and distribution without delving into the unrelated private affairs of a company, or exposing matters at the heart of its capacity to survive and grow in a highly competitive industry. In addition, it would be specified that this additional inspection authority does not extend to pharmacies, medical practitioners, and persons engaged in research, teaching, or chemical analysis.

A further amendment would permit the Food and Drug Administration to obtain injunctions against refusals to permit inspection.

QUALITY MANUFACTURING CONTROLS

Section 5, as it would read under the August 20 amendments, is designed to assure that drugs are manufactured according to good manufacturing practice. It would deem a drug to be adulterated and thus subject to seizure if made under facilities, methods, or controls that are inadequate to assure that the drug meets the specifications of a quality product. Adulteration could also be found if such facilities, methods, or controls were not operated or administered in conformity with good manufacturing practice.

Since the competitive position of responsible manufacturers depends in large part on the confidence of the medical profession and the public, it will be in their own interest to maintain high standards of current good manufacturing practice which will provide a readily determinable basis for enforcement proceedings against any substandard operator. The Secretary could use his general rulemaking authority under section 701(a) of the act to announce what he, in the administration of the act, considers to be good manufacturing practice insofar as methods, facilities, controls, and their operation and administration are concerned. As in the case of other regulations, the courts in the final analysis will pass upon the scope and effect of such regulations.

NEW DRUG CLEARANCE PROCEDURES

Section 6, in the context of the August 20 amendments, changes the procedure on original clearance of new drug applications. Under the present law, such applications become effective, and the drug thus cleared for the market, unless the Food and Drug Administration acts to block the drug within a period of 60 days—extendable to 180 days—after the filing of the application. The bill would change this procedure so that no new drug application would be cleared until

the Food and Drug Administration had issued an affirmative approval. Within the 180-day period after the filing of an application, it would have to be either approved or notice given for opportunity for a hearing. If the applicant within 30 days after such notice requests a hearing, the hearing must be commenced within 120 days after the notice and be conducted on an expedited basis.

These provisions give the Food and Drug Administration greater flexibility in the light of the volume of new drug applications, the more complex nature of new drugs, and the shortage of personnel for study and investigation. The 180-day maximum and the provision for expedited hearings will help to assure that no useful drug will be held off the market for an inordinate period because of bureaucratic inertia or inability to act. It is hoped that the Food and Drug Administration will, as it now does, advise the applicant as soon as practicable after the filing, of any deficiencies it observes in the completeness of the material presented. It is also hoped that in the administration of this new provision, there will continue to be close cooperation and liaison between the Food and Drug Administration and the new drug applicants so that the flow to the market of safe and effective new drugs will not be excessively retarded.

Section 6 would also designate the U.S. court of appeals, instead of the district courts, as the forum for appeal from the Secretary's orders under the new drug procedures.

RECORDS AND REPORTS AS TO EXPERIENCE ON NEW DRUGS AND ANTIBIOTICS

Section 7, which was not affected by the August 20 amendments, authorizes the Secretary to issue regulations requiring manufacturers to maintain records and to make reports as to investigational and clinical experience with new drugs and antibiotics, as requested by the administration. It should be pointed out in this connection that, under the act as it now reads, new drugs and antibiotics cannot be marketed or moved in interstate commerce unless they have passed the applicable tests and been cleared. The statute directs the Secretary to establish regulations exempting such products from these prohibitions to the extent necessary for investigational use. In issuing such regulations, the Food and Drug Administration could, under existing law, impose conditions relating to records and reports. In fact, the Food and Drug Administration has recently issued new regulations bearing on this subject. However, in view of the President's recommendations of April 10, the committee felt it desirable to add language specifically referring to records and reports.

EFFECTIVENESS AND SAFETY OF NEW DRUGS

Section 8 of the bill, as it would read under the August 20 amendment, makes major changes—in addition to the procedural changes in section 6—in the new drug provisions of the act.

DEFINITION OF "NEW DRUG"

The term "new drug" is presently defined as one not generally recognized to be safe for the claimed uses or one, which while so recognized, has not been used for a material time or to a material extent for such uses. The bill would expand this definition so that the term "new drug" would also include not generally recognized to be effective for the claimed uses or one, which while so recognized, has not been used for a material time or to a material extent for such uses. Thus, every brandnew product, and every new claim for an existing product, would be subject to the tests and procedures established in section 505 of the act.

NEW GROUNDS FOR REJECTION OF NEW DRUG APPLICATION

Section 505(d) of the act sets forth certain grounds for refusing to approve new drug applications. Since 1938 the grounds have been expressed in terms of failure to pass safety tests, without reference to the effectiveness of the drug for the uses claimed. Under the bill, there would be added the test of effectiveness. The committee recognized that legitimate differences of opinion may exist among responsible clinicians with respect to the effectiveness of a particular new drug. Experience has shown that a majority of so-called experts has often been wrong in initially condemning a new drug, just as new inventions in other fields are usually regarded with skepticism and often with hostility. The new ground for rejection of a new drug application is therefore expressed in terms of "a lack of substantial evidence," evaluated on the basis of all the information before him, that the drug will have the effect claimed for it. The term "substantial evidence" is defined in terms of the kind and quality of the investigations that must support the claims.

The bill would also provide for rejection of a new drug application upon a finding that the proposed labeling is false or misleading.

NEW GROUNDS FOR WITHDRAWAL OF APPROVAL

Section 505(e) of the act sets forth the grounds for withdrawal of approval of a new drug application. Since 1938 the grounds have been expressed in terms of lack of safety of the drug, without reference to the effectiveness of the drug for the uses claimed. The bill would accomplish the following:

First. Clarify and expand the authority to withdraw approval on safety grounds so that the manufacturer would continue to have the burden of showing that the drug is safe, as he has on the original submission.

Second. Provide for withdrawal of approval if on the basis of new evidence, evaluated with the evidence at the time of approval, the Secretary finds that there is a lack of substantial evidence that the drug will have the effects claimed. This is a corollary of, and subject to the definition of "substantial evidence" in, the provisions for rejection of a new drug application on the original submission.

Third. Permit withdrawal of approval upon a finding that the manufacturer has failed to establish a system for maintaining required records, or repeatedly or deliberately failed to maintain such records or make required reports, or refused access to such records.

Fourth. Permit withdrawal of approval upon a finding that the methods, facilities, and controls are not adequate and were not made adequate within a reasonable time after notice of inadequacy.

Fifth. Permit withdrawal of approval upon a finding that the labeling is false or misleading and was not corrected within a reasonable time after notice.

Withdrawal of approval of any new drug application on the basis of the foregoing grounds would be preceded by a hearing and an order with findings on the basis of the record. In addition, however, the bill includes a provision for immediate suspension of approval upon a finding of an imminent hazard to the public health; in this case, the applicant would have to be given prompt notice and an opportunity for an expedited hearing. The committee believes that this authority, which could have grave effects upon a manufacturer and upon the confidence of the public in a drug which might later be found appropriate for continued availability to physicians, should only be exercised under the most extreme conditions and with the utmost care. For that reason, it is provided that it may be exercised only by the Secretary or the Acting Secretary. I feel that it would be desirable, wherever possible, for the Secretary, before taking action, not only to confer with the manufacturer, but also to consult a committee of experts appointed by the National Research Council. It should not be forgotten also that there may be other remedies available to the Secretary to cope with the situation instead of using the potentially lethal weapon of immediate suspension.

TRANSITIONAL PROVISIONS

As a result of the change in the definition of "new drug" and the addition of the new effectiveness test, it is necessary to include transitional provisions. Under these provisions, the new effectiveness test, in the case of drugs previously cleared under a new drug application, will apply only to new or amended claims unless the application is withdrawn or suspended. Withdrawal on the ground of a lack of substantial evidence of effectiveness will not apply, for a period of 2 years, to existing claims, unless the approval of any of the claims is withdrawn on other grounds. Established drugs which have never been required to go through new drug procedures will not be affected by the new effectiveness test insofar as their existing claims are concerned.

NAMES ON LABELS AND LABELING

Section 9 of the bill, as it would read under the August 20 amendment, would require the label of a drug to bear the established name of the drug, the established name of each active ingredient, and, in the case of prescription drugs, the quantity of each active ingredient. On the label, and on any labeling on which the drug or any ingredient thereof is named, if a trade name is used for the

drug or the ingredient, the established name of the drug or the ingredient, as the case may be, must be shown in type at least half the size of the type used for the trade name. The term "established name" is defined as the name designated by the Secretary—under the authority granted in section 10 of the bill—or if there is none so designated, the name recognized in an official compendium, or if there is no such official name, the common or usual name.

These provisions preserve trademark rights, which give incentives to strive for excellence surpassing minimum standards. At the same time, they will make sure that established names are used so that physicians and pharmacists can more readily identify the characteristics of the product and more readily consider the use of competitive products where appropriate. The committee rejected proposals that would have required such subordination of trade names that the important functions of trademarks would have been weakened. There must be no loss of incentive for the manufacturer to build a reputation based on integrity and quality of product. In the pharmaceutical industry, above all, the individual manufacturer's pursuit of excellence is to be encouraged, not discouraged. Trade marks and trade names represent an important factor in assuring that this pursuit never flags.

DESIGNATION OF NAMES OF DRUGS

Section 10, which was not affected by the August 20 amendments, has to do with the designation of names of drugs. The Secretary of Health, Education, and Welfare is authorized to designate the name for any drug if he determines that such action is necessary or desirable in the interest of usefulness and simplicity. He is also directed to review existing names recognized in the official compendia to determine whether any revision is necessary or desirable in the interest of usefulness and simplicity. This provision is substantially as reported by the Antitrust Subcommittee.

INFORMATION TO PHYSICIANS

Section 11 would require manufacturers of prescription drugs to transmit to practitioners who request information about a drug, true and correct copies of all printed matter which is required to be included in any package in which that drug is distributed. This is to insure that every physician has ready access to full information about a drug. It would also require the Secretary to distribute such material to doctors, hospitals, medical schools, and libraries.

In addition, section 11 would add a new provision to the act applicable to the content of prescription drug advertising and other descriptive printed matter. This provision would require that such matter include the established name printed prominently and in type at least half as large as that used for any trade name. It would also require inclusion of the formula showing the quantity of each ingredient. Finally, it would require information relating to side effects, contraindications, and effectiveness; in this respect, the Secretary would be under a mandate to issue regulations setting forth the information to be included. Since heretofore the Federal Trade Commission has had jurisdiction of advertisements it would be provided that upon the issuance of regulations with respect to prescription drug advertising under the Food, Drug, and Cosmetic Act, such advertisements would, with respect to the matters covered by the new provision, be removed from the coverage of the Federal Trade Commission Act.

CERTIFICATION OF ANTIBIOTICS

Section 12 of the bill, as it would read under the August 20 amendments, extends batch certification controls, now applicable to five named antibiotics, to all other antibiotics. In the same connection, the provision of the act relating to exemptions of covered antibiotics from the batch certification controls would be strengthened by setting forth considerations which the Secretary must take into account in determining whether to grant an exemption. In order to keep exempted and covered manufacturers on an equal competitive basis, it would be made clear that, in labeling or advertising, an exempted manufacturer could represent that the product has been exempted and a covered manufacturer could represent that the product has been certified.

Mr. President, I believe that the committee has come up with a good drug bill which will protect the American people. Mr. President, I urge the passage of S. 1552 as amended by the committee.

Mr. KEFAUVER. Madam President——

The PRESIDING OFFICER (Mrs. NEUBERGER in the chair). Does the Senator from Tennessee have control of the time on his side?

Mr. KEFAUVER. Yes. Madam President, I yield myself 20 minutes.

The PRESIDING OFFICER. The Senator from Tennessee is recognized for 20 minutes.

Mr. KEFAUVER. Madam President, a parliamentary inquiry.

The PRESIDING OFFICER. The Senator from Tennessee will state it.

Mr. KEFAUVER. Senate bill 1552 was reported from the Judiciary Committee on July 19. An additional amendment, in the nature of a substitute, changing many sections of the bill, was reported on August 21. Do I correctly understand that, by unanimous consent, the August 21 amendment in the nature of a substitute has replaced the bill reported on July 19 which originally was before the Senate?

The PRESIDING OFFICER. That is correct.

Mr. KEFAUVER. Is the amendment in the nature of a substitute, reported on August 21, now the pending question, and is it subject to amendment?

The PRESIDING OFFICER. That is correct.

Mr. KEFAUVER. Madam President, I have heard that yesterday a unanimous-consent agreement was entered into. I trust that we shall be able to conclude the debate within the time allowed by the unanimous-consent agreement. However, several Senators have informed me that they wish to speak; and for fear that they might not have sufficient time under the limitation in the agreement, I ask unanimous consent that any time left over, during consideration of the amendments, may be added to the time available for general debate on the bill.

The PRESIDING OFFICER. Is there objection?

Mr. HRUSKA. Madam President, reserving the right to object, would that include any amendments which may be submitted, but are not now pending? If so, I can anticipate that the debate might be extended 3 or 4 additional days, and that it would be in violation of the spirit of the unanimous-consent agreement.

Mr. KEFAUVER. I do not know of any amendments which would be offered, but which are not now pending, although certainly I cannot say. But I do not think we shall go beyond the time. Several Senators have complained to me that they might not have sufficient time in which to speak. I have not complained.

Mr. HRUSKA. I suggest, Madam President, that the Senator from Tennessee withhold his request for unanimous consent until a later time.

Mr. KEFAUVER. Very well.

Mr. HRUSKA. Because, I say frankly, I do not know where that request might lead; and at this time we are not short of time.

Mr. KEFAUVER. Very well; I shall do that.

Mr. HRUSKA. I thank the Senator from Tennessee.

Mr. KEFAUVER. Madam President, the speech by the distinguished Senator from Mississippi [Mr. EASTLAND], the chairman of the Judiciary Committee, has accurately defined the provisions of the substitute which was reported on August 21. I wish to take this occasion to say that insofar as the Food and Drug Act is concerned, I think this measure is a good one. It is not as strong in some respects as I should like it to be. It is not as strong in some respects as the President recommended in the seven recommendations in his letter of August 3, or as has been recommended in the latest presentation in executive session by representatives of the Food and Drug Administration.

But this measure constitutes a genuine effort on the part of the majority and the minority of the Judiciary Committee—regardless of what may have happened in the past—and on the part of the President, the Food and Drug Administration, and the staff of the committees—to whom I pay the very highest tribute—and on the part of the industry itself to bring the food and drug law up to date and make it effective and modernized. If ever there was a law which needed to have new teeth put into it and needed to be modernized and made more effective, it is the food and drug law.

In my opinion, the bill now before us will assure the people of the United States safer, more effective and better prescription drugs; that physicians will have more accurate information as to

drugs; that false and misleading statements as to the efficacy and side effects in advertising and promotion material will be eliminated, that physicians will receive recent and accurate information about drugs, and that prescribing by generic names will be made simpler and safer.

The bill gives the Food and Drug Administration much needed powers. It will also go far toward preventing repetition of the near calamity with respect to the drug thalidomide, about which we have read so much, was kept off the market largely by the heroic efforts of Dr. Frances Kelsey.

Drugs are big business, sales of drugs and appliances being more than $3 billion a year, or more than the amount received by doctors.

If the bill is passed, drugs will be safer, purer, and more reliable; they will be more properly tested; and information going to physicians will be more accurate as to side effects, warnings, and contradictions.

I want to compliment all who have had anything to do with bringing out this bill. There has been give and take. There has been an honest effort to bring out a good bill so far as the food and drug provisions of the bill are concerned. I endorse it. I think it is in the public interest. I think it should be passed immediately, for the protection of the public.

If Senators will turn to the original bill, introduced on April 12, 1961, of which I had the privilege of being the chief sponsor, and of which the Senator from Michigan [Mr. HART] was a cosponsor, they will find the bill as originally introduced, with lines drawn through it. As a result of hearings by the Antitrust and Monopoly Subcommittee, refined certain changes and revisions were made.

The original bill was stronger, in most respects, than the bill we have before us at the present time, but the bill we have before us is good legislation and it is strong legislation.

On page 23 of the report of the Judiciary Committee filed on July 19, Senators will find the bill reported by the full committee on that date.

Then, as we all know, on August 3 the President of the United States sent a letter to the Chairman of the Judiciary Committee, the Senator from Mississippi [Mr. EASTLAND], in which he made seven excellent recommendations for strengthening the bill that had been reported by the full committee, the history of which is well known.

The chairman of the full committee immediately instituted hearings, day after day, for the consideration of the President's recommendations. They were considered seriously on their merits, with the aim of getting the best possible bill.

There was some give and take. Concessions were made by all sides. Some recommendations were weakened, but not fatally so. Others were even strengthened.

Thus, the bill is the product of a fine, genuine, and cooperative effort. I want to compliment every Senator who has had anything to do with this bill since the President's recommendations of August 3 came to the Judiciary Committee. Without going into detail, I shall try to state briefly what the bill does.

The first section requires that the Commissioner of Patents—who passes on patents for drugs, but who, unfortunately, does not have pharmacologists or doctors in the Patent Office to inspect and test drugs—may call upon the Secretary of Health, Education, and Welfare to furnish full and complete information concerning any drug application, and the Secretary of Health, Education, and Welfare is authorized and directed to do so. The Secretary, of course, may draw upon the doctors of the National Institutes of Health or other doctors in the Department of Health, Education, and Welfare. This information will be supplied to the Commissioner of Patents for his consideration in passing upon whether or not a drug should be patented.

The next section provides for registration. Companies engaged in the manufacture of drugs are required to file with the Secretary of Health, Education, and Welfare their names and places of business.

With respect to the factory inspection provision, section 4, as matters now stand, Food and Drug Administration inspectors are unable, unless the factory permits, to get certain types of information or have access to certain types of records. This provision is not as strong as had been recommended, but should be generally satisfactory. It applies to pharmacies only to the extent that a pharmacy is engaged in manufacture of drugs.

The provision for factory inspection does not apply to proprietary, that is, over-the-counter drugs. There has been some misunderstanding as to what I said, as chairman of the subcommittee, in connection with proprietary drugs. I did say that the investigation, as started back in 1959, was concerned with the ethical drug industry. The companies we wanted to examine were all manufacturers of ethical drugs, and, of course, some of them also manufactured proprietary drugs. As time went on, I said that certain sections of the bill did not apply to proprietary drugs. But, since some ethical drugs become proprietary drugs, it is difficult to arbitrarily make a distinction in all of the provisions of the food and drug law between proprietary drugs and ethical drugs.

Then, the bill which was filed on April 12, 1961, in some respects did apply to proprietary drugs. Yet, although hearings began in August 1961 and went through February 1962, representatives of the proprietary drug producers did not ask to testify. Then, after the hearings were over, they protested that they had not had a chance to be heard.

It must be recognized that in proprietary drugs there is not the same level of concentration. The consumer is not captive. A person who wants a proprietary drug can shop around. There are usually several different products, selling at different prices. There are several different brands of aspirin, for instance, or mouthwash, or other such products.

In contrast, in ethical drugs, when the doctor writes the prescription in terms of a trade name, the patient has no alternative. He has to purchase the brand which the doctor prescribes and pay for it. As I have said before, in ethical drugs, he who orders does not buy and he who buys does not order. This is not true in proprietary drugs. There the buyer and the orderer are the same.

Furthermore, proprietary drugs are not as dangerous, or otherwise they would not be sold across the counter.

Nonetheless, the factory inspection provision, in my opinion, should apply to proprietary drugs, but since whatever the reason, they did not have a hearing, I agreed to their exclusion from this bill, but I have filed a separate and companion bill applying the factory inspection provision to proprietary drugs. If they are included in the House bill, of course, that provision will go into conference.

Effectiveness, as well as safety, should apply to new proprietary drugs, but proprietaries now on the market are not to be subject under the present bill to the provisions requiring them, upon notice by the FOA, to support their claims for effectiveness. I think they should be so required. That is a matter which can be remedied in conference or by other legislation.

I think that there is validity to the suggestion that proprietary drugs should not have to disclose their exact formula, which may constitute a trade secret.

Quality manufacturing controls are covered in section 5. This provision has been strengthened considerably in comparison to the bill which was reported in July. It is not as strong as the President recommended, or as was recommended by the majority members of the Antitrust and Monopoly Subcommittee. The Department of Health, Education, and Welfare believes it to be adequate and I hope they are proved to be correct.

On this point the bill which the Senate is now considering differs from the bill recommendation by the majority of the Antitrust and Monopoly Subcommittee in that the original bill would have set up certain positive and explicit standards which anybody who wished to get into business would have had to meet. It would certainly have prevented "bathtub operators" from getting into the business and making improper drugs.

In respect to the manufacture of vaccines and other products a license must be secured upon a showing that the manufacturer is qualified to make that particular kind of drug. Under the original bill this same approach of licensing would have been extended to all drugs. It is a good approach.

The present approach calls for a combination of registration, a good inspection system and quality manufacturing controls. If the manufacturers do not live up to these provisions, their products can be seized by the Food and Drug Administration. This is an alternative

with which we are going along. It does represent a great improvement over what exists at the present time.

The next section covers the new drug clearance procedure. As has been stated, many drugs have been approved for sale on the market when they should not have been. Senators can look at page 43 of the report of the Committee on the Judiciary of July 19, 1962, and there they will find a list of drugs which have been approved for marketing but then had to be withdrawn because of serious side effects. Some have caused cataracts, blood disorders, kidney ailments, even death. Though not as dramatic as thalidomide, their side effects were serious.

The reason why some of these drugs have gotten onto the market is that the Food and Drug Administration simply did not have time to consider them, to test them, and to get all of the information needed with respect to the drugs before the time limit ran out and the drug was entitled under the present law to be put on the market automatically.

As stated by the chairman of the committee, the time period would be extended from 60 to 180 days. Thereafter, a 30-day notice could be given of a hearing. A hearing could be held. It would have to be commenced in 90 days. Then, if the new drug application were denied, the company would have a right to go to the U.S. court of appeals.

There would be no mandatory requirement that the Food and Drug Administration allow a drug to be put on the market automatically. There would have to be affirmative action by the Secretary, either approving or disapproving the application or giving notice of a hearing.

Section 7 relates to records and reports as to experience with new drugs and antibiotics. This section would require the keeping of records of experience on new drugs and antibiotics. A company would have to keep records as to the effectiveness and as to the side effects of drugs, and the Food and Drug Administration would have access to that information.

This has been one of the great failures in the past. Records have not been available to the Food and Drug Administration, it could not learn, for example, how many cases of aplastic anemias have been reported to a company because the records were not available to it. This can be a very effective provision.

The next section, section 8, relates to effectiveness and safety of new drugs.

The present situation, as was pointed out by former Secretary Ribicoff, of the Department of Health, Education, and Welfare, is that since 1913 manufacturers of drugs for hogs and other animals have been required to show not only that they were safe but also that they were efficacious for what it was claimed they would do. That has never been the rule as to prescription drugs used by human beings. Animals, but not humans, have been assured of receiving effective drugs.

This section would require, in addition to proof of safety, a showing by substantial evidence, by experts who are experienced in making investigations of the drug involved, that the drug will not only be safe but also will have the effect it purports or is represented to have.

The PRESIDING OFFICER. Does the Senator from Tennessee wish to extend his allotted time? His 20 minutes have expired.

Mr. KEFAUVER. Madam President, I yield myself an additional 15 minutes.

What I have described should have been done a long time ago. It is obviously very much in the public interest.

Theoretically—and it has almost happened in some cases—a certain almost completely inert drug might be safe, and claims might be made for its being efficacious for a certain purpose. Where safety is not involved the Food and Drug Administration has not had a basis for disapproving this new drug application.

Where a product does little or no good at all, physicians, because of claims by manufacturers, might be induced to give them to patients when they ought to be giving them older, proven effective medicines instead. Hence the proposal would be a great step toward the protection of the public health.

Another portion of the section would authorize the immediate suspension of a drug if there were an imminent hazard to public health. For example, suppose thalidomide had gotten on the market, and it was then found, as has unfortunately happened, that thousands of horribly deformed children were being born. Under that provision the Food and Drug Administration could immediately take the drug off the market if a hearing would be held after the action.

There are additional grounds for the withdrawal of a new drug from the market—if the manufacturer does not keep the proper records, or does not correct improper control procedures within a reasonable length of time, or does not comply with other provisions of that section.

Section 9 deals with the conspicuousness of official, or generic, names. We hope that as to nonpatented drugs, the bill will bring prices down substantially. Already as a result in part of the hearings before the Subcommittee on Antitrust and Monopoly, States and hospitals are buying drugs by generic names rather than by trade name. Mr. Ribicoff pointed out that in Connecticut hundreds of thousands of dollars had been saved. Sometimes when a drug is purchased by generic name, the price is one-half or one-third of what it would be under a trade name. Hospitals are buying drugs by generic name. The U.S. Government is buying drugs by generic name. In some cases, it is getting them for one-tenth of what it would otherwise pay if bought by trade name, even though they may be made by the same company and be exactly the same drug.

In times past the generic name has been printed in very small letters, both in advertisements and on the label. One must get a magnifying glass to see the generic name at times. It is often to be found in the corner somewhere in microscopic type. Often, it is simply omitted entirely. We recommended in the Subcommittee on Antitrust and Monopoly that the generic name be printed in letters as large as the trade name. Unfortunately, however, some generic names are very long. Finally, as a compromise, it was agreed that the Secretary should establish regulations that the generic name must be carried in print at least half as large as the trade name on the label as well as in advertisements.

Doctors would be able to see more readily the generic name of drugs, if they are in larger type. Knowing that all drug plants are inspected fully and have good control procedures, and that necessary safeguards are provided, there should be no doubt in the minds of any reasonable physicians that when they buy drugs by generic name instead of trade name, they are getting good and safe drugs.

With reference to section 10, as matters now stand, some drugs have no generic names; some have two or three. It is the company which coins the generic name. The U.S. Pharmacopoeia tries to persuade manufacturers to agree to generic names, and it has done a fine job. The AMA is setting up a committee to work on that subject. But, at the present time, unless the company agrees, nothing can be done about it. Under this section after the U.S. Pharmacopoeia has worked with the company and has been unable to reach a satisfactory generic name, the Secretary of HEW would have the standby authority to establish the generic name. In addition the Secretary would be required to make reviews of all the generic names—some of which are several inches long and entirely unpronounceable—and provide more simplified generic names so that physicians can remember, pronounce, and spell them.

Under section 11 advertisements must be accurate with respect to what it is said a drug will do. An advertisement must state the side effects and effectiveness, or a summary thereof, which must be approved by the Secretary of Health, Education, and Welfare.

This relates to advertisements in journals, promotion material, and any other similar type of material, including what is carried on the label, including the accompanying material.

We found cases concerning drugs that were addictive and in which nothing at all was said about side effects, and also cases in which drugs had other harmful side effects, but it was explicitly stated that there were no adverse side effects. That has been misleading to the physician. This proposal is a very important part of the bill. It will provide the physicians with honest and useful information.

There was an outdated provision in the law that longstanding antibiotics had to be batch-tested. But the new antibiotics, introduced since the law was passed, and are more in need of batch-testing than the old ones, were not covered. Section 12 requires the testing of all antibiotics, unless, as a

result of experience, the Secretary of Health, Education, and Welfare finds that any particular one no longer needs to be tested.

Madam President, insofar as the Food and Drug Administration is concerned, I think we have here a good bill, which will do the job required of it.

Later I shall discuss three amendments. If Senators will examine the individual views of the Senator from Colorado [Mr. CARROLL], the Senator from Connecticut [Mr. DODD], the Senator from Michigan [Mr. HART], the Senator from Missouri [Mr. LONG] and myself—the majority members of the Antitrust and Monopoly Subcommittee—in the earlier committee report, beginning at page 33, they will see the amendments that we had in mind offering at that time.

I wish to say that the first three have been adequately taken care of after reconsideration of the bill by the Judiciary Committee, following the President's recommendations. Later on I shall offer an amendment, which I believe will be acceptable, to make it possible for the Food and Drug Commissioner or to require, if he deems it necessary, the testing of a new drug on animals before it is actually given to human beings. If thalidomide had been tested on rabbits, before the drug was introduced, the resulting deformities of baby rabbits would have been discovered so that this whole catastrophe would have been avoided in the countries where it occurred. Apparently, some thalidomide children are being born in the United States also.

The second amendment relates to making available the agreements with reference to the settlement of interference proceedings in the Patent Office, so that the Department of Justice and the Federal Trade Commission can see if the Sherman Act or other antitrust laws have been violated.

This amendment, dealing with interference proceedings, would do much to bring the price of prescription drugs down, because we have found that in many cases when several companies apply for a patent, they agree that one of them will get it, and the others withdraw. Then the company that gets the patent usually licenses the others, but they all sell at the same high price.

The third amendment would require compulsory licensing after 3 years of a qualified applicant upon the payment of 8-percent royalty and open a finding by the Federal Trade Commission that the drug is sold by the manufacturer to the druggist at more than 500 percent of the production and research cost.

Madam President, I wish at this point to pay tribute to the very competent staff who worked in the entire investigation, including Dr. John Blair, Horace Flurry, Paul Rand Dixon—before he left the subcommittee—Dr. E. Wayles Browne, Jr., Dr. Irene Till Hamilton, Mrs. Lucille Wendt, Mrs. Emily Zayyani and Miss Jo Anne Youngblood. Their work was supplemented from time to time in particular aspects by excellent contributions from Bernard Fensterwald, Jr., Mrs. Dorothy Goodwin, Winslow Turner, George Clifford, Dr. Walter Measday, Herman Schwarts and Paul Green. I also wish to express appreciation for the work of the minority staff members—Peter Chumbris, Ronald Raitt, Nicholas Kittre and James Bailey. All worked devotedly on all or some parts of this long and difficult investigation.

The PRESIDING OFFICER. The time of the Senator has expired.

Mr. KEFAUVER. I yield myself 15 minutes on the bill.

The staff started its staff work early in 1959. The first hearing was held on December 7, 1959. For some 2 years we held investigatory hearings, and for almost another year we held hearings on the bill itself. There has been a great deal of acrimony, and much criticism has been heaped upon the chairman and upon some of the majority members of the staff. But we felt we were doing a good job. As far as I am concerned, that is past history. The record is available for anyone who is interested.

I believe that anyone who reads the 13 volumes of hearings in the investigation and the 7 volumes of hearings on the bill as well as the report, will find them detailed and accurate. I have had the privilege of heading many investigations, but I have never known a staff that has worked more effectively, conscientiously and accurately.

Every figure and every statement, aside from typographical or inadvertent errors, is based on fact. The tables and charts are accurate. I cannot pay too high a tribute to those who did the work.

To show what was taking place in the Food and Drug Administration, in May 1960 we held hearings with reference to Dr. Henry Welch, who had been the head of the Antibiotic Section of the Food and Drug Administration. There had been some rumors that he had been receiving honorariums for editorial work in connection with several medical publications, in one of which he was associated with Dr. Felix Marti-Ibanez. John Lear, science editor of the Saturday Review, wrote some articles about it. Mr. John Connor, the president of the Merck Co., and then the chairman of the Pharmaceutical Manufacturers Association, became alarmed about a possible conflict of interest. In 1956 Mr. Connor called it to the attention of the Food and Drug officials. Apparently he did not have the full facts. Perhaps he could not get them. Then the Food and Drug Administration released a statement to the effect that Dr. Welch was not going to accept any large fees in the future. But they never asked him how much he had received. During our hearings, we found that he had received some $280,000 from the magazine of which he was half owner, based on reprints of articles paid for by the very companies that he was supposed to be regulating.

It was estimated that half went to the cost of publishing the reprints, and the other half was divided 50–50 between him and Dr. Felix Marti-Ibanez. At about the time of our hearings into the matter he resigned. The matter now is the subject of a grand jury investigation.

I have always thought that the Food and Drug Administration, and its head, Mr. George Larrick, should have pursued the matter further and received the full information at the time the situation was first brought to their attention several years earlier. But that is past history. That kind of conflict of interest is highly reprehensible. I am confident there are no present similar cases in the Food and Drug Administration.

When Mr. Flemming, then Secretary of Health, Education, and Welfare, appeared before our committee, he stated he would appoint two committees, the Bronk committee, which made an outside or "scientific" investigation and the Kendall committee which made an "inside" investigation. They did a great deal of work, but I do not know exactly what if anything, has been done as a result of their recommendations and reports.

During our investigatory hearings the pharmaceutical manufacturers testified that everything was all right as it was. They were against everything we proposed. The companies and their associates, in their advertisements and public relations, were very critical of the staff of the committee. But it should be said to their credit that when the bill was introduced in April 1961—and the bill was not one recommended by the Food and Drug Administration, although the Food and Drug officials later recommended most of its provisions.

The bill was aimed at reducing the unreasonably high prices of drugs, at providing safer, sounder, more dependable drugs, and at insuring advertising that was truthful concerning the purpose of drugs and their side effects for the benefit of physicians and the Nation.

The bill before the Senate accomplishes two of those objectives. It does not accomplish anything with respect to lowering the price of patented drugs. The patent provisions were eliminated.

It should be said to the credit of the pharmaceutical manufacturers that when they returned to testify on the bill, they accepted about three-fourths of the provisions of the bill. They had become convinced that some reforms were needed.

In contrast, representatives of the American Medical Association who testified on the bill, stated that in this entire omnibus bill there was nothing which they could support. In my opinion, 90 percent of the doctors of the Nation, including members of the American Medical Association, favor the bill which is now before the Senate. Many members of the AMA appeared before the committee, including members of its own council on drugs, outstanding physicians and specialists in their respective fields, to favor the bill. I pay tribute to those outstanding physicians who took the time and trouble to come here to help us with our investigation and to produce a good bill.

The committee covered all the important ethical drugs, including the steroids, oral antidiabetic drugs, tranquilizers, and antibiotics—the wonder drugs which cost so much money.

That distinguished medical journal, the New England Journal of Medicine carried series of six editorials endorsing and recommending the passage of most of the bill.

The report on the drug investigation, including the individual views of several members of the subcommittee, was circulated in March 1961, and finally filed on June 27. It contains a wealth of information about the entire drug field.

Before introducing the bill, as a result of the investigation, I spoke with the distinguished senior Senator from Alabama [Mr. HILL], chairman of the Committee on Labor and Public Welfare, and pointed out to him that, as of that time, three of the provisions dealt with antitrust or patent matters within the jurisdiction of the Committee on the Judiciary, and that others dealt with the Food and Drug Act. I discussed with him recommending that the FDA section be referred to the Committee on the Judiciary. The Senator from Alabama replied that he was very busy with other legislative matters and would be glad to have the Committee on the Judiciary handle that part of the bill. So he joined with me in asking that the Parliamentarian refer the bill to the Committee on the Judiciary, and it was so referred. The Senator from Alabama is an outstanding leader on problems of health research, both in the Committee on Labor and Public Welfare and the Committee on Appropriations. His backing, help, and suggestions have been appreciated throughout the investigation. There have been no committee conflicts.

Because two of the provisions in the original bill related to patent policy, I spoke with the distinguished senior Senator from Arkansas [Mr. MCCELLAN], chairman of the Subcommittee on Patents, and he agreed that the Subcommittee on Antitrust and Monopoly should handle the whole matter. He said he was busy with other problems, particularly in the Committee on Government Operations, and that he would be glad to have the Subcommittee on Antitrust and Monopoly proceed with that part of the investigation. Thus, our subcommittee heard the testimony of a number of patent lawyers with respect to the patent sections, and the results of that investigation are contained in the report.

Representative CELLER introduced a companion bill in the House of Representatives on the same day the bill was introduced in the Senate.

The bill now before the Senate accomplishes two of the stated objectives of the subcommittee. In January 1962, in his message to the Congress, the President of the United States said that action should be taken to reduce the high cost of prescription drugs. Following that came the President's consumer message of March 13, 1962, describing in general language desirable objectives in connection with drugs.

About that time, the then Secretary of Health, Education, and Welfare, Mr. Ribicoff, made an excellent statement before our committee, endorsing strongly all the food and drug provisions of the bill. Although he thought that the patent and antitrust provisions of the bill were generally in the public interest, and he favored the objectives which they sought, he said they were not within the jurisdiction of his Department and that he would not, therefore, wish to express an official position with respect to them. Throughout the time he was Secretary of Health, Education, and Welfare, he gave the subcommittee consistent and strong backing. Mr. Larrick, Commissioner of the Food and Drug Administration, testified in favor, generally, of the food and drug provision. Likewise, he did not express any position as to the patent or the antitrust sections of the bill.

The bill was considered by the Antitrust and Monopoly Subcommittee. I wish to thank the Senator from Nebraska [Mr. HRUSKA] and the Senator from Illinois [Mr. DIRKSEN] for suggesting improvements in the bill at that time. But when the bill was reported, it was approved by a vote of 5 to 3, along party lines.

Then the bill was sent to the full Judiciary Committee. As everyone knows, the three patent sections then were referred to the Subcommittee on Patents, which recommended against two of them and in favor of one of them. But the full Judiciary Committee eliminated all three.

Senators are familiar with what occurred in July in the Judiciary Committee, which resulted in the reporting of the bill and the submission of a report on July 19.

The PRESIDING OFFICER. The time the Senator from Tennessee has yielded to himself has expired.

Mr. KEFAUVER. Madam President, I yield myself 5 additional minutes.

The PRESIDING OFFICER. The Senator from Tennessee is recognized for 5 additional minutes.

Mr. KEFAUVER. Madam President, as I have said, everyone has cooperated now in trying to bring before us a very fine bill, insofar as the food and drug provisions are concerned.

On April 10, the President wrote a letter in which he generally recommended the bill as reported by the Antitrust and Monopoly Subcommittee. I ask unanimous consent that the letter be printed at this point in the RECORD.

There being no objection, the letter was ordered to be printed in the RECORD, as follows:

THE WHITE HOUSE,
Washington, D.C., April 10, 1962.

Hon. JAMES O. EASTLAND,
U.S. Senate,
Washington, D.C.

Dear SENATOR: In the message I sent to the Congress on March 14, I called attention to the need for new legislative authority to advance and protect the interests of consumers in the marketing of drugs.

S. 1552, which is now pending before your committee, incorporates the major recommendations I made. It will strengthen and broaden existing laws in the food and drug field, contribute toward better, safer and less expensive medicines, and establish a better system of enforcement. As you know, the bill is the outgrowth of 28 months of intensive investigation and hearings by your Subcommittee on Antitrust and Monopoly. I believe that early passage of this legislation will substantially improve the ability of the drug industry to serve the Nation and help provide consumers with quality drugs at low, competitive prices.

I understand that the members of the Subcommittee on Patents have decided that the compulsory licensing feature of the legislation requires further study and consideration. I would hope that this would not, however, delay enactment of the other provisions of the bill—provisions which will establish necessary safeguards to assure the reliability and effectiveness of drugs placed on the market, provide for standardization of drug names, and thereby encourage physicians to prescribe drugs by nonproprietary rather than by brand names, require disclosure of adverse as well as beneficial effects of drugs in drug promotion, and assure consideration of therapeutic effectiveness in the granting of patents for drugs that are modifications of other drugs.

The message I sent to the Congress made several other suggestions which, it would seem to me, might appropriately be included in the bill now before your committee. They are:

1. Drug manufacturers should be required to keep records on and report to the Department of Health, Education, and Welfare any indications of adverse effects from the use of a new drug or antibiotic.

2. The Department of Health, Education, and Welfare should be empowered to withdraw approval of a new drug on the basis of a substantial doubt of its efficacy or safety.

3. The provisions requiring drug manufacturers to maintain facilities and controls to assure the reliability of their product, and to institute more effective inspection to determine whether drugs are being manufactured in accordance with the law, cannot feasibly be limited to a particular class of drugs and should therefore be made applicable to over-the-counter as well as prescription drugs.

4. An enforceable system of preventing the illicit distribution of habit-forming barbiturates and amphetamines should be provided.

The need for these amendments is based upon the accumulated years of experience of the Food and Drug Administration, and they appear to be properly within the scope of the subject matter dealt with in the extensive hearings of the Subcommittee on Antitrust and Monopoly.

In addition, I recommend two minor procedural changes:

1. In the section having to do with the rendering of advisory opinions by the Department of Health, Education, and Welfare to the Patent Office on the therapeutic effect of modifications and combinations, I suggest that the requirement providing the applicant with an opportunity for a plenary hearing be deleted. Under the provisions of S. 1552 in its earlier form, the Secretary's finding was conclusive and therefore should have required a formal hearing. But since the bill in its present form requires no binding decision to be made by the Secretary, the requirement of the hearing seems inappropriate and would tend to unduly delay the rendition of the Secretary's purely advisory opinion to the Commissioner. The action of the Commissioner is, of course, subject to well established de novo judicial review.

2. The provision requiring the filing of patent agreements with the Commissioner of Patents should more properly be in the form of an amendment to the Patent Act rather than the Sherman Act.

I have asked the Department of Health, Education, and Welfare to transmit to you promptly any additional recommendations to strengthen, clarify, or improve the bill that it may have and that will not require

additional hearings or substantially delay action on the bill.

It would not appear that the consideration of these proposed changes should occasion any further delay in the approval of this important measure.

With the above changes, S. 1552 adequately deals with the most pressing problems in the drug field, and it is my sincere wish that it be enacted during the current session of the Congress. Your cooperation and assistance to this end will be greatly appreciated.

Sincerely,

JOHN F. KENNEDY.

Mr. KEFAUVER. Madam President, we are also familiar with the fact that on August 4 the President wrote to the Senator from Mississippi [Mr. EASTLAND] a subsequent letter, making seven specific recommendations. Since then, regardless of what happened before, there has been a genuine effort, on all sides, to work out a strong, effective bill; and that has been done. The results of this effort are set forth in the supplemental report which I hope Senators will read—part 2 of Senate Report No. 1744.

In May, on the recommendation of the Food and Drug Administration, a bill was introduced by Representative OREN HARRIS, the chairman of the House Committee on Interstate and Foreign Commerce. That bill has many provisions similar to those in the measure now before us, although there are a number of differences. I am gratified that Representative HARRIS is holding hearings on that bill. I hope that as a result of the hearings and as a result of the conference to be held between the House and the Senate, the bill will be passed by both Houses of the Congress and will be sent to the President.

Madam President, in concluding this part of my presentation, let me say there are many important measures before the Congress, but none is more important than this for the protection of the public.

Madam President, we are about to accomplish a great deal; and I wish to thank the majority members and the minority members and the staff members of the subcommittee and the full committee. I wish to say that in recent weeks Tom Collins of the full Judiciary Committee has virtually worked his heart out; and I desire to thank all who have made this measure possible.

The PRESIDING OFFICER. The time the Senator from Tennessee has yielded to himself has expired.

Mr. SCOTT. Madam President, to the committee amendment, I offer an amendment which I send to the desk and ask to have stated.

The PRESIDING OFFICER. The amendment to the committee amendment will be stated.

The LEGISLATIVE CLERK. In the committee amendment on page 2, in line 23, it is proposed to strike out "December 31" and insert "June 30."

Mr. KEFAUVER. Madam President, I had difficulty hearing the amendment read. Is it offered to the bill?

Mr. SCOTT. Madam President, if the Senator from Tennessee will let me proceed for a moment with my remarks I think he will understand my purpose in offering the amendment. I expect to withdraw it at the conclusion of my remarks.

Mr. EASTLAND. Madam President, let me ask how long the Senator from Pennsylvania wishes to speak.

Mr. SCOTT. Between 15 and 20 minutes.

Mr. EASTLAND. Madam President, I ask unanimous consent that the Senator from Pennsylvania may proceed for 20 minutes. If consent is given, it will not be necessary for him to offer the amendment, which I judge is only a pretext.

Mr. KEFAUVER. Madam President, reserving the right to object, let me say—as I have previously stated—that several Senators were disappointed at the time limitation which was applied. Under the circumstances, why do we not let the Senator from Pennsylvania speak on his amendment?

Mr. SCOTT. I have no objection, if I can obtain unanimous consent to speak for 15 or 20 minutes on the bill.

Mr. EASTLAND. Madam President, I have propounded a unanimous-consent request.

The PRESIDING OFFICER. Is there objection to the request of the Senator from Mississippi?

Mr. HUMPHREY. Madam President, I shall be compelled to object; otherwise, there would be no use in having the unanimous-consent agreement entered into. The Senator from Pennsylvania has offered an amendment, and he is entitled to speak on it.

The PRESIDING OFFICER. Objection is heard.

Mr. DIRKSEN. Madam President, if the distinguished Senator from Pennsylvania will withdraw his amendment—for I suppose it is only a pro forma amendment——

Mr. SCOTT. That is correct.

Mr. DIRKSEN. If he will withdraw it, I will yield him 20 minutes on the bill.

Mr. SCOTT. I shall be happy to do so, with the understanding that the distinguished Senator from Illinois will yield me 20 minutes on the bill.

Mr. DIRKSEN. Madam President, I yield the Senator from Pennsylvania 20 minutes on the bill.

The PRESIDING OFFICER. The Senator from Pennsylvania is recognized for 20 minutes on the bill.

Mr. SCOTT. Madam President, I now withdraw my amendment.

The PRESIDING OFFICER. The amendment of the Senator from Pennsylvania is withdrawn.

Mr. SCOTT. Madam President, in my opinion this is a good bill. It has been carefully considered at great length in the subcommittees and in the Judiciary Committee. Many provisions of the original bill have been revised, altered, or omitted, in favor of carefully drawn legislation.

The President's wishes in regard to certain amendments, which have been referred to as the President's amendments, have been recognized and carried out in a bipartisan fashion. As a result, we now have what I believe is a far better bill than the original one, by virtue of the care and attention which have been given to the bill by the members of the committee, and also by reason of the expert assistance which has been rendered to us by the staff members.

COMMITTEE STAFFING

Madam President, in referring to the staff, I should like to address myself to the entire problem of minority staffing. I manage as well as I can with the assistants I have, and I have been considerately treated by the chairmen of my committees. We have a large and busy office, although we are not always able to do all that I should like to do as a Senator. But certainly it is true that if there were more minority staff members on the committees of which I am a member and on the other committees, more constructive contributions might be made by those of us on the minority side.

It is a most important problem if Congress is to meet its obligation to provide adequate research and staff assistance on a fair and equitable basis to members of both parties. As one who has served as a Member of both the House of Representatives and the Senate, I observe that this situation has too long suffered from neglect and indifference.

All Senators are familiar with the objectives of the Legislative Reorganization Act of 1946 in regard to committee staffs. The staffs were to be nonpartisan, and selected and promoted solely on the basis of merit. The report accompanying the act recommended that committee staff personnel "should be appointed without regard to political affiliation and should not be dismissed for political reasons." The intention was to establish a type of legislative civil service headed by a director of congressional personnel, but this body amended the act, empowering each committee of the Senate and House to choose its staff by majority vote. The ideal of the professional nonpartisan staff remained as the core of the resources—including the Legislative Reference Service and Legislative Counsel—that were to enable Congress to fulfill its historic and proper function in the legislative process.

Ernest S. Griffith, dean of the School of International Service of the American University, and former Director of the Legislative Reference Service of the Library of Congress, commented optimistically on the position of the Congress following the Legislative Reorganization Act. He suggested that—

> Congress has mastered, or has provided itself with the tools to master, the problem of assuring itself an unbiased, competent source of expert information and analysis which is its very own. By the same token it has mastered the problem of recapturing its constitutional role as the independent policy determiner, a self-respecting coequal of the bureaucracy, its legal master in policy matters, and in practice its competent partner or its intelligent critic. Congress has done this without sacrificing its own amateur standing as the elected representatives of the people. This has been no small contribution to the content of governance in a complex and technical age.

Since this has by no means occurred, I take a much less sanguine view of our situation. Not only have we failed to

Safety and effectiveness of self-managed medication abortion provided using online telemedicine in the United States: A population based study

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Summary

Background As access to clinical abortion care becomes increasingly restricted in the United States, the need for self-managed abortions (i.e. abortions taking place outside of the formal healthcare setting) may increase. We examine the safety, effectiveness, and acceptability of self-managed medication abortion provided using online telemedicine.

Methods We retrospectively examined records of the outcomes of abortions provided by the sole online telemedicine service providing self-managed medication abortion in the U.S. We calculated the prevalence of successful medication abortion (the proportion who ended their pregnancy without surgical intervention); the prevalence of serious adverse events (the proportions who received intravenous antibiotics and blood transfusion); and assessed whether any deaths were reported to the service. We also examined the proportions who were satisfied and felt self-management was the right choice.

Findings Between March 20th 2018 and March 20th 2019, abortion medications were mailed to 4,584 people and 3,186 (70%) provided follow-up information. Among these, 2,797 (88%) confirmed use of the medications and provided outcome information, while 389 (12%) confirmed non-use. Overall, 96.4% (95% CI 95.7% to 97.1%) of those who used the medications reported successfully ending their pregnancy without surgical intervention and 1.0% (CI 0.7%-1.5%) reported treatment for any serious adverse event. Among these, 0.6% (CI 0.4% to 1.0%) reported receiving a blood transfusion, and 0.5% (CI 0.3% to 0.9%) reported receiving intravenous antibiotics. No deaths were reported to the service by family, friends, the authorities, or the media. Among 2,268 who provided information about their experience, 98.4% were satisfied and 95.5% felt self-management was the right choice.

Interpretation Self-managed medication abortion provided using online telemedicine can be highly effective with low rates of serious adverse events. In light of increasingly restricted access to in-clinic abortion in the U.S., it may offer a safe and effective option for those who cannot access clinical care.

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Introduction

Abortion access is approaching cross-roads in the United States. The Supreme Court is currently considering an enacted Mississippi law that bans abortion at 15 weeks' gestation[1] and recently allowed a 6-week ban in effect in Texas to stand.[2] Although the right to choose established by *Roe v. Wade* in 1973 still currently stands, access to abortion in the clinic setting is moving further out of reach due to restrictive state legislation. One hundred and eight abortion restrictions were enacted in state legislatures in 2021, more than any other year since *Roe*.[3] These laws make clinical abortion harder to access by imposing waiting periods and medically unnecessary medical tests on patients and requiring clinics and providers to conform to unnecessary administrative regulations.[3]

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Research in context

Evidence before this study

In many U.S. states, access to abortion in the clinic setting is becoming increasingly restricted. In the face of dwindling access, there is evidence that people in the United States are self-managing their abortions (i.e. sourcing and conducting them outside of the formal healthcare setting). While self-managed abortions have been happening in North America for centuries using botanicals, and later misoprostol, one important contemporary method of self-management is the use of online telemedicine to provide the abortion medications mifepristone and misoprostol. No studies, however, have examined the safety, effectiveness, and acceptability of self-managed medication abortion using this model in the United States. We conducted a systematic search of MEDLINE and PubMed using the MeSH terms 'Abortion', 'Self-managed', 'United States', 'Safety' and 'Effectiveness' with no language or date restrictions, and found no relevant reports as of September 2021. Using data from the sole online telemedicine organization that provides self-managed medication abortion to people in the United States, we provide here an analysis of the reported outcomes of self-managed abortions provided between March 20th 2018 and March 20th 2019. We report both the proportion that resulted in successful termination of pregnancy and the proportion that resulted in serious adverse events. We also describe the acceptability of these self-managed abortions based on user experience.

Added value of this study

This study presents the first evidence that self-managed medication abortion provided through online telemedicine in the United States is effective, acceptable to users, and has a very low rate of serious adverse outcomes. This evidence adds to a global body of data showing that self-managed medication abortion is safe and effective. In this study, 70% of those to whom medications were shipped provided follow-up information about their abortions, and among these 2,797 (88%) confirmed use of the medications and provided outcome information, while 389 (12%) confirmed non-use. Among those who used the medications, 96% were able to end their pregnancies without surgical intervention from a clinical provider, a rate comparable with the in-clinic setting. Treatment for serious adverse events was uncommon with 1% receiving a blood transfusion or intravenous antibiotics. No deaths were reported to the service by family, friends, the authorities, or the media. Among the 2,268 people who provided information about their experience, 98% expressed satisfaction with their abortion experience and 96% said it was the right choice.

Implications of all the available evidence

As restrictive abortion legislation continues to create substantial barriers to in-clinic abortion in many U.S. states, abortion self-managed outside of the formal healthcare setting is an important option for those who cannot or prefer not to access clinical care. This study provides key evidence for clinicians, policymakers, and the public that safe, effective, self-managed medication abortion is available in the United States. However, people who self-manage are still vulnerable to legal risks and in some states unjust prosecutions have occurred. Rather than being subject to criminalization, self-managed abortion should be a legitimate part of a spectrum of options for abortion care that must be made available in the United States.

Recent research suggests that one possible consequence of increasing barriers to in-clinic abortion is that more people will self-manage.[4,5] A self-managed abortion is one that takes place outside of the formal healthcare setting, and includes a spectrum of methods, such as the abortion pills mifepristone and/or misoprostol, menstrual extraction, botanicals, herbs, vitamins, beverages, and ingestion of toxic substances and physical injury. Self-managed abortion has been happening in North America for centuries and recent estimates suggest that approximately 7 percent of U.S. women have attempted a self-managed abortion in their lifetime.[6]

An important consideration for people who self-manage is the safety and effectiveness of the method they are using. Since 2018, self-managed abortion using mifepristone and misoprostol has been available through online telemedicine in the U.S. via a non-profit service called Aid Access.[7] The service received 57,506 requests from people in the U.S. in its first two years of operation.[4] While clinic-based and physician-led telemedicine models that provide medication abortion within the formal healthcare setting are also available in some U.S. states,[8–10] Aid Access is distinct from these service models because it offers self-managed abortion, operating outside of the formal U.S. healthcare setting in all 50 states. Provision of self-managed medication abortion using similar services, such as Women on Web and Women Help Women, has been explored in other countries,[11–13] but outcomes have not been studied in any U.S.-based population. Using data from Aid Access, the objective of this study is to examine the safety, effectiveness, and acceptability of self-managed medication abortion provided via online telemedicine in the U.S.

Methods

Data

Aid Access currently provides medication abortion up to 10 weeks gestation at the time of request, which is made using an online consultation form. A doctor reviews the form to ensure no contraindications and provides a prescription of 200mg mifepristone to be taken orally and 800mcg misoprostol to be taken sublingually, along with an additional 800mcg of

misoprostol for use if needed, according to the World Health Organization (WHO) recommended dosage regimen for medication abortion.[14] A partner organization then mails the medications along with usage instructions. A donation of $110 to support the service is requested, but those who cannot afford it are asked to donate what they can. An online non-clinical helpdesk team is available to answer questions. Four weeks after receipt of the medications, users are invited to report their abortion outcomes using an online evaluation form or via an email to the helpdesk.

Our dataset includes all U.S. residents to whom abortion medications were shipped between March 20th 2018 and March 20th 2019. Since Aid Access is the sole organization of its kind serving the U.S., our sample represents the universe of people in the U.S. self-managing a medication abortion using online telemedicine outside the formal healthcare system. De-identified data from the online consultation form, follow-up form, and emails were provided by Aid Access. All individuals in the sample consented to the anonymized use of their data at the aggregate level for research purposes.

The online consultation form includes self-reported information about age, weeks' gestation, parity, feelings about the decision to have an abortion, any medical contraindications, whether or not a person has had an ultrasound scan for the current pregnancy, knows someone who can be with them during their abortion, and lives within 60 min of a hospital. We categorized age as "Under 20 years", "20–24 years" and into 5-year increments thereafter, with a final group of "40 years and over". Gestation was reported as "< 7 weeks" or "7–10 weeks", which represents gestation at the time of the consultation. Those who did not have an ultrasound scan used a pregnancy calculator based on their last menstrual period. Number of children was reported numerically, and we constructed categories of "0" and "1 or more". Feelings about the decision to have an abortion were reported as "I can cope with my feelings regarding my decision" and "I have some worries about my decision and would like further information". Those who expressed worries were directed to appropriate sources of information. Medical history questions included the presence of any contraindications (e.g. bleeding disorders, inherited porphyrias, allergies to mifepristone or misoprostol) or medical conditions that required additional medical screening (e.g. having an IUD in place or having a suspected STI).

The evaluation form is based on similar follow-up instruments used in the clinical setting and is sent to participants 4 weeks after receipt of the medication. Available information included the number who confirmed delivery of the medications, the number who confirmed whether or not they used the medications, and the outcome of the pregnancy or abortion. Those who confirmed using the medications were asked about gestation at the time of use, whether or not they were still pregnant, whether or not they received any clinical intervention to help end the pregnancy (Dilation and Curettage (D&C) or vacuum aspiration), and any other treatment they received for a possible serious adverse event following their abortion. Those who confirmed not using the medications were asked about the outcome of their pregnancy.

Analysis

We compared available clinical and demographic characteristics among those who provided follow-up information and those who did not. We conducted chi-squared difference of proportions tests using an alpha level of 0.05 to indicate statistical significance to check for any systematic differences between the two groups that might affect the outcome of their abortions.

Among those for whom self-reported information on outcomes was available, we examined these in the overall sample as well as constructing two groups: those reported a gestation of 10 weeks or fewer at the time of using the pills, and those who reported a gestation of over 10 weeks. This threshold was chosen to allow comparison with outcomes of medication abortion in the clinic setting, where the mifepristone-misoprostol combined regimen is approved by the FDA through 70 days gestation.[15] While requestors must be 10 weeks pregnant or less at the time of filling out the consultation form, the medications may take 1–3 weeks to arrive and thus some individuals may be over 10 weeks at the time of use. We first examined the proportion who reported that they were no longer pregnant, and then the proportion for whom medication abortion was successful according to the standard definition of success in the Medical Abortion Reporting of Efficacy (MARE) Guidelines, *i.e.* the proportion who were able to expel their pregnancy without the need for surgical intervention.[16] Next, we examined the prevalence of reported serious adverse events, following to the extent possible the categories defined by Cleland et al.[17] Information was available on receipt of IV antibiotics and blood transfusion and we also assessed whether any deaths were reported, recognizing that we are relying on reporting by friends, family members, the authorities, or the media. We calculated point-estimates and exact binomial 95% confidence intervals (CI) both for the overall population and for the binary gestation categories available in our dataset. To compare outcomes between the two gestation groups we used Fisher's exact test and considered findings statistically significant at an alpha level of 0.05.

The follow-up form also included a series of "yes/no" questions asking about the abortion experience, including satisfaction with the service, and whether: using it had been the right choice; affording the full donation (which at the time of data collection was $90) had been difficult; enough information had been provided about

the abortion process; and enough support was available from family and friends. We calculated the proportions of people answering "yes" and "no" to each question.

Data analysis was conducted using Stata version 15.1.[18] The Institutional Review Board of the University of Texas at Austin approved the study.

Role of the funding source

Neither funding source that supported the investigators during the study had any involvement in study design, data collection, analysis or interpretation, and had no role in the writing of this manuscript or the decision to submit for publication.

Results

Between 20th March 2018 and 20th March 2019, Aid Access provided mifepristone and misoprostol by mail to 4584 people. Among these, 3,186 provided follow-up information for a follow-up rate of 70% (Figure 1). Of those who provided follow-up information, 2797 (88%) confirmed use of the medications and provided information on the outcome of their abortion, while 389 (12%) confirmed non-use of the medications. Reasons for non-use included spontaneous pregnancy loss (45%), accessing abortion care in a clinic (21%), deciding to continue the pregnancy (19%), shipping delays (6%), having self-managed using another method (3%), the pregnancy being a false alarm (3%); and experiencing symptoms of an ectopic pregnancy, for which they reported receiving clinical treatment (0.5%). An additional 3% did not specify a reason for not using the medications.

The demographic and clinical characteristics of those who provided follow-up information vs. those who did not are shown in Table 1. Among those who provided follow-up, 94.9% reported being under 7 weeks pregnant at the time of requesting the service. The majority (63.1%) were aged under 30. Virtually all (99.4%) felt OK about their decision to have an abortion and none had any contraindications to abortion medications. A greater proportion of those who provided follow-up were aged 20 or over (89.1% vs. 85.4%, $p < 0.01$), already had children (58.1% vs. 48.4%, $p < 0.001$), and had not received an ultrasound scan prior to their abortion (90.4% vs. 87. 6%, $p=0.005$). There were no significant differences in any characteristic, including gestation, that might reasonably bias the follow-up group towards more favorable outcomes.

Among those who confirmed use of the medications ($n=2,797$), 2402 (86%) reported being under 10 weeks pregnant, while 395 (14%) reported being 10 weeks pregnant or more. Overall, 99.0% of all those who used the medications reported having ended their pregnancies (Table 2), and 96.4% reported a successful medication abortion (i.e., ending their pregnancies with no surgical intervention). There was no significant difference by gestation in the proportion reporting ending their pregnancies (99.1% vs. 98.2%, $p=0.097$), but those who were less than 10 weeks pregnant had a lower rate of surgical intervention compared to those who were 10 weeks or more (2.0% vs. 6.1%, $p < 0.001$). Overall, among the 72 people who reported receiving a procedure to help end their pregnancy, 54 received D&C, 12 received aspiration, and 6 did not specify procedure type. No ectopic pregnancies were reported among those who confirmed use of the medications.

Potentially serious adverse events were not common (Table 3). Overall, 29 people (1.0%) reported experiencing any serious adverse event. Of these, 18 people (0.6%) reported receiving a blood transfusion and 15 (0.5%) reported receiving IV antibiotics (4 people reported receiving both). No deaths were reported by family, friends, clinicians, the authorities, or the media. Rates of adverse events overall were more common among those who reported a gestation of 10 weeks or more as compared with those who were less than 10 weeks (2.3% vs. 0.8%, $p=0.009$).

Among the 2797 people who provided follow-up information, 2268 (81%) reported on the acceptability of their self-management experience (Table 4). Almost



Figure 1. U.S. residents accessing abortion medications through Aid Access.

Characteristic	Provided follow-up information (*N*=3,186)	Did not provide follow-up information (*N*=1,398)	*P*-value
Gestation (weeks)			
7 weeks or fewer	3,025 (94.9)	1,337 (95.6)	0.317
8-10 weeks	161 (5.1)	61 (4.4)	
Age (years)			
Under 20	347 (10.9)	206 (14.7)	0.005
20-24	795 (25.0)	357 (25.5)	
25-29	867 (27.2)	359 (25.7)	
30-34	661 (20.7)	269 (19.2)	
35-39	376 (11.8)	152 (10.9)	
40 and over	140 (4.4)	55 (3.9)	
Children			
0	1,335 (41.9)	721 (51.6)	<0.001
1 or more	1,851 (58.1)	677 (48.4)	
Feelings about abortion decision			
Ok with decision	3,167 (99.4)	1,386 (99.1)	0.317
Troubled by decision	19 (0.6)	12 (0.9)	
Contraindications to medication abortion			
Yes	0 (0.0)	0 (0.0)	–
No	3,186 (100.0)	1,398 (100.0)	
Ultrasound Scan			
Yes	305 (9.6)	172 (12.4)	0.005
No	2,881 (90.4)	1,226 (87.6)	
Current STI			
Yes	14 (0.4)	9 (0.6)	0.367
No	3,172 (99.6)	1,389 (99.4)	
IUD in place			
Yes	6 (0.2)	3 (0.2)	0.853
No	3,180 (99.8)	1,395 (99.8)	
Knows somebody who can be present during the abortion			
Yes	3,111 (97.6)	1,363 (97.5)	0.761
No	75 (2.4)	35 (2.5)	
Within 60 mins of a hospital			
Yes	3,139 (98.5)	1,369 (97.9)	0.144
No	47 (1.5)	29 (2.1)	

***Table 1*: Demographic and clinical characteristics of those to whom abortion medications were provided by Aid Access (*N*=4584).**

all (98.4%) felt satisfied with the service, and 95.5% felt it was the right choice for them. Most (98.1%) felt they had enough information on how to use the medications, and 93.4% felt they had enough information on what to expect from the process. Fewer (81%) felt that they had enough support from family or friends, and 61.8% had difficulty affording the full requested donation.

Outcome	All gestations (*N*=2797) Frequency (percent, 95% CI)	Up to 10 weeks (*N*=2402) Frequency (percent, 95% CI)	Over 10 weeks (*N*=395) Frequency (percent, 95% CI)	*P*-value
Pregnancy				
No longer pregnant	2,769 (99.0, 98.6-99.3)	2,381 (99.1, 98.7-99.5)	388 (98.2, 96.4-99.3)	0.097
Surgical Intervention				
Reported surgical intervention	72 (2.6, 2.0-3.2)	48 (2.0, 1.5-2.6)	24 (6.1, 3.9-8.9)	<0.001
Successful medication abortion				
No longer pregnant and no surgical intervention	2,697 (96.4, 95.7-97.1)	2,333 (97.1, 96.4-97.8)	364 (92.1, 89.1-94.6)	<0.001

***Table 2*: Outcome of abortion reported by people who self-managed a medication abortion using Aid Access (*N*=2797).**

Outcome	All gestations (*N*=2797) Frequency (percent, 95% CI)	Up to 10 weeks (*N*=2402) Frequency (percent, 95% CI)	Over 10 weeks (*N*=395) Frequency (percent, 95% CI)	*P*-value
Serious Adverse Event				
Blood transfusion	18 (0.6, 0.4-1.0)	11 (0.5, 0.2-0.8)	7 (1.8, 0.7-3.6)	0.002
IV Antibiotics	15 (0.5, 0.3-0.9)	12 (0.5, 0.3-0.9)	3 (0.8, 0.2-2.2)	0.509
Death	0 (0.0, 0.0-0.0)	0 (0.0, 0.0-0.0)	0 (0.0, 0.0-0.0)	–
Any serious adverse event*	29 (1.0, 0.7-1.5)	20 (0.8, 0.5-1.3)	9 (2.3, 1.1-4.3)	0.009

***Table 3*: Serious adverse events reported by people who self-managed a medication abortion through Aid Access (*N*=2797).**
* Each serious adverse event is counted only once.

Discussion

We used a data set containing all available outcomes of self-managed medication abortions provided through online telemedicine, outside the formal healthcare system, in the U.S. for one year. We found that abortions self-managed using this model were highly effective, with reported success rates comparing favorably with medication abortions carried out up to 10 weeks within the formal U.S. healthcare setting.[19] The reported prevalence of serious adverse events was very low, and the users of service reported high levels of satisfaction.

Our results offer the first insight into the outcomes of self-managed medication abortions provided using online telemedicine in the U.S. The high effectiveness rates and low prevalence of serious adverse events we found mirror findings from other countries where medication self-management is used.[20–22] We note that although most people in our study did not receive an ultrasound, they reported awareness of the duration of their pregnancy at the time of medication use. These findings are in line with prior evidence suggesting that last menstrual period is an accurate method for determining gestation in early pregnancy[23] and WHO guidelines, which clearly specifies that ultrasound is not a necessary pre-requisite for medication abortion.[14]

Our findings also add to evidence on the safety and effectiveness of self-managed medication abortion beyond 10 weeks. While rates of surgical intervention were higher among the small proportion in our study who used the medications after 10 weeks compared to those at 10 weeks or under, almost all were able to end their pregnancies and the rate of successful medication abortion was similar to other studies examining medication abortion in the late first trimester,[24] and medication self-management after 13 weeks using an accompaniment model.[25] Those self-managing after 10 weeks in our study also tended to have experienced shipping delays and some received modified instructions according to the WHO protocol for medication abortion at 12 weeks and over[14] and additional support from Aid Access. In addition, no ectopic pregnancies were reported after using the medications and indeed a small number were diagnosed quickly by the service at the time of initial contact.

This study has several limitations. The first is that abortion outcomes were self-reported by people who self-managed. However, since these abortions take place outside of the formal healthcare system, self-reporting is by definition the only possible method of follow-up. Moreover, a previous large randomized controlled trial showed that self-assessment of the outcome of medication abortion was non-inferior to clinical follow-up, indicating that people are capable of determining on their own whether or not their abortion has been successful.[26] Since an examination of the outcomes of medication abortions taking place outside the formal healthcare setting cannot be dealt with by a randomized controlled trial or clinical trial, we have drawn on the best available "real world" data to answer these important questions.

Second, although the 70% follow-up rate in this study is incomplete, it is on par with or better than many clinical studies, since most outcomes are only recorded if patients decide to follow up with the clinic.[27]

Outcome	All gestations (*N*=2268)* Frequency (percent)
Felt satisfied with the service	2,231 (98.4)
Felt self-management using the service was the right choice	2,166 (95.5)
Felt had enough information on how to use pills	2,225 (98.1)
Felt had enough information on what to expect to see and feel	2,118 (93.4)
Felt had enough support from family/friends	1,837 (81.0)
Had difficulty affording the full requested donation	1,401 (61.8)

***Table 4*: Experiences reported by people who self-managed a medication abortion through Aid Access (*N*=2268).**
* 529 people who confirmed using medications did not provide information on acceptability outcomes.

Moreover, we took a more conversative approach than most clinical studies in that we did not consider those for whom no outcome data were available as presumed successful abortions. Third, while self-reporting could be subject to recall or social desirability bias, the short time period between the abortion and the collection of follow-up information should minimize recall bias.

While treatment for serious adverse events was a rarely reported outcome in our study, rates were still higher than those reported in studies of abortions taking place in the clinical setting.[19,28] We note, however, that we are not able to verify whether the treatment received by users of the service who did engage with the formal healthcare system was appropriate to their situation. For example, most of those who reported receiving surgical intervention also received antibiotics, which may have been given prophylactically or to treat an existing infection. Studies in other countries have shown that rates of intervention and additional treatment during clinical abortion follow-up are highly variable, especially in countries where hospital staff are not trained to care for abortion patients.[29] While we did examine whether any deaths were reported to the service, we were of course unable to fully assess whether any deaths occurred in the group that did not provide follow-up information.

It is also important to consider the rates of self-reported adverse events shown in this study in the context of the other possible outcomes for people in the U.S. who cannot access in-clinic abortion care. Between 200,000 and 1.2 million unsafe abortions are estimated to have taken place per year in the U.S. in the 1950s and 1960s pre-*Roe*, with the resulting burden of morbidity and mortality falling disproportionately on racially minoritised people.[30] While we do not expect the same prevalence of unsafe abortion today, we cannot assume that none will occur. Moreover, those forced to carry a pregnancy to term would also be at higher risk than those who self-manage using Aid Access. Rates of hemorrhage postpartum in the U.S. are over five times higher than those reported in this study, with Black women at disproportionately high risk.[31,32]

The trajectory of highly restricted access to in-clinic abortion in the U.S. and the future possibility of full abortion bans in some states means that self-managed abortion is likely to become an increasingly used alternative. The FDA recently permanently suspended the in-person dispensing requirement on mifepristone, paving the way for expanded clinic-based telemedicine abortion services. However, at least 19 states already have laws banning telemedicine for medication abortion and in these jurisdictions the FDA ruling will have little effect.[33] These states are the also the ones with the highest rates of requests to Aid Access.[4] In the majority of U.S. states, self-management is not illegal, and clinicians who may provide follow-up care have no reporting obligation.[34] It is important to note, however, that there have been 24 cases of unjust prosecution for alleged self-management since 2000, with populations already subject to increased surveillance and biased treatment, including people with low incomes and racially minoritised people, at highest risk.[35] While legal risks remain, our findings demonstrate that self-management using medications provided through online telemedicine is a safe, effective, and acceptable option for people in the U.S. and thus it is both an important method of harm reduction and a means of preserving reproductive autonomy.

Contributors

ARAA conceived of the original research question. All authors contributed to the study design. RG, ER, and JM compiled and provided the de-identified Aid Access data. ARAA conducted the statistical analyses and prepared the tables and figures. ARAA and RG did the initial data interpretation. ARAA, wrote the first draft of the manuscript. All authors contributed to final data interpretation and contributed to and approved the final draft of the manuscript. ARAA and RG verified the underlying data. All authors had full access to all the data and all authors accept responsibility to submit the manuscript for publication. No medical writers were involved in the preparation of the manuscript.

Data sharing statement

Authors are not able to directly provide access to data. Any direct requests submitted to Aid Access will be dealt with according to their internal policies and procedures.

Declaration of interests

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Self reported outcomes and adverse events after medical abortion through online telemedicine: population based study in the Republic of Ireland and Northern Ireland

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ABSTRACT

OBJECTIVES

To assess self reported outcomes and adverse events after self sourced medical abortion through online telemedicine.

DESIGN

Population based study.

SETTING

Republic of Ireland and Northern Ireland, where abortion is unavailable through the formal healthcare system except in a few restricted circumstances.

POPULATION

1000 women who underwent self sourced medical abortion through Women on Web (WoW), an online telemedicine service, between 1 January 2010 and 31 December 2012.

MAIN OUTCOME MEASURES

Successful medical abortion: the proportion of women who reported ending their pregnancy without surgical intervention. Rates of adverse events: the proportion who reported treatment for adverse events, including receipt of antibiotics and blood transfusion, and deaths reported by family members, friends, or the authorities. Care seeking for symptoms of potential complications: the frequency with which women reported experiencing symptoms of a potentially serious complication and the proportion who reported seeking medical attention as advised.

RESULTS

In 2010-12, abortion medications (mifepristone and misoprostol) were sent to 1636 women and follow-up information was obtained for 1158 (71%). Among these, 1023 women confirmed use of the medications, and follow-up information was available for 1000. At the time women requested help from WoW, 781 (78%) were <7 weeks pregnant and 219 (22%) were 7-9 weeks pregnant. Overall, 94.7% (95% confidence interval 93.1% to 96.0%) reported successfully ending their pregnancy without surgical intervention. Seven women (0.7%, 0.3% to 1.5%) reported receiving a blood transfusion, and 26 (2.6%, 1.7% to 3.8%) reported receiving antibiotics (route of administration (IV or oral) could not be determined). No deaths resulting from the intervention were reported by family, friends, the authorities, or the media. Ninety two women (9.3%, 7.6% to 11.3%) reported experiencing any symptom for which they were advised to seek medical advice, and, of these, 87 (95%, 87.8% to 98.2%) sought attention. None of the five women who did not seek medical attention reported experiencing an adverse outcome.

CONCLUSIONS

Self sourced medical abortion using online telemedicine can be highly effective, and outcomes compare favourably with in clinic protocols. Reported rates of adverse events are low. Women are able to self identify the symptoms of potentially serious complications, and most report seeking medical attention when advised. Results have important implications for women worldwide living in areas where access to abortion is restricted.

WHAT IS ALREADY KNOWN ON THIS TOPIC

In many countries where abortion through the formal healthcare system is restricted, self sourced medical abortion through online telemedicine provides an alternative to methods such as sharp objects or noxious substances

Little is known about the safety and effectiveness of medical abortion provided through this online pathway

Previous studies have been limited by small sample sizes, high losses to follow-up, and inability to examine self screening for potentially serious complications

WHAT THIS STUDY ADDS

This study is based on women's self reports of outcomes and complications of medical abortion and provides the best evidence to date that self sourced medical abortion through online telemedicine is highly effective and that rates of adverse events are low

Reported rates of successful medical abortion are comparable with protocols in clinics, and women report successfully self screening for potentially serious complications and seeking medical assistance when necessary

For the millions of women worldwide living in areas where access to abortion is restricted, the findings show the vital role played by self sourced medical abortion in providing an option with high effectiveness rates and few reported adverse outcomes

Introduction

About a quarter of the world's population lives in countries with highly restrictive abortion laws.[1] Women in these countries often resort to unsafe methods to end their pregnancies. Globally, each year an estimated 43000 women die as a result of lack of access to safe legal abortion services through their countries' formal healthcare systems.[2] Millions more have complications.[3] Worldwide, the fourth leading cause of maternal mortality is unsafe abortion.[4]

Yet in many countries, self sourced medical abortion provides a vital alternative to dangerous methods such as using sharp objects or noxious substances. Women source mifepristone and misoprostol (or misoprostol alone) themselves and use the medications outside the formal healthcare system. In some settings, women buy the medications from pharmacies or markets.[5] In other settings, they can self source using online telemedicine

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initiatives that provide medications as well as help and support by email or instant messaging.[6]

One setting in which online telemedicine has dramatically changed women's access to abortion is in the Republic of Ireland and Northern Ireland. Abortion laws in both the Republic and Northern Ireland are among the most restrictive in the world.[1] Abortion is allowed only to save a women's life and, in Northern Ireland only, her permanent physical and mental health.[7 8] Although Northern Ireland is part of the UK, the Northern Irish legislature did not adopt the 1967 Abortion Act, which legalised abortion carried out by registered medical practitioners in England, Scotland, and Wales. As a result, abortion under most circumstances remains illegal there under the Offences Against the Person Act of 1861, which provides a maximum penalty for the woman undergoing the abortion of life imprisonment.[9]

Women from the Republic and Northern Ireland who do not want to, or feel they cannot, continue with a pregnancy have traditionally had three options: those with the requisite financial and logistical means can travel abroad to access abortion in a clinic, while those who do not must either self induce using an unsafe method or continue their unwanted pregnancy. For the past decade, however, women of all financial means have also had the option to self source early medical abortion through online telemedicine.[10 11]

Despite having been used by thousands of women in the Republic and Northern Ireland[11] and tens of thousands of women worldwide,[12] little is known about the outcomes of these self sourced medical abortions. Two existing studies have examined data from telemedicine initiatives: one across various settings[6] and the other in Brazil.[13] These studies showed encouraging results with respect to efficacy but were limited by small sample sizes and relatively high losses to follow-up. Moreover, no study has examined whether women are able to safely manage their own abortions by identifying the symptoms of serious complications and presenting for medical advice when appropriate.

Using data from an online telemedicine initiative, we conducted a population based analysis of women in the Republic of Ireland and Northern Ireland who self sourced medical abortion during a three year period. We examined self reported outcomes and complications after medical abortion through online telemedicine and assessed women's ability to self screen for the symptoms of potentially serious complications of abortion and their propensity to seek medical attention. In light of current policy debates,[9 14] the Republic and Northern Ireland provide a particularly important and timely opportunity to examine women's self reported outcomes.

Methods

We examined data from Women on Web (WoW), a non-profit organisation that provides early medical abortion through online telemedicine in countries where access to safe abortion is restricted. The service is currently available for women up to 10 weeks' gestation at the time of request. To make a request, women fill out a consultation form on the WoW website (www.womenonweb.org/en/i-need-an-abortion).[15] A doctor reviews the medical information on the form and, if clinical criteria are met, provides a prescription according to the WHO recommended dose regimen for medical abortion.[16] Mifepristone and misoprostol are sent through the mail by a partner organisation. Women either make a donation to support the service or, if they cannot afford to do so, the service is donated to them. Real time instruction about how to use the medications, as well as help and support during and after the abortion process, are provided by a multilingual specially trained helpdesk team.[6] Women are invited to share their experiences four weeks later using an online evaluation form or by emailing the helpdesk.

Our dataset includes all women in the Republic and Northern Ireland who filled out an online consultation form and to whom mifepristone and misoprostol were sent from 1 January 2010 to 31 December 2012. We chose this date range for three reasons. Firstly, although WoW began providing online telemedicine abortion in 2006, changes to the software used to handle requests mean that data are available only from 1 January 2010 onwards. Secondly, in January 2013, a change to the evaluation form reduced the level of detail available on symptoms of potential complications and help seeking behaviour. Thirdly, WoW was the only telemedicine service operating in the Republic and Northern Ireland in 2010-13. Our sample therefore represents all women accessing medical abortion through online telemedicine during this period. Overall, 2150 women contacted the WoW helpdesk to request an abortion from 1 January 2010 to 31 December 2012. Among these, 514 cancelled their request or discontinued contact with the helpdesk, and no medications were sent to them. The analytic sample size was determined by the number of women remaining to whom medications were sent and who subsequently confirmed using them and provided follow-up information about the outcome of their abortion.

We did not distinguish between women who live in the Republic and Northern Ireland in our analyses. All women living in the Republic who access abortion through WoW have their medications sent to an address outside the Republic because the import by mail of prescription medications is prohibited and all incoming medications are confiscated by Irish customs.[17] Some women from the Republic are already aware of the customs situation and select Northern Ireland as their country of origin on the consultation form. The border between the two countries, however, is, at present, barely discernible and fully open to travel. Moreover, the practicalities women face in terms of accessing abortion in the two countries is similar.

The online consultation form includes self reported information about age, weeks' gestation, feelings about the decision to have an abortion, and any medical contraindications or conditions requiring additional screening. We categorised age as <20, 20-24, and into 5 year increments thereafter, with a final group of ≥45.

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Gestational age was reported as <7 weeks' or 7-9 weeks', which represents gestational age at the time of the consultation. During the time period of our study, WoW collected data on gestational age according to these categories to reflect the change in the registered use of mifepristone from up to 7 weeks' to up to 9 weeks' gestation in 2009.[18] In our sample, 58% of women reported having gestational age confirmed through ultrasonography, and the remainder used a pregnancy calculator based on the date of their last menstrual period, which has been shown to be an accurate method of determining gestational age for early medical abortion.[19] The estimated time for the medications to arrive in the Republic/Northern Ireland is between five and seven days, and 94% of women who used them reported doing so less than a week after they arrived. Thus, while we do not have information on women's exact gestational ages at the time they took the medications, we can estimate that for most women it was less than two weeks after the consultation.

Feelings about the decision to have an abortion were reported as "I can cope with my feelings regarding my decision" and "I have some worries about my decision and would like further information." Women who expressed worries were directed to appropriate sources of information. Questions on medical history included the presence of any contraindications (such as bleeding disorders, inherited porphyrias, allergies to mifepristone or misoprostol) or medical conditions that required additional medical screening (such as hypertension and diabetes).

We retrieved follow-up information for as many women as possible through either an evaluation form sent out four weeks after the medications were sent or email follow-up through the helpdesk. The evaluation form is based on similar follow-up instruments used in the clinical setting. Available information included the number of women who confirmed delivery of mifepristone and misoprostol, the number who confirmed whether or not they had used the medications, and, among those who confirmed use, the outcome of the abortion. The number of women who confirm using the medications is inevitably lower than the number to whom the medications are sent because some experience a spontaneous miscarriage, decide travel to obtain an abortion abroad, decide to continue with their pregnancy, or simply do not respond to follow-up from the helpdesk.

Women who confirmed using the medications were asked whether or not they are still pregnant, whether they received any surgical intervention (dilatation and evacuation or vacuum aspiration), and whether they received any other treatment after their abortion, including antibiotics and blood transfusion. Women were also asked if they experienced any symptoms of potentially serious complications, including: "bleeding requiring more than two maxi pads an hour for more than two hours"; "fever over 39°C or abnormal vaginal discharge"; and "persistent pain continuing for several days after the abortion." They were then asked whether they went to a hospital or to see a doctor. WoW advises women to seek medical attention if any of the above symptoms arise.

For women who completed medical abortion at home and for whom self reported information on outcome was available, we first examined the age distribution, gestational age, feelings about abortion, and prevalence of contraindications and comorbidities. We then examined the proportion for whom medical abortion was successful according to the standard definition of success in the Medical Abortion Reporting of Efficacy (MARE) Guidelines—that is, the proportion who were able to expel their pregnancy without the need for surgical intervention.[20] Next, we examined the prevalence of reported adverse events, following to the extent possible the categories defined by Cleland and colleagues.[21] Information was available on antibiotics, blood transfusion, and death. The highly politicised nature of abortion in the Republic and Northern Ireland means that any death suspected to be related to abortion would be extremely high profile news. We think it is likely that WoW would either have known if the woman in question had accessed their service or would have been notified by the authorities or the woman's family or friends. Finally, we examined the prevalence with which women reported symptoms of possibly serious complications and the frequency with which those who reported such symptoms sought medical attention.

Data analysis was conducted with Stata version 13.1 (StataCorp. 2013. College Station, TX). We calculated point estimates and exact binomial 95% confidence intervals for the overall population and for the binary categories of gestational age available in our dataset. Characteristics and outcomes by category of gestational age were compared with the Fisher-Freeman-Halton test and Fisher's exact test, respectively. Findings were considered significant at an α level of 0.05. Anonymised data were provided to us by WoW.

Patient involvement

Patients were not involved in the design or conduct of the study. The follow-up that WoW provides, however, is designed to deal with the priorities and experiences of women who access the service. Thus, though this study is an analysis of secondary, anonymised data, with no direct participant involvement, the research questions were informed by the needs of women who rely on WoW to access abortion.

Results

From 1 January 2010 to 31 December 2012, WoW sent 200 mg mifepristone and 1200 µg misoprostol to 1636 women living in the Republic and Northern Ireland (fig 1). Among these, 1181 women confirmed subsequent use or non-use of the medications. Among the remainder, 24 women confirmed delivery but offered no further follow-up information, while 431 neither confirmed delivery nor offered further follow-up information. Among the 1181 women who confirmed use or non-use of the medications, 1023 used the pills, and 158 did not. Follow-up information on abortion outcome (that is, whether or not a woman was still pregnant after using

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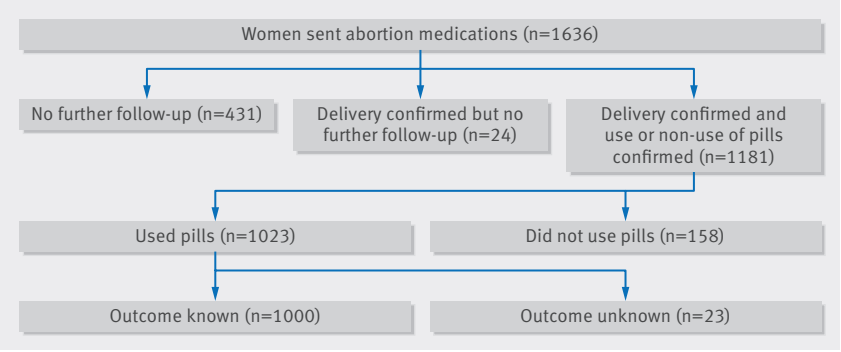

Fig 1 | **Women accessing medical abortion through WoW (Women on the Web)**

the medications) was available for 1000 of the 1023 women who confirmed use of the medications. Thus, outcome data were available for 1158 women who were sent mifepristone and misoprostol, representing 71% follow-up. Reasons for not using the medications included having had a spontaneous miscarriage in the meantime, accessing abortion through another pathway such as travelling abroad, and deciding to continue the pregnancy. One woman elected not to use the medications because she discovered her pregnancy was ectopic. No other ectopic pregnancies were reported either before or after use of the medications.

Among the 1000 women who used the medications and for whom we had information about the outcome of the abortion, 781 (78%) reported being <7 weeks pregnant at the time of requesting help from WoW, and 219 (22%) reported being 7-9 weeks pregnant (table 1). Almost a third (n=306) of women were aged 30-34, 236 were 35-39, and 195 were 25-29, 79 were aged ≤24, and 184 were ≥40. Virtually all (997) reported being able to cope with their decision to have an abortion. None had any contraindications to medical abortion, and 23 had a medical condition that required extra screening to ensure that it could be carried out safely. Comparison of the characteristics of the 1158 women for whom follow-up information was available versus the 478 women for whom no follow-up information was available showed no clinically or statistically significant differences between the two groups (see appendix).

Virtually all women (99.2%, 95% confidence interval 98.4% to 99.7%) reported having ended their pregnancies, and 94.7% (93.1% to 96.0%) reported a successful medical abortion (that is, ending their pregnancies with no surgical intervention) (table 2). Women with a reported gestational age of 7-9 weeks at the time they requested an abortion more commonly reported receiving a surgical intervention than women with a reported gestational age of <7 weeks (7.3% (4.2% to 11.6% *v* 3.7% (2.5% to 5.3%), respectively, P=0.04). There were, however, no statistically or clinically significant differences by gestational age in the proportions reporting a successful medical abortion (95.4% (93.7% to 96.8%) *v* 92.2% (87.9% to 95.4%); P=0.09).

Among the 1000 women for whom information about the outcome of their abortion was available, information about adverse events and symptoms of potentially serious complications was available for 987 (99%). Rates of self reported treatment for adverse events were low: 3.1% (95% confidence interval: 2.1% to 4.4%)

Table 1 | **Medical and demographic characteristics of women conducting self sourced medical abortion through online telemedicine. Figures are number (percentage) of women**

Characteristic	All gestations (n=1000)	<7 weeks' gestation (n=781)	7-9 weeks' gestation (n=219)	P value
Age (years):				
<20	4 (0.4)	3 (0.4)	1 (0.5)	0.17
20-24	75 (7.5)	53 (6.8)	22 (10.1)	
25-29	195 (19.5)	146 (18.7)	49 (22.4)	
30-34	306 (30.6)	238 (30.5)	68 (31.1)	
35-39	236 (23.6)	190 (24.3)	46 (21.0)	
40-44	135 (13.5)	115 (14.7)	20 (9.1)	
≥45	49 (4.9)	36 (4.6)	13 (5.9)	
Gestational age (weeks):				
<7	78 (78.0)	—	—	—
7-9	22 (22.0)	—	—	
Feelings about decision to have an abortion:				
I can cope with my feelings	997 (99.7)	778 (99.7)	219 (100.0)	0.36
I have some worries about my feelings	3 (0.3)	3 (0.3)	0 (0.0)	
Contraindications to abortion:				
No contraindication	1000 (100.0)	781 (100.0)	219 (100.0)	1.0
Comorbidities:				
Heart disease	1 (0.1)	1 (0.1)	0 (0.0)	0.62
Epilepsy	1 (0.1)	1 (0.1)	0 (0.0)	
Hypertension	4 (0.4)	3 (0.4)	1 (0.5)	
Diabetes	4 (0.4)	2 (0.3)	2 (0.9)	
Hepatic disease	1 (0.1)	1 (0.1)	0 (0.0)	
Renal disease	0 (0.0)	0 (0.0)	0 (0.0)	
Thyroid disease	13 (1.3)	10 (1.3)	3 (1.4)	
Any co-morbidity	23 (2.3)	17 (2.2)	6 (2.7)	

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Table 2 | Outcome of abortion reported by women conducting medical abortion through online telemedicine. Figures are number of women (percentage, 95% confidence interval)

Abortion outcome	All gestations (n=1000)	<7 weeks' gestation (n=781)	7-9 weeks' gestation (n=219)	P value
Pregnancy				
No longer pregnant	992 (99.2, 98.4 to 99.7)	774 (99.1, 98.2 to 99.6)	218 (99.5, 97.5 to 100.0)	1.0
Surgical intervention				
Reported surgical intervention*	45 (4.5, 3.3 to 6.0)	29 (3.7, 2.5 to 5.3)	16 (7.3, 4.2 to 11.6)	0.04
Successful medical abortion				
No longer pregnant and no surgical intervention	947 (94.7, 93.1 to 96.0)	745 (95.4, 93.7 to 96.8)	202 (92.2, 87.9 to 95.4)	0.09

*Dilatation and evacuation; vacuum aspiration.

Table 3 | Treatment for adverse events reported by women conducting medical abortion through online telemedicine. Figures are number of women (percentage, 95% confidence interval)

Treatment	All gestations (n=987)	<7 weeks' gestation (n=768)	7-9 weeks' gestation (n=219)	P value
Antibiotics	26 (2.6, 1.7 to 3.8)	19 (2.5, 1.5 to 3.8)	7 (3.2, 1.3 to 6.5)	0.63
Blood transfusion	7 (0.7, 0.3 to 1.5)	4 (0.5, 0.1 to 1.3)	3 (1.4, 0.3 to 4.0)	0.19
Death	0 (0, 0.0 to 0.4)	0 (0, 0.0 to 0.5)	0 (0, 0.0 to 1.7)	1.0
Any adverse event	31 (3.1, 2.1 to 4.4)	21 (2.7, 1.7 to 4.1)	10 (4.6, 2.2 to 8.2)	0.19

reported any treatment for a possible adverse event (table 3). Overall, 2.6% (1.7% to 3.8%) reported receiving antibiotics by any route of administration, 0.7% (0.3% to 1.5%) reported receiving a blood transfusion, and no deaths were reported by family, friends, the authorities, or the media. Rates of reported adverse events were not significantly more prevalent in the 7-9 week group than in the <7 weeks group (4.6% (2.2% to 8.2%) *v* 2.7% (1.7% to 4.1%), respectively, P=0.19).

Among the 987 women for whom we had information on self reported symptoms, 9.3% (95% confidence interval 7.6% to 11.3%) reported experiencing symptoms of a potentially serious complication (table 4). The prevalence of reporting any such symptom was higher in the 7-9 weeks group than the <7 weeks group (13.7% (9.4% to 19.0%) *v* 8.1% (6.2% to 10.2%), respectively, P=0.02). Bleeding requiring more than two maxi pads an hour for more than two hours was the most commonly reported of the symptoms (5.2%, 3.9% to 6.7%). Overall, 95% (87.8% to 98.2%) of women who reported symptoms of a potentially serious complication for which they were advised to seek medical assistance said they went to a hospital or clinic. There were no substantive or significant differences in the proportions of women who sought advised medical attention by reported gestational age (94% (84.3% to 98.2%) in the <7 weeks group *v* 96.7% (82.8% to 99.9%) in the 7-9 weeks group, P=1.0). None of the five women who did not seek medical help reported an adverse outcome or treatment for a complication, and none of the women who did not report symptoms of a potentially serious complication reported an adverse event.

Discussion

Among women in the Republic of Ireland and Northern Ireland, early medical abortion provided through online telemedicine was highly effective. The reported rate of successful medical abortion compares favourably with the rates of those carried out within the formal healthcare system, both when mifepristone and misoprostol are administered in clinic and when mifepristone is administered in clinic and misoprostol is taken at home.[22] The reported prevalence of adverse events is low, and, critically, when women reported experiencing symptoms of a potentially serious complication, almost all reported seeking medical attention as advised.

Limitations and strengths of study

The main limitation of our study is that we relied on women's self reports with respect to the outcome and complications of abortion. Many studies in the clinical setting, however, have the same limitation as women often do not return to the clinic and either self report by phone or are simply lost to follow-up. Moreover, as the women in our study are by definition conducting their

Table 4 | Reported symptoms and care seeking for potentially serious complications among women conducting medical abortion through online telemedicine. Figures are number of women (percentage, 95% confidence interval)

	All gestations	<7 weeks' gestation	7-9 weeks' gestation	P value
Reported symptoms:				
No of women	987	768	291	—
Bleeding >2 maxi pads/hr for >2 hours	51 (5.2, 3.9 to 6.7)	33 (4.3, 3.0 to 6.0)	18 (8.2, 4.9 to 12.7)	0.02
Fever >39°C or abnormal vaginal discharge	17 (1.7, 1.0 to 2.7)	10 (1.3, 0.6 to 2.4)	7 (3.2, 1.3 to 6.5)	0.07
Persistent pain continuing several days after abortion	24 (2.4, 1.6 to 3.6)	19 (2.5, 1.5 to 3.8)	5 (2.3, 0.8 to 5.3)	1.0
Any of above symptoms	92 (9.3, 7.6 to 11.3)	62 (8.1, 6.2 to 10.2)	30 (13.7, 9.4 to 19.0)	0.02
Advised to seek medical care given reporting any of above symptoms:				
No of women	92	62	30	—
Sought medical care as advised	87 (95.0, 87.8 to 98.2)	58 (94.0, 84.3 to 98.2)	29 (96.7, 82.8 to 99.9)	1.0

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abortions outside the formal healthcare setting, self report is the only possible method of follow-up. While self reporting could be subject to recall or social desirability bias, the short time period between the abortion and the collection of follow-up information should minimise recall bias. A previous large randomised controlled trial showed that self assessment of the outcome of medical abortion was non-inferior to clinical follow-up, indicating that women are capable of determining on their own whether or not their abortion has been successful.[23] Although judgment of the symptoms of potentially serious complications is subjective, and not all will actually be indicative of an adverse event, it is reassuring that virtually all women who reported experiencing such symptoms said they sought medical advice. It is also unlikely that women had much incentive to give inaccurate reports of adverse events or complications. WoW was their main source of advice during their abortion, and so women who reported problems tended to have communicated with the helpdesk.

Another important limitation is that we were unable to ascertain whether the treatment women received for potential adverse events was appropriate and necessary. Previous work has shown that rates of surgical intervention after medical abortion provided through online telemedicine vary widely by setting.[24] The surgical intervention rate of 4.5% that we found is similar to equivalent rates found in studies of medical abortion in the clinical setting (which typically range from 3% to 5%).[22] It is possible, however, that providers in countries where abortion is highly restricted might intervene inappropriately because of lack of experience or overcautious management. They could also cause further complications through unnecessary or inappropriate interventions, and we are unable to distinguish these from adverse events relating to the abortion itself (for example, surgical intervention could lead to the need for a blood transfusion). The rate of reported receipt of an antibiotic in our sample was higher than previous reports of receipt of intravenous antibiotics after medical abortion in a clinic.[21] We could not distinguish between antibiotics administered intravenously versus orally, the latter being much more common after medical abortion. Additionally, some healthcare professionals might provide oral antibiotics "just in case" or for an incidentally discovered urinary tract or sexually transmitted infection. Our rate of reported blood transfusion was also higher than in previous large studies of abortion in a clinic[21 25] but still low at less than 1%. We also lacked information on two other adverse events−−hospital admission and emergency room treatment.[21] Previous studies, however, have shown considerable overlap between these events and the receipt of blood transfusion or antibiotics,[26] both of which we were able to include.

Key strengths of our study include the large sample size and high follow-up rate, which is comparable with or, in some cases, better than studies of abortion within the formal healthcare setting.[27] Additionally, we included data on the entire population of women in the Republic and Northern Ireland who accessed medical abortion through online telemedicine. While we must acknowledge the limitations of necessary reliance on self reporting and incomplete follow-up, the questions we sought to answer about medical abortion provided outside the formal healthcare system in a setting where abortion is highly restricted cannot be dealt with by a randomised controlled trial, clinical trial, or prospective cohort study. We have drawn on the best available "real world" data to answer these important questions.

We consider that the rates of reported complications and successful abortion in our study might be conservative estimates. A previous study using telephone follow-up among a smaller sample of women who self sourced their own abortions using WoW shows that those to whom medications were sent but who did not spontaneously provide follow-up information by email or an online evaluation form were less likely to have experienced complications and more likely to have had a successful medical abortion.[6] This possibility must still be balanced against the biases discussed above. We are also unable to definitively identify gestational age at the time of abortion, and some women might have had higher gestational ages than they were willing to disclose or might have experienced delays in receipt of the medications. Thus, we might reasonably expect the reported rates of adverse events to be slightly higher than those reported in clinical studies of medical abortion,which generally include gestational ages up to a maximum of 7 or 9 weeks.[21 22 25 26] Moreover, a systematic review of the safety of regimens of medical abortion at home up to 8 weeks' gestation indicates average rates of transfusion of 0.1%, which although higher than for studies of medical abortion in a clinic, is still considered low.[22]

It is also important to view the rates of self reported adverse events shown in this study in the context of the other options available to women in the Republic and Northern Ireland who have an unwanted pregnancy. The complication rates we found are lower than the risk of equivalent complications during delivery in the UK.[28] They are also much lower than the equivalent risks associated with unsafe methods of abortion.[3] While some could also raise ethical questions about the provision of medications without formal in person consultation with a doctor, it is worth noting that similar models of telemedicine are used in the US to prescribe and dispense numerous other medications (with the exception of controlled substances)[29] and that both mifepristone and misoprostol are on the WHO list of essential medicines.[30] Additionally, one might view the provision of abortion medications by telemedicine as an ethical response to the unethical practice of criminalising women for choosing abortion. A growing body of literature documents the negative health impacts experienced by women denied a wanted abortion and forced to continue an unwanted pregnancy compared with those who were able to access an abortion.[31 32] In 2016, the United Nations Human Rights Council found Ireland in violation of its human rights obligations, stating that its abortion laws subject women to "suffering and discrimination."[33]

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Applicability

Our results might not be generalisable to all settings where women self source using online telemedicine. A recent review of the acceptability of self managed abortion in both legal and legally restricted contexts emphasises the role of local attitudes surrounding abortion on women's experiences.[34] Higher levels of education and medical knowledge as well as better access to healthcare compared with women in developing settings might mean that women in the Republic and Northern Ireland are more likely to use the medications correctly and to seek follow-up care. The stigma surrounding abortion experienced by Irish women, however, is considerable. Women in both countries face the possibility of prosecution and jail sentences if they are found to have conducted an abortion at home. Recently, several women in Northern Ireland have been charged after being reported to the authorities by housemates or medical staff.[35 36] Women who have had a self sourced abortion and those who have had an early pregnancy loss are clinically indistinguishable, but these events raise the concerning possibility of a chilling effect, whereby women might be reluctant to seek care for fear of being reported.

On average, women who access abortion through online telemedicine are older than women who access abortion in a clinic setting in the UK.[37] This difference might be because younger women are less likely to recognise their pregnancy sufficiently early to choose medical abortion if they have not been pregnant before, or they might be more likely to be able to travel abroad to access abortion because of parental assistance or fewer childcare commitments, or they might already be overseas pursuing higher education. Alternatively, older women might be more likely to have had abortions or deliveries before and thus be more confident about self managing their abortion at home. A previous study examining the decision making and experiences of Irish women who self sourced medical abortion through WoW indicated that some do so because they lack the financial or social resources to travel elsewhere.[11] Thus, our sample could be less socioeconomically advantaged than women who travel to access abortion care. The same study also showed, however, that others access abortion through online telemedicine because they prefer the privacy of using the medications at home, they lack the required documentation to travel, or they prefer medical abortion to a surgical alternative.[11]

Implications and conclusions

Our results have important implications for the perception of abortion self sourced outside the formal health system using online telemedicine. Firstly, they clearly show that not at all abortions taking place outside the law are unsafe abortions. Secondly, they add an important dimension to existing evidence that women themselves report abortion through online telemedicine as a positive experience with benefits for health and wellbeing.[11] Millions of women worldwide live in countries where self sourced medical abortion is a potentially lifesaving option, and strengthening services outside the formal healthcare setting could be a vital component of strategies to reduce maternal mortality from unsafe abortion. Finally, given the trajectory of abortion policy in Europe and the US, the visibility and importance of self sourced medical abortion will continue to increase. There are already reports of women seeking abortion outside the formal healthcare setting in the US.[38] Investigating women's experiences, preferences, outcomes, and unmet needs in various settings is a critical goal for future research.

Contributors: ARAA conceived the original research question, conducted the statistical analyses and prepared the tables and figures, and wrote the first draft of the manuscript. ARAA, RG, and JT contributed to the study design. RG and ID provided the de-identified data. ARAA and JT did the initial data interpretation. All authors contributed to final data interpretation, revised first and subsequent drafts critically for intellectual content, and approved the final manuscript. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ARAA is guarantor.

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Ethical approval: The University of Texas at Austin institutional review board reviewed and approved study protocols and declared the use of the de-identified database for research purposes exempt from full board review. All women consented to the anonymised use of their data at the aggregate level for research purposes.

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained

Data sharing: No additional data available.

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Appendix: Supplementary table

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Original Article
General gynaecology

Effectiveness, safety and acceptability of no-test medical abortion (termination of pregnancy) provided via telemedicine: a national cohort study

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Objective To compare outcomes before and after implementation of medical abortion (termination of pregnancy) without ultrasound via telemedicine.

Design Cohort analysis.

Setting The three main abortion providers.

Population or sample Medical abortions at home at ≤69 days' gestation in two cohorts: traditional model (in-person with ultrasound, n = 22 158) from January to March 2020 versus telemedicine-hybrid model (either in person or via telemedicine without ultrasound, n = 29 984, of whom 18 435 had no-test telemedicine) between April and June 2020. Sample (n = 52 142) comprises 85% of all medical abortions provided nationally.

Methods Data from electronic records and incident databases were used to compare outcomes between cohorts, adjusted for baseline differences.

Main outcome measures Treatment success, serious adverse events, waiting times, gestation at treatment, acceptability.

Results Mean waiting time from referral to treatment was 4.2 days shorter in the telemedicine-hybrid model and more abortions were provided at ≤6 weeks' gestation (40% versus 25%, $P < 0.001$). Treatment success (98.8% versus 98.2%, $P > 0.999$), serious adverse events (0.02% versus 0.04%, $P = 0.557$) and incidence of ectopic pregnancy (0.2% versus 0.2%, $P = 0.796$) were not different between models. In the telemedicine-hybrid model, 0.04% were estimated to be over 10 weeks' gestation at the time of the abortion; all were completed safely at home. Within the telemedicine-hybrid model, effectiveness was higher with telemedicine than in-person care (99.2% versus 98.1%, $P < 0.001$). Acceptability of telemedicine was high (96% satisfied) and 80% reported a future preference for telemedicine.

Conclusions A telemedicine-hybrid model for medical abortion that includes no-test telemedicine and treatment without an ultrasound is effective, safe, acceptable and improves access to care.

Keywords Abortion, induced [E04.520.050], ambulatory care facilities [N02.278.035], health planning [N03.349], mifepristone [D04.210.500.365.415.580], misoprostol [D23.469.700.660.500], pregnancy complications [C13.703], telemedicine [N04.590.374.800], termination of pregnancy.

Tweetable abstract Compelling evidence from 52 142 women shows no-test telemedicine abortion is safe, effective and improves care.

Linked article This article is commented on by A Glasier and L Regan, pp. 1475–1476 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.16740.

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Introduction

Improved access to care for induced abortion (termination of pregnancy) would deliver significant advantages for both healthcare systems and the women who use them. There is clear evidence that restricting access to abortion does not reduce abortion rates, it simply makes the procedure less safe.[1,2] Improving access is likely to benefit those who are

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most vulnerable,[3] especially in resource-poor settings or where care has to be self-funded. In its 2019 guideline on abortion care, the National Institute for Health and Care Excellence (NICE) stated that improving access to abortion was a key priority.[4]

Telemedicine, the use of information and communication technologies to improve patient outcomes by increasing access to care and medical information,[5] has been noted to decrease costs and increase convenience and safety.[6] It is an established service delivery model for abortion care in many settings[7] and it is recommended to improve access.[4] The COVID-19 pandemic required urgent action to ensure delivery of essential health services, with the Royal College of Obstetricians and Gynaecologists (RCOG) publishing guidelines to safeguard abortion care in the UK.[8] These guidelines profoundly changed the way medical such care is delivered in Great Britain. Prior to the emergence of COVID-19, all patients seeking medical abortion were required to attend in-person to receive an ultrasound scan and have mifepristone administered within the clinic. Under the new guidelines, consultations were encouraged to take place by telephone or video call; an ultrasound scan was required only if indicated. By 30 March 2020, all the governments in Great Britain had issued emergency legal orders to allow mifepristone to be used at home along with misoprostol up to 10 weeks' gestation.[9–11] These approvals permitted abortion providers to implement a fully telemedical service delivery model, including 'no test medical abortion' and direct-to-patient delivery of abortifacient medications.

Great Britain's new pathway for no-test medical abortion is unusual among existing models because it is fully remote: no clinic visit, tests or ultrasound scan are performed and both mifepristone and misoprostol are delivered by mail or collected from a clinic for use at home. This new service model thus presents an important opportunity to evaluate a potentially better way to provide medical abortion that could improve access and reduce the barriers posed by in-person care.[12] We examined and compared the effectiveness, safety and acceptability of medical abortion provided up to 10 weeks' gestation before and after the widespread implementation of no-test telemedicine.

Methods

Population and cohorts

The study population comprised all patients who accessed an early medical abortion (EMA) at the three largest abortion providers in England – British Pregnancy Advisory Service (BPAS), MSI Reproductive Choices (MSUK) and the National Unplanned Pregnancy Advisory Service (NUPAS) – 2 months before and after the service model change. Medical abortion is defined as the use of medications to terminate a pregnancy without primary surgical intervention and 'EMA' applies to these procedures, commonly within the first trimester.[13] The recommended EMA regimen uses the anti-progestogen mifepristone in an oral dose of 200 mg, then, after 24–48 hours, 800 mcg of the prostaglandin analogue misoprostol by the sublingual, vaginal or buccal route. In the UK, an additional dose of misoprostol is recommended if expulsion has not occurred 3–4 hours after the first dose.[8,14] Prior to telemedicine, patients would have returned to clinic to receive this, but in the new model the additional dose was provided in the treatment pack. Patients are advised to call the abortion provider on their 24-hour phone service in the event of any problems, if bleeding is unexpectedly light or heavy, if pregnancy symptoms fail to resolve quickly or if a low-sensitivity pregnancy test (1000 IU) is positive 3 weeks after using misoprostol. This information is conveyed in a variety of formats, including verbally at consultation, in writing and through on-line resources. Women are offered self-assessment with a low-sensitivity pregnancy test to determine success of the abortion, with instructions to report back to the abortion provider if there are any ongoing issues or a positive test, in line with national guidelines[15] and high quality evidence that self-assessment is safe, effective and preferred by women.[16]

Our dataset consisted of information on EMAs extracted directly from each provider's electronic records and included fully de-identified patient clinical and demographic characteristics. Each providers' clinical incident database was cross-referenced to patients in each cohort to determine rates of unsuccessful medical abortion and adverse events. All data were extracted 6 weeks after the end of the study period to ensure the reporting of complications was as complete as possible. We also consulted with regulators and national agencies to ensure that we accounted for incident reports made directly to them. The independent regulator of all health and social care services in England, the Care Quality Commission (CQC), confirmed that all cases reported directly to them through various routes, for example, statutory notifications and the central NHS database of patient safety incident reports (the National Reporting and Learning System [NRLS] and the Strategic Executive Information System [StEIS]), were known to the providers.

Two cohorts were defined. The 'traditional' cohort comprises all patients having an EMA between 1 January and 1 March 2020, prior to service model change. All patients in this cohort received an in-person assessment and an ultrasound scan, had mifepristone administered in the clinic, and were supplied with misoprostol for use at home. The 'telemedicine-hybrid' cohort comprises all patients accessing an EMA between 6 April and 30 June 2020, in a 2-month period after the service model change at each

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provider. Patients in this cohort were offered a consultation via phone or video call, during which an assessment of eligibility for treatment via telemedicine was made. Patients were deemed eligible for no-test medical abortion via telemedicine if they had a low risk of ectopic pregnancy and their self-reported last menstrual period (LMP) indicated a gestation of <10 weeks. Medications were then delivered to patients via post or were made available for collection from a clinic for use at home. Those deemed ineligible for no-test medical abortion via telemedicine had an in-person assessment with ultrasound as per the 'traditional' model. After the in-person assessment, medications for this group were then provided from the clinic for home use. The medications provided to both groups in the hybrid cohort were the same. Providers followed organisation-specific evidence-based policies informed by the RCOG[8] and associated decision aid[17] (Figures 1 and 2) and earlier RCOG and NICE guidelines.[14,15]

Outcome measures

Access

Waiting time and gestation at treatment were used to assess how the two models impacted access. Waiting time was defined as the interval from first contact with the abortion provider to when medication was dispensed (either in-person in clinic or posted). Gestation was recorded as that applicable on the date mifepristone was dispensed or provided. Analysis was of mean gestation and the proportion of abortions performed at ≤6 weeks' gestation.

Effectiveness

Effectiveness was defined as the proportion of medical abortions that were successful. Success was defined according to the MARE Guidelines as successful expulsion of an intrauterine pregnancy without need for surgical intervention,[13] using the sub-categories as listed in Table 2.

Safety

Safety was defined according to the proportions of medical abortions that involved one or more significant adverse events. We defined significant adverse events as haemorrhage requiring transfusion, significant infection requiring hospital admission, major surgery and death. We also examined the incidence of ectopic pregnancy and when it was diagnosed in the care pathway. For the analysis of ectopic pregnancies, we included all abortion consultations rather than all abortions provided because some patients with suspected ectopic pregnancies were referred to Early Pregnancy Assessment Units (EPAU) and did not proceed to abortion. All patients referred for further diagnostics (e.g. serial human chorionic gonadotropin [βhCG] monitoring) but who had no further treatment are included in the ectopic pregnancy group, although a proportion of these will be pregnancy of unknown locations (PULs), which includes failed early intrauterine pregnancies. We analysed the proportion of cases where treatment was reported to have occurred at ≥10 weeks' gestation in the telemedicine-hybrid cohort.

Acceptability

Given the constraints of delivering healthcare during COVID-19, it was not possible to follow up all patients to capture patient-reported outcomes. Two of the providers (BPAS and MSUK) collected patient feedback during the study period. Patients were invited to provide feedback 1–3 weeks after treatment, either by telephone using a structured interview tool (MSUK)[18] or using an online form (BPAS).[19] We analysed data on questions reporting on satisfaction, future preference and privacy. Although the questions were similar, only the MSUK survey included questions on the privacy of teleconsultation. All contact was by a non-clinician who had not been involved in the patient's care.

Analysis

The primary analysis was to assess whether the telemedicine-hybrid model was non-inferior to the traditional model. We compare effectiveness and safety in the two cohorts by testing the hypotheses that the telemedicine-hybrid model is less effective and has a higher complication rate.

We first compared patient demographic and clinical characteristics between the cohorts to assess the need to covariate-adjust our hypothesis tests for systematic differences in the two groups that might affect outcomes of abortion. All hypothesis tests were covariate adjusted for patient age, race/ethnicity, gestational age, parity and prior abortions using logistic regression and weighted risk differences.[20]

We evaluated effectiveness by testing the alternative hypothesis that the rate of successful medical abortion in the telemedicine-hybrid cohort is lower than in the traditional cohort using a covariate-adjusted test of difference in proportions. We also performed a Chi-square test to evaluate whether the distribution of unsuccessful abortion subcategories differed between the cohorts. We evaluated safety by testing the alternative hypothesis that significant adverse events occurred at higher rates in the telemedicine-hybrid cohort than in the traditional cohort using a covariate-adjusted hypothesis test for difference of proportions. We reported one-sided *P*-values for both of these tests. We also evaluated whether the prevalence of ectopic pregnancies managed before EMA and after EMA were different between the traditional and telemedicine-hybrid cohorts using Chi-square difference of proportion tests.

The secondary analysis was to compare effectiveness and safety of medical abortion for patients who received

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Figure 1. Summary of early medical abortion care management during COVID-19 pandemic (adapted with permission from RCOG Coronavirus [COVID-19] Infection and Abortion Care – Information for Healthcare Professionals[8]).

fully remote no-test telemedicine versus in-person care in the telemedicine-hybrid cohort, primarily to assess whether any differences between the cohort service models were driven by one particular group. We performed covariate-adjusted hypothesis tests under the null hypothesis of equal effectiveness and equal rates of significant adverse events in the telemedicine versus in-person groups.

All analyses were performed using R, version 3.6.2 (R Foundation for Statistical Computing, c/o Institute for Statistics and Mathematics, Vienna, Austria). Statistical significance was defined using an alpha level of 0.05.

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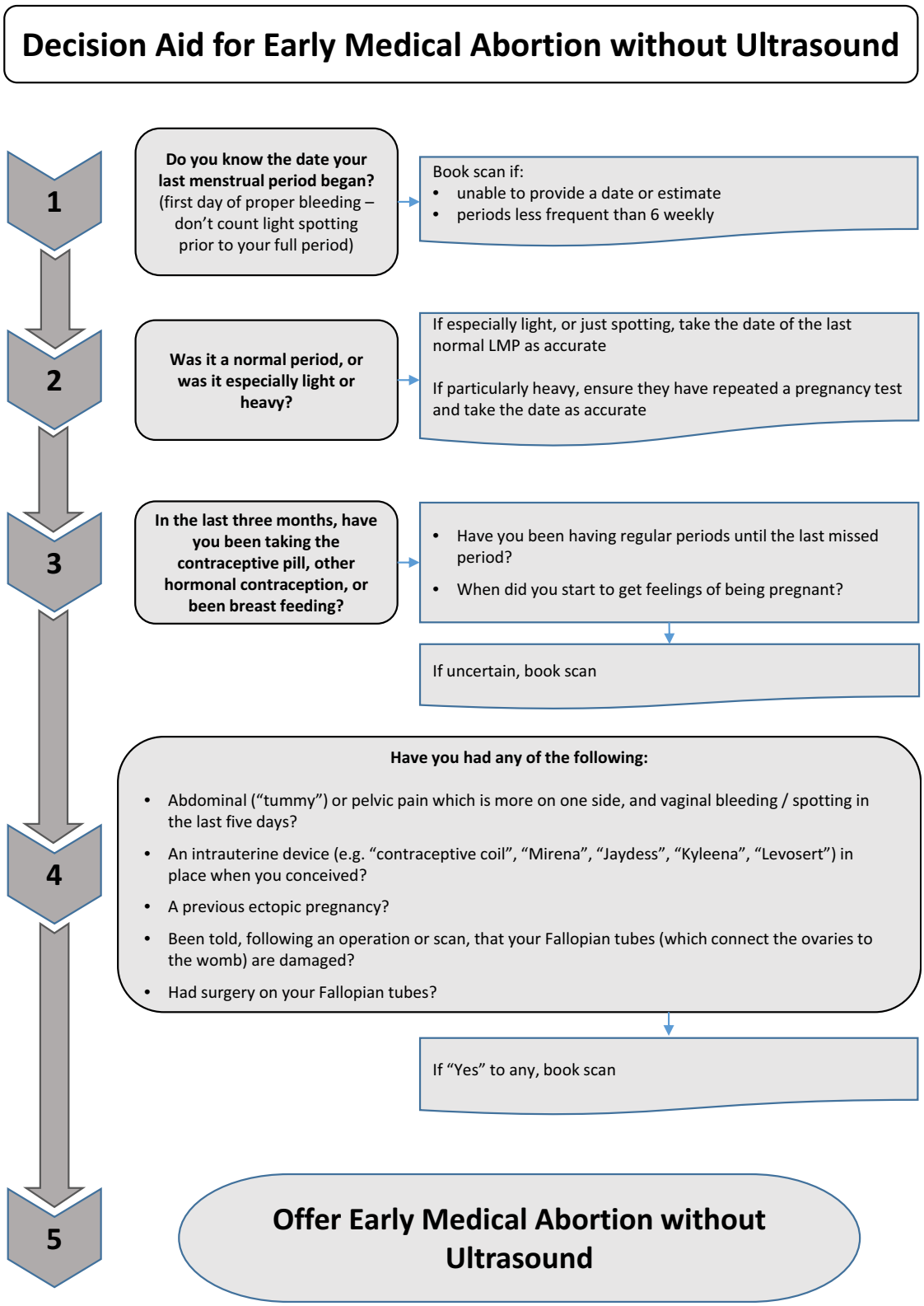

Figure 2. Decision aid for early medical abortion without ultrasound (adapted with permission from RCOG Coronavirus (COVID-19) infection and abortion care – information for healthcare professionals; 2020-06-04-decision-aid-for-early-medical-abortion-without-ultrasound.pdf [rcog.org.uk][17])

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Ethics approval

The study was reviewed by the Institutional Review Board (IRB) at the University of Texas at Austin, and a determination was made that the research did not meet the criteria for human subject research as defined in the Common Rule (45 CFR 46) or FDA Regulations (21 CFR 56). Each provider ensured compliance with their own internal ethics and governance systems. This study is classed as service evaluation by the NHS Health Research Authority[21] and therefore did not require review by an NHS Research Ethics Committee (REC).[22] The principles of the STROBE statement, and the MARE supplement, were followed.[13] Patients were not involved in the development of the study.

Results

In total, 52 142 medical abortions were provided during the study period: 22 158 in the traditional cohort and 29 984 in the telemedicine-hybrid cohort. Among those that took place in the telemedicine-hybrid cohort, 18 435 (61%) were provided via telemedicine and 11 549 (39%) in-person. Our sample represents 85% of the total number of medical abortions performed in England and Wales during the study period.[23] The clinical and demographic characteristics of patients in the two cohorts are described in Table 1.

Table 1. Clinical and demographic characteristics in the traditional and telemedicine-hybrid cohorts (n = 52 142). n (%)

Patient characteristics	Traditional (n = 22 158)	Telemedicine-hybrid (n = 29 984)	P-value
Mean gestational age in weeks (SD)	6.4 (1.3)	6.0 (1.4)	<0.001
Gestational age at treatment*			
≤6 weeks	5582 (25.2)	11 947 (39.8)	<0.001
>6 weeks	16 576 (74.8)	18 037 (60.2)	
Mean age in years (SD)	27.8 (6.6)	28.5 (6.7)	<0.001
Ethnicity			
Asian	2038 (9.2)	2652 (8.8)	<0.001
Black	1656 (7.5)	2282 (7.6)	
Multiracial	1004 (4.5)	1361 (4.5)	
White	15 840 (71.5)	20 910 (69.7)	
Other	489 (2.2)	638 (2.1)	
Unknown	1131 (5.1)	2141 (7.1)	
Previous abortions			
0	13 098 (59.1)	16 741 (55.8)	<0.001
1+	9060 (40.9)	13 243 (44.2)	
Parity			
0	10 133 (45.7)	11 741 (39.2)	<0.001
1+	12 025 (54.3)	18 243 (60.8)	
Mean waiting time in days (SD)*	10.7 (19.9)	6.5 (13.5)	<0.001

*After checking for normality, these variables were non-parametric and therefore two-sample Wilcoxon tests were used.

Access

Mean waiting time to treatment declined from 10.7 days (SD 19.9) in the traditional pathway to 6.5 days (SD 13.5) in the telemedicine-hybrid cohort ($P < 0.001$). Mean gestational age at treatment also declined in the telemedicine-hybrid cohort, resulting in 40% of abortions performed at 6 weeks' gestation or less versus 25% in the traditional cohort ($P < 0.001$).

Effectiveness

Rates of successful medical abortion were high under both service delivery models (Table 2) – 98.2% in the traditional cohort versus 98.8% in the telemedicine-hybrid cohort. We found no evidence of a lower success rate with the telemedicine-hybrid pathway ($P > 0.999$). The distribution of the different sub-categories of unsuccessful medical abortion did not differ between the cohorts ($P = 0.268$).

Safety

Significant adverse events in both cohorts were rare (Table 3). Haemorrhage requiring transfusion was reported in eight (0.04%) cases in the traditional cohort and in seven (0.02%) cases in the telemedicine-hybrid cohort. No cases of significant infection requiring hospital admission, major surgery or death were reported. We found no evidence that significant adverse events were higher in the telemedicine-hybrid cohort ($P = 0.557$).

The overall incidence of ectopic pregnancy was equivalent in both cohorts – 39 (0.2%) in the traditional cohort and 49 (0.2%) in the telemedicine-hybrid cohort, $P = 0.796$ (Table 4). The proportions managed after EMA were not significantly different between the cohorts (0.01% in the traditional pathway and 0.03% in the telemedicine-hybrid pathway, $P = 0.123$). There were 11 cases (0.04%) in the telemedicine-hybrid cohort where the gestational age after abortion was reported by the patient or an admitting hospital as being greater than the expected 10 weeks. In all these cases, the abortion was completed at home without additional medical complications.

Acceptability

Patient-reported outcome data were available from 2453 respondents: 96% were 'satisfied' or 'very satisfied' with their care, or rated their experience as 'good' or 'very good'; 80% reported that they would choose telemedicine in the future or that it was their preferred option, with 13% choosing in-person care and the remainder being unsure. No patient reported that they were unable to consult in private using teleconsultation (n = 1243).

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Table 2. Comparison of effectiveness of medical abortions conducted in the traditional and telemedicine-hybrid cohorts (n = 52 142). n (%)

Outcome	Traditional n = 22 158	Telemedicine-hybrid n = 29 984	P-value
Successful medical abortion	21 769 (98.2)	29 618 (98.8)	1.0
Unsuccessful medical abortion	389 (1.8)	366 (1.2)	
Continuing pregnancy: treated with surgical management	161 (0.7)	150 (0.5)	0.268
Continuing pregnancy: opted to continue or unknown	3 (0.01)	8 (0.03)	
Retained products treated with surgical management (ERPC)	225 (1.0)	208 (0.7)	

As explained in the methods section, the P-value for successful medical abortion is the co-variate-adjusted P-value (i.e. all differences in patient clinical and demographic characteristics, including gestational age, are controlled for) and was calculated using a hypothesis test where the null hypothesis is that the traditional cohort has the same effectiveness rate as the telemedicine-hybrid cohort and the alternative hypothesis is that the traditional cohort has a higher effectiveness rate than the telemedicine-hybrid cohort. The P-value for unsuccessful medication abortion is the Chi-square test of whether the distribution of types of failure differ between the cohorts.

Table 3. Comparison of significant adverse events following medical abortions conducted in the traditional and telemedicine-hybrid cohorts (n = 52 142). n (%)

Outcome	Traditional (n = 22 158)	Telemedicine-hybrid (n = 29 984)	P-value
Haemorrhage requiring transfusion	8 (0.04)	7 (0.02)	0.557
Infection requiring hospital admission	0 (0.0)	0 (0.0)	
Major surgery	0 (0.0)	0 (0.0)	
Death	0 (0.0)	0 (0.0)	

As explained in the methods section, the P-value was calculated using a hypothesis test where the null hypothesis is that the traditional cohort has the same rate of adverse events as the telemedicine-hybrid cohort and the alternative hypothesis is that the traditional cohort has a lower rate of adverse events than the telemedicine-hybrid cohort.

Table 4. Significant outcomes among patients presenting for medical abortion in the traditional and telemedicine-hybrid cohorts (n = 52 218). n (%)

Outcome	Traditional (n = 22 197)	Telemedicine-hybrid (n = 30 021)	P-value
Ectopic managed pretreatment	37 (0.17)	39 (0.13)	0.796
Ectopic managed post-treatment	2 (0.01)	10 (0.03)	0.123
Gestational age later than expected*	0 (0.0)	11 (0.04)	N/A

The column numbers include patients who presented for an EMA but did not receive one because their ectopic pregnancy was identified pretreatment.
*The column numbers for the gestational age later than expected category are the same as those in Table 3, (all EMAs performed in the two cohorts, i.e. n = 52 142).

Secondary outcome measures

Comparison of clinical outcomes for the telemedicine versus in-person groups in the telemedicine-hybrid cohort is shown in Tables S1–S3. Rates of successful medical abortion were higher in the telemedicine group (99.2% versus 98.1%, $P < 0.001$), but rates of significant adverse outcomes were not significantly different between the two groups – three (0.02%) for telemedicine versus four (0.03%) for in-person ($P = 0.532$).

Discussion

Main findings

We found that no-test medical abortion via telemedicine without routine ultrasound up to 10 weeks' gestation is an effective, safe and acceptable service model. Clinical outcomes with telemedicine are equivalent to in-person care and access to abortion care is better, with both waiting times and gestational age at the time of the abortion significantly reduced. Although gestation could be influenced by different behaviour during the pandemic, resulting in earlier presentation, in most other areas of healthcare, access has been severely impacted, with waiting times increasing substantially,[24] and so reductions in both seem relevant. Even small reductions in waiting time are significant – NICE noted that a reduction of 1 day resulted in annual savings of £1.6 million to the health services in England owing to reduced complications and fewer needing to opt for a surgical abortion.[4] Further evidence that the new telemedicine-hybrid model improves access comes from a study showing that the rate of women seeking abortion medication outside the formal healthcare setting was significantly reduced in the UK following its implementation.[25] The implication is that those previously too vulnerable to

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attend in-person have been able to access care through telemedicine, potentially benefitting from the safeguarding, counselling and contraceptive services provided by regulated providers.[26]

Our study confirms previous literature that medical abortion is safe and effective. Our findings of low rates of significant complications and failure are similar to those reported from other high quality studies.[27,28] The slight increase in effectiveness we observed in the group that received telemedicine – even after controlling for lower average gestational age compared with the in-person group – may be due to the ability of patients to control better the time at which they took the medication.

The telemedicine-hybrid model resulted in very low rates of undiagnosed ectopic pregnancy and later than expected gestations. Although the rate of ectopic pregnancy in the general population in the UK and USA is reported as 1–2%,[29,30] the rate reported among patients having a termination of pregnancy is 10 times lower,[31] which is consistent with our findings. Ultrasound is not used to screen for ectopic pregnancy in the general population – it is only used where signs and symptoms suggest a need.[30] Routine screening of symptom-free women is associated with a high false-positive rate when the prevalence of ectopic pregnancy is low, as is the case in women seeking abortion, and therefore it is unlikely there would be significant benefits.[32] There is no clinical justification for maintaining this inconsistency in care between women wishing to continue their pregnancies and those choosing EMA.[33,34]

However, given that over 200 000 people access abortion care each year in the UK alone, some will inevitably have an asymptomatic ectopic pregnancy and so will proceed with having mifepristone and misoprostol either through telemedicine or after a false-negative scan. The essential issue for safety is that these are detected prior to causing harm rather than prior to beginning the medical abortion treatment; treatment with mifepristone and misoprostol in itself will have no effect on an underlying ectopic pregnancy. Indeed, the reduction in waiting times afforded by the telemedicine model may facilitate earlier detection than traditional pathways where women present later or are sent away to give additional time to visualise an intrauterine pregnancy on scan. Proceeding with early medical abortion without a scan may permit earlier diagnosis of a developing ectopic pregnancy owing to increased surveillance and index of suspicion, for example where there is minimal bleeding after misoprostol.[8,15]

The proportion of cases where gestational age was later than expected based on LMP was low, as might have been expected given the evidence that women can determine the gestational age of their pregnancy with reasonable accuracy by LMP alone.[33] Nevertheless, inadvertent treatment of gestations over 10 weeks is inevitable and, consistent with our findings, the consequences for most are unlikely to be medically significant.[35] The 10-week gestation limit in the English government's approval order is arbitrary and is not based on evidence of safety or effectiveness. The Scottish government did not stipulate a limit, leaving the decision to the discretion of the clinician in consultation with their patient. Moreover, the reported success of self-managed terminations of pregnancy at >12–24 weeks' gestation is 93%, with safety similar to that expected in earlier gestations.[36,37]

Strengths and limitations

Although the study is not a clinical trial, we were able to evaluate the outcomes of both the telemedicine-hybrid and traditional in-person services as they operate in the real world, and we were able to adjust for key covariates. A key strength of the study is the generalisability of our findings, given that our sample included 85% of all medical abortions provided in England and Wales during the study period.

The main limitation of this study is that we were unable actively to follow up patients after their abortion. There is a potential gap in the consistency of reporting incidents, due to some complications not meeting the threshold of serious incidents, multiple routes of entry into the NHS and informal communication between the NHS and abortion providers. Although it is possible that some patients presented to other providers and a significant adverse event was not reported in our dataset, the risk management and reporting systems within the NHS are well defined, with serious incidents being routinely shared. The governing body of the NHS in England alerted all commissioners of the need to report incidents relating to telemedicine and there were review meetings of key stakeholders to ensure compliance. No additional cases were identified from regulators that were not already recorded by the providers' clinical incident processes. More importantly, there is no reason that any under-reporting would be systematically more likely in either cohort to introduce bias. Although patient behaviour may have been altered in the pandemic, it seems unlikely patients would not have reported problems to their provider given that there is immediate access to help via 24-hour telephone services. It is also possible that with NHS acute services (e.g. early pregnancy units) harder to access, patients would be more likely to engage with their abortion provider first. Finally, evidence from an equivalent population to ours in Scotland gave almost identical results. This was a smaller cohort study that followed up all patients (n = 663) and cross-checked NHS hospital records (reporting successful medical abortion 98%, haemorrhage requiring transfusion 0%, infection requiring hospital admission 0%, choosing telemedicine again in future 71%).[39]

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Interpretation

NICE conducted a systematic review and recommended using telemedicine to improve access to medical abortion care.[3] Several models for using telemedicine to facilitate medical abortion have been described but most existing trials are small, and many required attendances to have medicines administered, an ultrasound scan or blood tests.[7,38] Our study is the first to assess a real-world no-test telemedicine abortion care pathway in a national population. This new national model demonstrates how a permissive framework for medical abortion can deliver significant quality improvements to those needing to access abortion care.

Conclusion

This large study of 52 142 medical abortions demonstrates that incorporating no-test telemedicine into the care pathway is not inferior to the traditional pathway where all patients are seen in person and have an ultrasound scan. There are advantages – waiting times and gestation at abortion are reduced and it is highly rated by patients. There was no evidence of worse outcomes in failure rate, haemorrhage, need for surgery or failure to detect ectopic pregnancy. In the 0.04% of cases where the abortion appeared to have been provided at over 10 weeks' gestation, these were all completed at home without additional medical complications. Given the advantages of improving access to care, especially in vulnerable groups and in resource-poor healthcare systems or where patients have to fund their own care, the evidence is compelling that no-test telemedicine should become routine in the provision of abortion care.

Disclosure of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work beyond that described under the roles held by each individual. AA – Member of the Council of the British Society of Abortion Care Providers (BSACP); NG and JS – nothing to disclose; PL – Co-author/committee member of national guidelines cited in this paper from RCOG and NICE; member RCOG abortion taskforce; council member of British Society of Abortion Care Providers (BSACP); Medical Director of BPAS; JL – Co-author/committee member of national guidelines cited in this paper from RCOG and NICE; co-chair of RCOG Abortion Taskforce and British Society of Abortion Care Providers (BSACP); primary employment includes work as termination of pregnancy care provider as a consultant gynaecologist and medical director. Completed disclosure of interests forms are available to view online as supporting information.

Contribution to authorship

AA – Initial concept, developing study protocol, data analysis, writing first draft and subsequent revisions, verification of data. Overall responsibility for data analysis and principal investigator. Guarantor; NG – Developing study protocol, revision of draft paper. Overall responsibility for conduct of study including data collection at NUPAS; PL – Initial concept, developing study protocol, writing first draft and subsequent revisions. Overall responsibility for conduct of study including data collection at BPAS; JL – Initial concept, developing study protocol, writing first draft and subsequent revisions, co-ordination and liaison. Overall responsibility for conduct of study including data collection at MSUK; JS – Data analysis including statistical advice, writing first draft and subsequent revisions, verification of data.

Details of ethics approval

The study was reviewed by the Institutional Review Board (IRB) of the University of Texas at Austin and a determination was made on 21 April 2020 that the research did not meet the criteria for human subjects research as defined in the Common Rule (45 CFR 46) or FDA Regulations (21 CFR 56). Each provider ensured compliance with their own internal ethics and governance systems. The principles of the STROBE statement, and the MARE supplement, were followed.[13]

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Data-sharing statement

The collated datasets, which include participant data with anonymised identifiers, are held by AA at the University of Texas. Consideration will be given to sharing this with bona fide researchers on application. The original data reside with the co-authors' own institutions. Although the data are de-identified, some relate to very rare events and could therefore result in identification. Therefore data on complications, and data arising from clinical incident reports, will be subject to the same access restrictions as those of the organisation supplying it.

Transparency statement

The authors affirm that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Data availability

Data available on request due to privacy/ethical restrictions.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Patient clinical and demographic characteristics in the in-person versus telemedicine groups for the telemedicine-hybrid cohort (n = 29 984). Number (%).

Table S2. Comparison of effectiveness of medical terminations of pregnancy conducted in the in-person versus telemedicine groups for the telemedicine-hybrid cohort (n = 29 984). n (%).

Table S3. Comparison of significant adverse events following medical terminations of pregnancy in the in-person versus telemedicine groups for the telemedicine-hybrid cohort (n = 29 984). n (%).

Video S1. Author insights. ■

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ACOG | Clinical

The American College of Obstetricians and Gynecologists

Medication Abortion Up to 70 Days of Gestation

Practice Bulletin | Number 225 | October 2020

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The following supplemental information has been issued for this document:

View the Clinical Practice Update, Rh D Immune Globulin Administration After Abortion or Pregnancy Loss at Less Than 12 Weeks of Gestation

View the March 2024 Practice Advisory

View the January 2023 Practice Advisory

Number 225 (Replaces Practice Bulletin Number 143, March 2014. Reaffirmed 2023)

Committee on Practice Bulletins—Gynecology and the Society of Family Planning. This Practice Bulletin was developed jointly by the Committee on Practice Bulletins—Gynecology and the Society of Family Planning in collaboration with Mitchell D. Creinin, MD, and Daniel A. Grossman, MD.

GBP-PET00037

ABSTRACT: Medication abortion, also referred to as medical abortion, is a safe and effective method of providing abortion. Medication abortion involves the use of medicines rather than uterine aspiration to induce an abortion. The U.S. Food and Drug Administration (FDA)-approved medication abortion regimen includes mifepristone and misoprostol. The purpose of this document is to provide updated evidence-based guidance on the provision of medication abortion up to 70 days (or 10 weeks) of gestation. Information about medication abortion after 70 days of gestation is provided in other ACOG publications [1].

Background

Epidemiology

An estimated one in four women in the United States will have an abortion in her lifetime. In 2017, an estimated 60% of abortions in the United States occurred at or before 10 weeks of gestation and medication abortion comprised 39% of all abortions [2]. Between 2006 and 2015, there was a shift in the timing of abortion, with abortions taking place at earlier gestational ages; this is likely due, in part, to availability of medication abortion [3]. From 2014 to 2017, the number of nonhospital facilities that provided medication abortion increased by 25% [2]. A recent survey of American College of Obstetricians and Gynecologists (ACOG) Fellows and Junior Fellows found that 14% had provided medication abortion in the prior year [4].

Medication Abortion

GBP-PET00038

The medication abortion regimen supported by major medical organizations nationally and internationally includes two medications, mifepristone and misoprostol [5] [6]. If mifepristone is unavailable, then a misoprostol-only regimen is an acceptable alternative [5]. Mifepristone is a selective progesterone receptor modulator that binds to the progesterone receptor with an affinity greater than progesterone itself but does not activate the receptor, thereby acting as an antiprogestin [7]. Mifepristone's known actions on a uterus during pregnancy include decidual necrosis, cervical softening, and increased uterine contractility and prostaglandin sensitivity [8] [9]. Misoprostol is a prostaglandin E1 analogue that causes cervical softening and uterine contractions. It is approved by the FDA for oral administration to prevent gastric ulcers in individuals who take anti-inflammatory drugs on a long-term basis, and it is included in the FDA-approved labeling of mifepristone for use in abortion [10].

The FDA currently restricts mifepristone access under the risk evaluation and mitigation strategy (REMS) program, which includes a requirement that the drug be "dispensed to patients only in certain health-care settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber" [10]. However, the REMS restrictions for mifepristone do not make the care safer, are not based on medical evidence or need, and create barriers to clinician and patient access to medication abortion [4] [11] [12]. The American College of Obstetricians and Gynecologists advocates the removal of REMS restrictions for mifepristone [12].

Clinical Considerations and Recommendations

How should patients be counseled about abortion methods?

GBP-PET00039

Only when patients have considered their options and decided to have an abortion does the discussion about the different methods become clinically relevant. Patients who choose abortion should be counseled about all methods available as well as the risks, advantages, disadvantages, and the different features of these options **5** **6** . Most patients who initially are unsure about the method will have some preference after counseling **13** . Generally, patients are satisfied with the method they choose **12** **14** **15** . Patients who choose medication abortion tend to do so because of a desire to avoid a procedural intervention; a perception that medication abortion is safer, more natural, and private compared with uterine aspiration; or a combination of these reasons **16** . Compared with uterine aspiration, medication abortion takes longer to complete and requires more active patient participation as the pregnancy expels outside of a clinical setting. The uterine aspiration procedure for a first-trimester abortion takes place most commonly in one visit, is slightly more effective, and allows for direct assessment of pregnancy tissue by the clinician.

What information and counseling should be provided to patients who are considering medication abortion?

Eligibility and Contraindications

Most patients at 70 days of gestation or less who desire abortion are eligible for a medication abortion. There are medical conditions for which a medication abortion may be preferable to uterine aspiration. Such examples include uterine fibroids that significantly distort the cervical canal or uterine cavity **17** **18** , congenital uterine anomalies **19** , or introital scarring related to infibulation **20** . Patients with asthma are candidates for medication abortion because misoprostol does not cause bronchoconstriction and actually acts as a weak bronchodilator **21** . Multiple gestation pregnancy is not a contraindication; patients with twin gestations can be treated with the same regimens as those with singleton gestations **22** .

GBP-PET00040

Medication abortion is not recommended for patients with any of the following: confirmed or suspected ectopic pregnancy, intrauterine device (IUD) in place (the IUD can be removed before medication abortion), current long-term systemic corticosteroid therapy, chronic adrenal failure, known coagulopathy or anticoagulant therapy, inherited porphyria, or intolerance or allergy to mifepristone or misoprostol **23** . Patients with significant comorbidities may still have a medication abortion but may need more monitoring during the process depending on the stability of the conditions. The safety of medication abortion in patients with anemia is unknown because studies have excluded patients with anemia who have hemoglobin levels of less than 9.5 or 10 g/dL. Although the transfusion rates associated with medication abortion are low (less than 0.1%), they exceed those reported for uterine evacuation procedures in early pregnancy (0.01%) **24** **25** . Patients may also not be good candidates for medication abortion if they are unable or unwilling to adhere to care instructions, desire quick completion of the abortion process, are not available for follow-up contact or evaluation, or cannot understand the instructions because of comprehension barriers.

What to Expect

Most patients who have a medication abortion will experience bleeding and cramping, which are necessary for the process to occur. Patient counseling should emphasize that bleeding likely will be much heavier than menses (and potentially with severe cramping).

Adverse effects can occur after mifepristone administration but are more typically experienced after misoprostol administration. Adverse effects commonly associated with misoprostol use include nausea (43–66%), vomiting (23–40%), diarrhea (23–35%), headache (13–40%), dizziness (28–39%), and thermoregulatory effects such as fever, warmth, hot flushes, or chills (32–69%) **26** **27** **28** **29** . The incidence of each adverse effect varies by regimen used, the dose and route of administration of the prostaglandin analogue, and the gestational age.

Patient counseling before medication abortion should include discussion of when patients should contact their clinician in the case of heavy bleeding (soaking more than two maxi pads per hour for 2 consecutive hours) and when to access urgent intervention **5** **6** **30** . In rare cases, patients who undergo medication abortion may need to obtain an additional intervention, such as uterine aspiration. If the prescribing clinician does not perform the intervention, it is medically appropriate to provide a referral. In patients who receive mifepristone and vaginal misoprostol, the need for intervention within the first 24 hours of treatment is rare, occurring in 0.2% of patients **31** . The need for intervention is based on how the patient is feeling and whether the bleeding seems to be slowing. For patients with heavy bleeding, a baseline hemoglobin or hematocrit, if known, may also influence when to seek urgent care. Overall, less than 1% of patients will obtain an emergency intervention for excessive bleeding **13** **14** **15** **32** , and the need for blood transfusion is rare (0.1% of patients or less) **24** **33** . Should a rare medical emergency arise, patients should be advised to seek care at the closest emergency facility.

Teratogenicity and Ongoing Pregnancy

Before undergoing medication abortion, patients should be counseled regarding the teratogenicity of misoprostol in the event of an unsuccessful medication abortion. All patients with a continuing pregnancy after using mifepristone and misoprostol should be provided with all pregnancy options and a thorough discussion of the risks and benefits of each. Most individuals with a continuing pregnancy opt to complete the abortion, but patients should be supported in their choice of how to proceed. No evidence exists to date of a teratogenic effect of mifepristone **34** . However, misoprostol can result in congenital anomalies, such as limb defects with or without Möbius' syndrome (ie, facial paralysis), when used during the first trimester **35** **36** **37** **38** **39** . Because misoprostol is the common agent used with every medication abortion regimen, clinicians should counsel all patients regarding potential teratogenic effects.

In the very rare case that patients change their mind about having an abortion after taking mifepristone and want to continue the pregnancy, they should be monitored expectantly **40** . There is no evidence that treatment with progesterone after taking mifepristone increases the likelihood of the pregnancy continuing **41** **42** . However, limited available evidence suggests that use of mifepristone alone without subsequent administration of misoprostol may be associated with an increased risk of hemorrhage **43** .

What evaluation and ancillary testing are needed before a medication abortion?

GBP-PET00042

Before medication abortion is performed, the clinician should confirm pregnancy and estimate gestational age. For patients with regular menstrual cycles, a certain last menstrual period within the prior 56 days, and no signs, symptoms, or risk factors for ectopic pregnancy, a clinical examination or ultrasound examination is not necessary before medication abortion. Rh testing is recommended in patients with unknown Rh status before medication abortion, and Rh D immunoglobulin should be administered if indicated **44** . In situations where Rh testing and Rh D immunoglobulin administration are not available or would significantly delay medication abortion, shared decision making is recommended so that patients can make an informed choice about their care. Other laboratory evaluations are not routinely indicated but may be required by local and state laws **2** . Preoperative assessment of hemoglobin or hematocrit is indicated only when anemia is suspected.

Most abortion care globally is provided without ultrasound examination. Although most U.S.-based studies have used ultrasonography to confirm gestational age and intrauterine location of the pregnancy, more recent evidence has shown that a patient's certain last menstrual period when within the prior 56 to 63 days is accurate **45** **46** **47** **48** . In one study, use of certain last menstrual period alone would have resulted in medication abortion being provided to only 26 of 3,041 (0.8%) patients with pregnancies beyond 70 days of gestation **45** .

A potential concern when providing early abortion services is the possibility of an undiagnosed ectopic pregnancy. The overall ectopic pregnancy rate in the U.S. general population is low and declining and is approximately 6 per 1,000 pregnancies among insured patients and 14 per 1,000 among patients who receive Medicaid **49** **50** . However, in studies of patients who seek abortion, ectopic pregnancy rates generally are lower. A U.S. study of uterine evacuation procedures performed at less than 6 weeks of gestation found the ectopic pregnancy rate to be 5.9 per 1,000 pregnancies **51** at a time when the national rate was three times higher **52** . The largest published study of first-trimester medication abortion patients involved 16,369 patients with pregnancies of 49 days of gestation or less and yielded a calculated ectopic pregnancy rate of 1.3 per 1,000 pregnancies **53** . Although ectopic pregnancy among individuals who seek early abortion is rare, patients with a medical history of ectopic pregnancy, medical risk factors (prior tubal surgery, pregnancy with progestin-only or IUD contraception use) or symptoms (ie, unilateral pain, vaginal bleeding) suggestive of ectopic pregnancy should have pretreatment clinical evaluation, which may include ultrasonography **5** **6** .

GBP-PET00043

Most patients with clinical indications for an ultrasound examination before medication abortion can be initially screened with transabdominal ultrasonography, reserving transvaginal ultrasonography for situations in which further clarification is required **54** **55** . If ultrasonography is medically indicated, transabdominal ultrasonography is sensitive for diagnosing the presence or absence of a gestational sac in patients who are not obese **54** . A randomized trial that compared the use of transabdominal ultrasonography with transvaginal ultrasonography for eligibility assessment before medication abortion found that 80% of patients who received initial transabdominal ultrasonography did not require further testing to proceed with medication abortion, thus avoiding use of more invasive and resource-intensive screening with transvaginal ultrasonography **55** .

Recommendations on whether Rh D immune globulin should be given to patients before medication abortion in early pregnancy are primarily based on expert opinion because available evidence is limited **6** **56** . Rh D alloimmunization that is left undiagnosed and untreated can lead to significant perinatal morbidity and mortality in future pregnancies **57** . And, guidelines from ACOG and various other major medical societies include recommendations for Rh D immune globulin prophylaxis for Rh D-negative patients undergoing medication abortion within the first 12 weeks of gestation **44** **58** **59** **60** . For patients undergoing medication abortion before 10 weeks of gestation, some experts recommend against routine Rh testing and anti-D prophylaxis **6** or advise that forgoing Rh typing and Rh prophylaxis can be considered **61** . Research regarding Rh alloimmunization during early pregnancy continues to evolve **62** . However, based on currently available indirect evidence and the theoretical risk of Rh D alloimmunization in future pregnancies, ACOG recommends Rh D immune globulin prophylaxis for Rh D-negative patients undergoing medication abortion. In situations where Rh testing and anti-D prophylaxis are not available or would significantly delay medication abortion, shared decision making is recommended so that patients can weigh the benefits and risks of their options and make an informed decision about their care.

What regimens are used for medication abortion, and how do they compare in effectiveness for treatment?

GBP-PET00044

Combined mifepristone–misoprostol regimens are recommended as the preferred therapy for medication abortion because they are significantly more effective than misoprostol-only regimens. If a combined mifepristone–misoprostol regimen is not available, a misoprostol-only regimen is the recommended alternative **5** **63** **64** . Mifepristone is approved by the U.S. FDA to be used with misoprostol for medication abortion through 70 days of gestation **23** , but evidence also exists to support use with more advanced gestations **1** **5** . The recommended medication abortion regimens are listed in **Table 1** . With all regimens, the mifepristone dose is the same: 200 mg taken orally. The misoprostol portion of the regimen is more variable in terms of dose, route, and timing. Oral use of misoprostol is not recommended because it may result in lower overall efficacy **65** . In general, patients prefer a shorter interval between the two medications **66** . These regimens have been extensively studied and are similarly safe and effective **5** . Offering options provides patients with flexibility in the timing of abortion and the ability to avoid possible adverse effects related to the misoprostol route. Gastrointestinal adverse effects are less common when misoprostol is administered vaginally as compared with regimens that use oral, buccal, or sublingual misoprostol **65** **67** . Buccal and sublingual administration cause similar adverse effects, with the sublingual route associated with a higher rate of chills **68** .

Table 1. Medication Abortion Regimens Up to 70 Days of Gestation

Regimen	Mifepristone Dose	Misoprostol Dose	Interval Between Drugs
Preferred			
Combination, FDA-approved*	200 mg (orally)	800 micrograms (buccally)	24–48 h
Combination, WHO recommended†	200 mg (orally)	800 micrograms (vaginally, sublingually, or buccally)	24–48 h
Alternative			
Misoprostol only	N/A	800 micrograms (vaginally, sublingually, or buccally)	Repeat every 3 h for up to 3 doses‡

Abbreviations: h, hours; FDA, U.S. Food and Drug Administration; N/A, not applicable; WHO, World Health Organization.

*U.S. Food and Drug Administration. Mifeprex (mifepristone) information. Postmarket drug safety information for patients and providers. Silver Spring, MD: FDA; 2018. Available at: https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111323.htm. Retrieved March 3, 2020.

†World Health Organization. Medical management of abortion. Geneva: WHO; 2018. Available at: https://apps.who.int/iris/bitstream/handle/10665/278968/9789241550406-eng.pdf?ua=1. Retrieved March 3, 2020.

‡Although studies typically use no more than three doses for the initial treatment regimen, the World Health Organization guidelines do not specify a maximum number of misoprostol doses (Raymond EG, Harrison MS, Weaver MA. Efficacy of misoprostol alone for first-trimester medical abortion: a systematic review. Obstet Gynecol 2019;133:137-47 *and* World Health Organization. Medical management of abortion. Geneva: WHO; 2018. Available at: https://apps.who.int/iris/bitstream/handle/10665/278968/9789241550406-eng.pdf?ua=1. Retrieved March 3, 2020).

GBP-PET00045

Complete abortion rates with all regimens are highest at earlier gestational ages **Table 2** . *Medication abortion failure* (defined as the need for uterine aspiration because of ongoing pregnancy or retained tissue) increases with advancing gestational age through 70 days of gestation **Table 2** , although failure rates remain low even at this point. Clinicians should counsel patients that medication abortion failure rates, especially continuing pregnancy rates, increase as gestational age approaches 10 weeks.

Table 2. Outcome by Gestational Age After Mifepristone 200 mg and Misoprostol for Outpatient Medication Abortion

	Misoprostol Dose	Interval Between Mifepristone and Misoprostol (h)	Gestational Age			
			≤49 days	50–56 days	57–63 days	64–70 days
Complete abortion	800 micrograms buccally[*]	24–48	98.1%	96.8%	94.7%	92.7%
	800 micrograms vaginally[†‡§‖¶‡‡]	24–72	98.3–99.7%	95.3–98.6%	95.1–98.3%	94.9%
	800 micrograms vaginally[§]	6–8	97.1%	94.2%	95.2%	N/A
	800 micrograms vaginally[‖¶]	0–0.25	95.5–95.7%	93.7–94.3%	91.6–95.3%	N/A
	400 micrograms sublingually[#**]	24–48	95.4%	N/A	94.8%	91.9%
Ongoing pregnancy	800 micrograms buccally[*]	24–48	0.3%	0.8%	2.0%	3.1%
	800 micrograms vaginally[†‡§‖¶‡‡]	24–72	0–0.4%	0–1.2%	0–2.2%	3.4%
	800 micrograms vaginally[§]	6–8	0.4%	0	0.8%	N/A
	800 micrograms vaginally[‖¶]	0–0.25	1.4–2.3%	1.9–2.8%	1.6–5.0%	N/A
	400 micrograms sublingually[#**††]	24–48	N/A	N/A	1.8–3.5%	2.2%

Abbreviations: h, hours; N/A, not available.

*U.S. Food and Drug Administration. Mifeprex (mifepristone) information. Postmarket drug safety information for patients and providers. Silver Spring, MD: FDA; 2018. Available at: https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111323.htm. Retrieved March 3, 2020.

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‡‡Hsia JK, Lohr PA, Taylor J, Creinin MD. Medical abortion with mifepristone and vaginal misoprostol between 64 and 70 days' gestation. Contraception 2019;100:178–81.

GBP-PET00046

Who is qualified to provide medication abortion, and in what settings can medication abortion be provided?

Any clinician with the skills to screen patients for eligibility for medication abortion and to provide appropriate follow-up can provide medication abortion. Clinicians who wish to provide medication abortion services should be trained to perform uterine evacuation procedures or should be able to refer to a clinician who has this training **5** **69** .

In addition to physicians, advanced practice clinicians, such as nurse–midwives, physician assistants, and nurse practitioners, possess the clinical and counseling skills necessary to provide first-trimester medication abortion **70** . Randomized trials in Mexico, Nepal, and Sweden have consistently found that patients randomized to receive medication abortion under the care of a nurse or nurse–midwife had a statistically equivalent risk of complete abortion compared with those under the care of a physician, without increased risk of adverse events **71** **72** **73** . In some U.S. states, advance practice clinicians can provide medication abortion; however, many states require that a physician perform an abortion and prohibit provision of medication abortion by nonphysician clinicians **2** .

According to the requirements of the FDA REMS program, clinicians who want to prescribe mifepristone must complete a “prescriber agreement form” before ordering and dispensing mifepristone, and the clinician and patient need to sign a “patient agreement form” before the drug is dispensed **10** .

The actual location of where a patient takes the medication abortion drugs has evolved over time. Although the FDA REMS program for mifepristone continues to require dispensing in the clinician's office, the U.S. labeling for mifepristone no longer indicates that the medication should be used only in the clinician's office **10** . Patients can safely and effectively use mifepristone at home for medication abortion **74** **75** **76** **77** . A clinician can prescribe misoprostol and pain medications or can maintain an office supply and directly dispense to the patient. Patients can safely and effectively self-administer misoprostol at home for medication abortion **5** **78** **79** **80** .

GBP-PET00047

Medication abortion can be provided safely and effectively by telemedicine with a high level of patient satisfaction, and telemedicine improves access to early abortion care, particularly in areas that lack a health care practitioner **81** **82** . Telemedicine involves the use of video and information technology to provide a medical service at a distance. Medication abortion through telemedicine has been evaluated in observational studies and found to be equally effective as an in-person visit **33** **83** **84** **85** . In an analysis of nearly 20,000 medication abortions, adverse events were rare (0.3% overall) and did not differ between those who choose telemedicine or in-person services **33** **84** . Patients who choose telemedicine medication abortion are significantly more likely to say they would recommend the service to a friend compared with those who have an in-person visit (90% versus 83%) **83** . Telemedicine also may help reduce the rate of delays to care because of barriers in access to abortion care in remote areas **82** . After medication abortion through telemedicine was introduced in Iowa, a significant reduction in second-trimester abortion was reported, and patients in remote parts of the state were more likely to obtain a medication abortion **82** . Despite this evidence, some states have passed legislation that bans the use of telemedicine to provide medication abortion **86** .

Should prophylactic antibiotics be used in medication abortion?

The routine use of prophylactic antibiotics is not recommended for medication abortion **6** . Following concern about serious, rare, and deadly infection with clostridial bacteria in patients undergoing medication abortion, it has since become evident that no specific connection exists between clostridial organisms and medication abortion **87** **88** . Uterine infection with medication abortion is uncommon, and published data do not support the routine use of prophylactic antibiotics in medication abortion. In a systematic review of 65 studies of heterogeneous design (prospective, retrospective, and randomized), the overall proportion of diagnosed or treated infection after medication abortion was 0.9% in more than 46,000 patients **89** . In these studies, as in most studies of abortion by uterine evacuation, the diagnostic criteria for infection were variable, leading to possible overestimation of infection.

GBP-PET00048

Although serious infections occur rarely in patients after medication abortion, clinicians need to be aware of the signs and symptoms. Tachycardia, severe abdominal pain, or general malaise with or without fever that occur more than 24 hours after misoprostol administration should increase suspicion of a serious infection **90** . Clostridial toxic shock often resembles a flu-like illness, so clinicians should have a high level of suspicion for infection when symptoms consistent with flu are present **90** . Patients with such infections typically have hemoconcentration and significant leukocytosis without fever and can rapidly progress to refractory hypotension and death **91** .

What is the recommended pain management approach for patients undergoing medication abortion?

Nonsteroidal anti-inflammatory drugs are recommended for pain management in patients who undergo a medication abortion. Pain management during medication abortion is an important consideration because many patients report pain that requires analgesia. Studies of pain control and medication abortion have found that the duration of pain for most patients is no longer than 24 hours after misoprostol administration **92** **93** . The most severe pain occurs approximately 2.5–4 hours after misoprostol use and lasts about 1 hour **94** . One randomized trial found that ibuprofen taken when needed was more effective than acetaminophen to reduce pain associated with medication abortion **95** . Another randomized trial found ibuprofen given prophylactically at the time of misoprostol administration did not significantly reduce pain associated with medication abortion compared with ibuprofen taken when needed **93** . Nonsteroidal anti-inflammatory drugs do not appear to counteract misoprostol or affect the success of the medication abortion **96** . Opioids have not been found to decrease the amount or duration of maximum pain associated with medication abortion up to 70 days of gestation **94** . Other medications, like pregabalin, have been studied for pain control but have not been effective **97** .

Patients should be sent home with appropriate instructions for analgesia with over-the-counter medications. If opioids are requested or desired, the Centers for Disease Control and Prevention (CDC) advises that “clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids” **98** .

What kind of assessment is recommended after medication abortion?

GBP-PET00049

Routine in-person follow-up is not necessary after uncomplicated medication abortion. Clinicians should offer patients the choice of self-assessment or clinical follow-up evaluation to assess medication abortion success. If medically indicated or preferred by the patient, follow-up evaluation can be performed by medical history, clinical examination, serum human chorionic gonadotropin (hCG) testing, or ultrasonography **5** **6** **99** .

The type of follow-up visit after medication abortion has evolved over time. The mifepristone FDA label includes recommendations for follow up **23** . However, some patients choose not to return for follow-up; this likely is due to the high success rates and because patients are able to self-assess abortion completion **100** **101** **102** .

Remote Assessment and Self-Assessment

Follow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility **103** **104** **105** **106** . Most studies have used a short series of questions that ask patients whether they have experienced bleeding and cramping (including how much and for how long) and whether they still feel pregnant or if they think the pregnancy has passed **104** **107** . When the clinician and the patient think that expulsion has occurred based on symptomatology, they are correct 96–99% of the time **104** **108** . Although urine pregnancy testing alone with standard high-sensitivity or low-sensitivity tests has not been shown to be a viable alternative to other forms of follow-up, newer semiquantitative or multilevel at-home urine hCG tests have shown promise in accurately identifying ongoing pregnancies after medication abortion **109** **110** **111** **112** .

Clinical Follow-Up

When a patient obtains in-person follow-up after medication abortion, transvaginal ultrasonography is commonly used, although it is not required **5** . Incorrect interpretation of ultrasound examination results can lead to unnecessary interventions such as an unneeded uterine aspiration **5** . If an ultrasound examination is performed at follow-up after medication abortion, the sole purpose is to determine whether the gestational sac is present or absent. The measurement of endometrial thickness or other findings do not predict the need for subsequent uterine aspiration **113** . In research trials, when a transvaginal ultrasound examination shows no evidence of a gestational sac 1 week after mifepristone use, only 1.6% of patients needed subsequent uterine evacuation **113** .

GBP-PET00050

Serum hCG testing before treatment and 1 week after treatment is another option for follow-up examination after medication abortion; however, data about use of this approach are lacking for gestations beyond 63 days. This strategy may be more effective than ultrasonography to confirm abortion completion in patients who were below the threshold for visualization of a gestational sac at the time of their medication abortion **114**. Patients do not need to return to the same facility; they can obtain serum hCG testing at a convenient location **114** **115**. The patient should then be informed of the result. A serum hCG level decrease of at least 80% over 6–7 days after initiating treatment with mifepristone and misoprostol indicates a successful abortion **114**. In a randomized trial of in-clinic transvaginal ultrasound examination or serum hCG testing follow-up, 24.5% of patients were lost to follow-up, there were no significant differences reported in unplanned visits and interventions by 2 weeks (6.6% versus 8.2%, respectively) or in uterine evacuation rates by 4 weeks (4.4% and 1.4%, respectively) **116**.

How is incomplete medication abortion or ongoing pregnancy managed?

Guidelines for intervention vary for patients who have delayed expulsion, an incomplete medication abortion (ie, persistent gestational sac on ultrasonography without evidence of embryonic cardiac activity or retained tissue), or an ongoing pregnancy (ie, continuing development with embryonic cardiac activity).

Delayed Expulsion

After induced or spontaneous expulsion, the uterus will normally contain sonographically hyperechoic tissue or “thick” endometrial stripe that consists of blood, blood clots, and decidua. Rarely does this ultrasound finding in patients who have undergone medication abortion indicate a need for intervention. In the absence of excessive bleeding or pain by patient report, clinicians can monitor such patients based on symptoms.

Incomplete Medication Abortion

GBP-PET00051

An incomplete medication abortion can be treated with a repeat dose of misoprostol, uterine aspiration, or expectant management, depending on the clinical circumstances and patient preference **23** **30** **117** **118**. Studies indicate that even with a retained sac at 2 weeks after medication abortion, intervention is unnecessary, and that expulsion will typically occur in the ensuing weeks **30**. However, some patients with incomplete expulsion will have bothersome symptoms, such as prolonged and irregular bleeding episodes. Patients with incomplete medication abortion 1 week after treatment can safely receive another dose of misoprostol **28** **118** or repeat misoprostol doses can be used for a persistent gestational sac **117**. Patients who prefer not to wait or do not desire medical management can choose to have a uterine evacuation at any time.

Ongoing Pregnancy

Ongoing pregnancy after medication abortion can be treated with a repeat dose of misoprostol or uterine aspiration, depending on the clinical circumstances and patient preference. In an analysis of data from two randomized trials with 14 cases of ongoing pregnancy, treatment with a repeat dose of misoprostol, 800 micrograms administered vaginally, resulted in expulsion of the products of pregnancy in five cases (36%); in an additional four cases (29%), gestational cardiac activity was no longer present at the next follow-up visit **118**. If gestational cardiac activity persists at follow-up after a second dose of misoprostol, uterine aspiration should be performed.

What is the recommended timing of contraception initiation after medication abortion?

Patients undergoing medication abortion who desire contraception should be counseled that

- almost all contraceptive methods, except IUDs and permanent contraception, can be safely initiated immediately on day 1 (mifepristone intake) of medication abortion.
- all contraceptive methods can be safely initiated after successful medication abortion.

Patients who select depot medroxyprogesterone acetate (DMPA) for contraception should be counseled that administration of DMPA on day 1 of the medication abortion regimen may increase the risk of ongoing pregnancy **119**.

GBP-PET00052

Providing desired contraception as soon as possible to patients undergoing medication abortion enables the greatest flexibility in care and decreases barriers to initiating contraception. The CDC and World Health Organization (WHO) support the initiation of almost all methods of contraception on day 1 of the medication abortion or on the same day as mifepristone administration **5** **6** **120**. Permanent contraception procedures may be performed once abortion is confirmed complete.

Concern has been raised that the immediate use of hormonal contraception that contains progestins could theoretically interfere with medication abortion efficacy. Etonogestrel implant use does not affect medication abortion outcomes **121** **122**. However, DMPA injection at the time of mifepristone administration may slightly increase the risk of an ongoing pregnancy **119**. In a randomized trial that evaluated the effects of DMPA injection timing on medication abortion outcomes, ongoing pregnancy was more common among those randomized to receive DMPA injection on the day of mifepristone administration compared with those who received DMPA at a follow-up visit (3.6% versus 0.9%; 90% CI, 2.7 [0.4–5.6]), although the proportion undergoing aspiration for any reason did not significantly vary (6.4% versus 5.3%; 90% CI, 1.1 [−2.8 to 4.9]) **119**. Patients should be counseled about this small risk of ongoing pregnancy, which needs to be weighed against the risk of potentially not receiving their desired method of contraception.

Patients do not experience a higher rate of IUD expulsion with placement in the first week after medication abortion as compared with 3 to 6 weeks later **123** **124**. However, IUD placement within 6 weeks after medication abortion is associated with a higher expulsion rate compared with IUD placement remote from pregnancy; the time frame after 6 weeks at which this rate decreases is unknown. Placement of a copper or levonorgestrel IUD close to the time of abortion results in improved uptake of a desired IUD compared with placement at an additional follow-up visit several weeks after the abortion **123** **124** **125**, although overall use rates at 6 months may not differ **126**. The IUD expulsion risk should be weighed against the potential for more patients to receive their desired IUD if it is placed sooner rather than later.

How should patients be counseled about the effect of medication abortion on future fertility and pregnancy outcomes?

GBP-PET00053

Patients can be counseled that medication abortion does not have an adverse effect on future fertility or future pregnancy outcomes [5] [6]. Studies consistently demonstrate that medication abortion has no negative effect on future fertility or pregnancy outcomes. A study from China found that patients who had a prior mifepristone abortion had lower odds of preterm birth compared with those who had never been pregnant (adjusted OR, 0.77; 95% CI, 0.61–0.98), and the frequencies of low-birth-weight infants and mean lengths of pregnancy were similar in both groups [127]. No significant differences were reported in risk of preterm delivery, frequency of low-birth-weight infants, or mean infant birth weight in the comparisons of patients who had previous mifepristone abortion and patients who had uterine evacuation. In a registry-based study from Scotland, no association was found between prior abortion and subsequent preterm birth during the period 2000–2008, when 68% of abortions were medication-induced [128].

Summary of Recommendations

The following recommendations are based on good and consistent scientific evidence (Level A):

- Combined mifepristone–misoprostol regimens are recommended as the preferred therapy for medication abortion because they are significantly more effective than misoprostol-only regimens. If a combined mifepristone–misoprostol regimen is not available, a misoprostol-only regimen is the recommended alternative.

- Clinicians should counsel patients that medication abortion failure rates, especially continuing pregnancy rates, increase as gestational age approaches 10 weeks.

- Any clinician with the skills to screen patients for eligibility for medication abortion and to provide appropriate follow-up can provide medication abortion.

- Patients can safely and effectively use mifepristone at home for medication abortion.

- Patients can safely and effectively self-administer misoprostol at home for medication abortion.

- Nonsteroidal anti-inflammatory drugs are recommended for pain management in patients who undergo a medication abortion.

- Routine in-person follow-up is not necessary after uncomplicated medication abortion. Clinicians should offer patients the choice of self-assessment or clinical follow-up evaluation to assess medication abortion success. If medically indicated or preferred by the patient, follow-up evaluation can be performed by medical history, clinical examination, serum human chorionic gonadotropin (hCG) testing, or ultrasonography.

- If an ultrasound examination is performed at follow-up after medication abortion, the sole purpose is to determine whether the gestational sac is present or absent. The measurement of endometrial thickness or other findings do not predict the need for subsequent uterine aspiration.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Medication abortion is not recommended for patients with any of the following: confirmed or suspected ectopic pregnancy, intrauterine device (IUD) in place (the IUD can be removed before medication abortion), current long-term systemic corticosteroid therapy, chronic adrenal failure, known coagulopathy or anticoagulant therapy, inherited porphyria, or intolerance or allergy to mifepristone or misoprostol.

- Before undergoing medication abortion, patients should be counseled regarding the teratogenicity of misoprostol in the event of an unsuccessful medication abortion.

- Before medication abortion is performed, the clinician should confirm pregnancy and estimate gestational age. For patients with regular menstrual cycles, a certain last menstrual period within the prior 56 days, and no signs, symptoms, or risk factors for ectopic pregnancy, a clinical examination or ultrasound examination is not necessary before medication abortion.

- Most patients with clinical indications for an ultrasound examination before medication abortion can be initially screened with transabdominal ultrasonography, reserving transvaginal ultrasonography for situations in which further clarification is required.

GBP-PET00055

- Medication abortion can be provided safely and effectively by telemedicine with a high level of patient satisfaction.

- The routine use of prophylactic antibiotics is not recommended for medication abortion.

- An incomplete medication abortion can be treated with a repeat dose of misoprostol, uterine aspiration, or expectant management, depending on the clinical circumstances and patient preference.

- Ongoing pregnancy after medication abortion can be treated with a repeat dose of misoprostol or uterine aspiration, depending on the clinical circumstances and patient preference.

- Patients undergoing medication abortion who desire contraception should be counseled that

  - almost all contraceptive methods, except IUDs and permanent contraception, can be safely initiated immediately on day 1 (mifepristone intake) of medication abortion.

  - all contraceptive methods can be safely initiated after successful medication abortion.

- Patients who select depot medroxyprogesterone acetate (DMPA) for contraception should be counseled that administration of DMPA on day 1 of the medication abortion regimen may increase the risk of ongoing pregnancy.

- Patients can be counseled that medication abortion does not have an adverse effect on future fertility or future pregnancy outcomes.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- Patients who choose abortion should be counseled about all methods available as well as the risks, advantages, disadvantages, and the different features of these options.

- Most patients at 70 days of gestation or less who desire abortion are eligible for a medication abortion.

GBP-PET00056

- Patient counseling before medication abortion should include discussion of when patients should contact their clinician in the case of heavy bleeding (soaking more than two maxi pads per hour for 2 consecutive hours) and when to access urgent intervention.

- All patients with a continuing pregnancy after using mifepristone and misoprostol should be provided with all pregnancy options and a thorough discussion of the risks and benefits of each.

- In the very rare case that patients change their mind about having an abortion after taking mifepristone and want to continue the pregnancy, they should be monitored expectantly.

- Rh testing is recommended in patients with unknown Rh status before medication abortion, and Rh D immunoglobulin should be administered if indicated. In situations where Rh testing and Rh D immunoglobulin administration are not available or would significantly delay medication abortion, shared decision making is recommended so that patients can make an informed choice about their care.

- Clinicians who wish to provide medication abortion services should be trained to perform uterine evacuation procedures or should be able to refer to a clinician who has this training.

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Medication abortion up to 70 days of gestation. ACOG Practice Bulletin No. 225. American College of Obstetricians and Gynecologists. Obstet Gynecol 2020;136:e31–47.

The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000 and February 2020. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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Topics

Abortifacient agents | Counseling | Diagnostic imaging | First pregnancy trimester | Induced abortion | Obstetric surgical procedures | Pregnancy | Pregnancy trimesters | Reproductive control agents | Rh-Hr blood-group system | Ultrasonography

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Original Research Article

Clinical and service delivery implications of omitting ultrasound before medication abortion provided via direct-to-patient telemedicine and mail in the U.S

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ABSTRACT

Objectives: To compare outcomes among patients who did or did not have pre-abortion ultrasound or pelvic exam before obtaining medication abortion (MA) via direct-to-patient telemedicine and mail.

Study design: We analyzed data from participants screened for enrollment into the TelAbortion study at five sites from March 25 to September 15, 2020. We compared participants who had preabortion ultrasound or pelvic exam ("test-MA") to those who did not ("no-test MA"). Outcomes were: abortion not complete with pills alone (i.e., had procedure intervention or ongoing pregnancy), ongoing pregnancy separately, ectopic pregnancy, hospitalization and/or blood transfusion, and unplanned clinical encounters. We used propensity score weighting and multivariable logistic regression to adjust for baseline characteristics.

Results: Our analysis included 287 participants who had no-test MA and 125 who had test-MA. Abortion was not complete with pills alone in 16of 287 (5.6%) no-test MA patients compared to 2of 123 (1.9%) test-MA patients (adjusted risk difference [aRD] = 4.3%, 95% confidence interval [CI]: 1.4%–7.1%). No ectopic pregnancies were detected. Groups did not differ regarding hospitalization and/or blood transfusion ($p = 0.76$) or ongoing pregnancy diagnosis ($p = 0.59$). Unplanned clinical encounters were more common in no-test MA patients (35of 287, 12.5%) than test-MA patients (10of 125, 8.0%, aRD = 6.7%, 95% CI: 0.5%–13.1%).

Conclusions: Compared to patients who had pre-abortion ultrasound, patients who had no-test MA via telemedicine were more likely to have abortions that were not complete with pills alone and/or unplanned clinical encounters. However, both no-test and test-MA patients had similar and very low rates of ongoing pregnancy and hospitalization or blood transfusion.

Implications: Omitting pre-abortion ultrasound before provision of medication abortion via telemedicine does not appear to compromise safety or result in more ongoing pregnancies. However, compared to patients who have preabortion ultrasound, patients who do not have pre-abortion tests may be more likely to seek post-treatment care and have procedural interventions.

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1. Introduction

The COVID-19 pandemic triggered intense interest in delivery of abortion care by telehealth. Clinical guidelines for medication abortion (MA) in the United States [1–3] and elsewhere [4], were revised to enable providers to communicate with patients virtually to assess eligibility and evaluate outcomes using history and

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self-administered urine tests without examination, ultrasound, or laboratory tests, and to deliver abortion medications by mail. In some countries that have adopted all of these elements, most people can now legally obtain MA without leaving their homes. Recent retrospective studies from the United Kingdom and Canada indicate that this approach is highly acceptable to patients and can decrease waiting times for MA without compromizing safety or efficacy [5–8].

Information on the safety and efficacy of a fully remote MA approach in the US is critical for informing regulatory and programmatic decisions about MA service provision in this country. Our ongoing TelAbortion study has offered MA by direct-to-patient telemedicine and mail to people in multiple US states for the past 5 years [9,10]. Although the investigational plan had required participants to obtain an ultrasound or pelvic exam before shipment of MA drugs, when the COVID crisis worsened in 2020, some study investigators began waiving this requirement, as well as all laboratory tests, when they judged that doing so was safe and necessary to protect the participant's wellbeing. In this analysis, we used data from the TelAbortion study to explore the effect of this approach on clinical outcomes, service delivery parameters, and participant satisfaction.

2. Materials and methods

TelAbortion is a prospective, multicenter single-arm trial initiated in 2016 designed to assess the safety and feasibility of providing medication abortion via direct-to-patient telemedicine and mail. Details of the protocol are described elsewhere [9,10].

Individuals expressing interest in the TelAbortion service first had a conversation with site staff via telephone or video conference to learn more about study procedures and undergo preliminary eligibility screening. After providing signed informed consent (documented via electronic signature), each participant had a videoconference with a study clinician who assessed eligibility for treatment. In early March, in response to exigencies of the COVID-19 pandemic, study clinicians at 5 of the 9 sites began on a case-by-case basis to provide treatment without screening ultrasound, which had previously been uniformly used in the study. These five sites enrolled participants in 10 jurisdictions: Colorado, Georgia, Illinois, Maine, Maryland, Minnesota, Montana, New Mexico, New York, and District of Columbia. In selecting patients for this simplified service, clinicians followed recently released clinical guidelines [3]; although specific criteria were not uniform, an ultrasound was typically not required if the patient reported a sure menstrual period starting within the past 69 days and had no symptoms of or risk factors for ectopic pregnancy. In addition, clinicians omitted ultrasound only if they judged that the process of obtaining the test would compromise the welfare of the patient, e.g., by delaying the abortion. With or without a screening ultrasound, if the gestational duration was ≤69 days and the participant was eligible for MA, the participant selected a plan for follow-up tests (ultrasound, serum HCG measurements, or home urine pregnancy test), and the clinic mailed a package containing abortion medications and instructions. Participants were told to take mifepristone (200 mg orally) followed by misoprostol (800 or 1600 mcg, at the clinician's discretion). The clinician assessed abortion outcome using information provided by participants via telephone call or online survey. Participants or their insurance carriers were charged for all services they received from study sites and from any non-study facilities. Participants also completed an exit questionnaire via phone or on-line survey about satisfaction of the TelAbortion service and out-of-pocket costs.

This analysis includes all enrolled participants who were screened at the five sites that were omitting preabortion tests for some patients between March 24, 2020 and September 15, 2020. Patients included in this analysis must have also taken mifepristone, reported the last menstrual period (LMP) onset date, and had a known abortion outcome based on tests or history alone. March 24, 2020 was the screening date of the first participant after the onset of the COVID-19 pandemic who had a "no-test MA," i.e., MA without pretreatment ultrasound or pelvic exam. We included only the first TelAbortion had by each individual during this interval.

Our aim was to compare post-treatment clinical, service delivery, and acceptability outcomes of two groups of participants: those who had no-test MA ("no-test MA" group) and those who had a pre-treatment ultrasound or pelvic exam ("test-MA" group). We examined five clinical outcomes: abortion not complete with pills alone (defined as the patient having a procedure such as aspiration to complete the abortion and/or had a viable pregnancy documented by ultrasound at any time during follow-up); diagnosis of ongoing pregnancy separately; diagnosis of ectopic pregnancy; unplanned clinical encounters (i.e., instances when a patient sought in-person medical care related to the abortion and the visit was not planned before package shipment); and serious adverse events (hospitalization or blood transfusion). We examined 2 service delivery outcomes to determine if no-test MA helped the telemedicine process move quicker and enable patients to initiate MA sooner: interval > 7 days between the initial participant contact with study staff and package shipment; and gestational duration > 63 days (per LMP onset) at the time of mifepristone ingestion. We assessed the latter only among participants with gestational duration ≤ 63 days from LMP onset to first contact. Finally, we examined three acceptability outcomes: participant-reported satisfaction with the overall TelAbortion service; future preference for abortion care (i.e., TelAbortion or in-person scare); and out-of-pocket abortion-related costs (categorized as ≤ $100, $101-250, $251-400, $400-550, > $550).

We compared clinical outcomes between test-MA and no-test MA groups using unadjusted and adjusted logistic regression models to estimate risk differences (RDs) with 95% confidence intervals (CIs). The adjusted models included propensity scores using inverse probability of treatment weights to address potential confounding between groups. We calculated propensity scores using logistic regression to model the probability of having no-test MA based on the following variables: age group, race/ethnicity, education, number of previous pregnancies (0, 1, ≥ 2), gestational age (GA) by LMP at time of videoconference (≤ 42, 43–63, or > 63 days), urban or rural residence (using U.S. Census designation), distance from participant's residence to the study site, insurance used to pay for the abortion service, and study site. We assessed whether propensity score weighting achieved balance among baseline characteristics between study groups by calculating standardized differences before and after weighting; a standardized difference of -0.1 to 0.1 indicated adequate balance [11]. Our multivariable logistic regression models of clinical outcomes were weighted on the propensity score and included the following covariates for double robust estimation on these characteristics: site, GA at videoconference, and any variable not adequately balanced by propensity score weighting.

We used the same method for analysis of service delivery outcomes, except that in the outcome of GA > 63 days at time of mifepristone ingestion, we used GA by LMP at first contact with the site in lieu of GA at videoconference in the propensity score calculation and multivariable model of the outcome.

For acceptability outcomes, we used a Fisher's exact test to compare participant-reported satisfaction and future preference for abortion care by study group. For out-of-pocket costs, we analyzed the range estimates reported by no-test MA and test-MA patients and stratified by whether insurance was used to pay for any part of abortion care. We used univariable and multivariable log-binomial regression to determine if no-test MA participants were less likely

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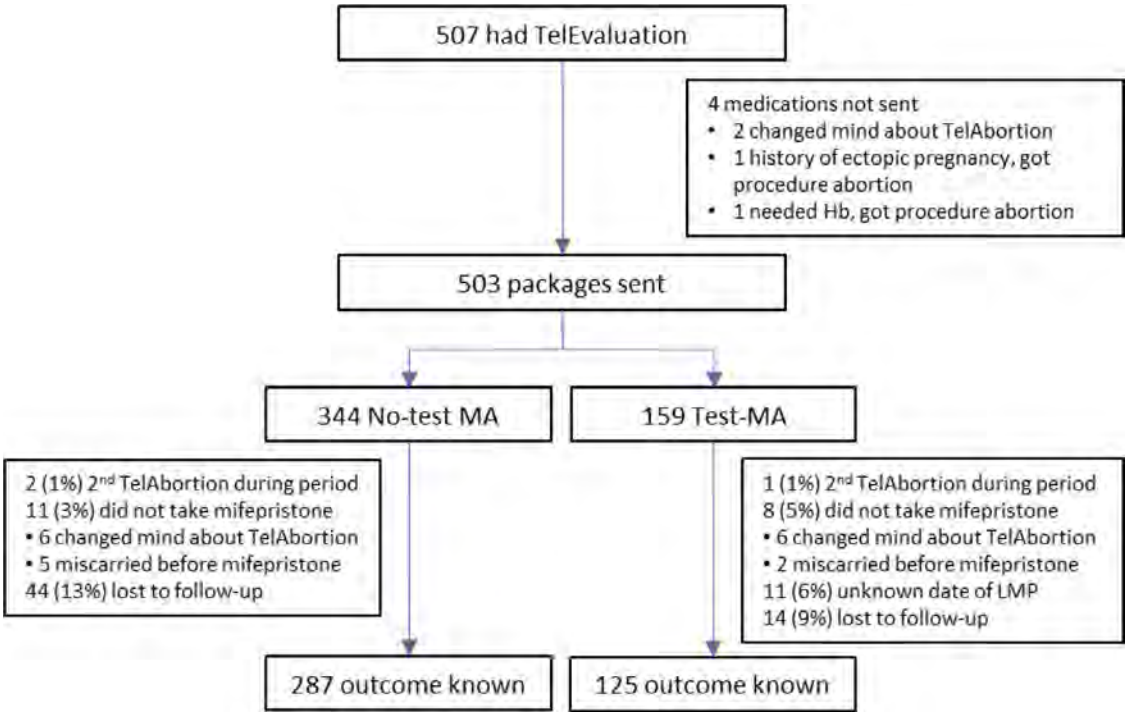

Fig. 1. U.S. TelAbortion study population included in analysis comparing use of no-test medication abortion (no-test MA) and use of preabortion ultrasound or pelvic exam before medication abortion (Test-MA), March 24 – September 15, 2020.

than test-MA participants to report out-of-pocket costs exceeding $400 for abortion-related care. The multivariable regression model included adjustment for use of insurance and the cost of abortion service charged by sites. We chose the $400 threshold for this outcome because it was the cost category closest to the median cost of service charged by sites (median: $375, range $250–450).

We conducted sensitivity analyses of clinical outcomes to examine whether results were robust after excluding participants who: (1) had abortion outcome determined based on history alone (i.e., without ultrasonography, serum HCG measurement, or HSPT); (2) had GA > 63 days or (3) had GA ≤ 35 days by LMP at time of the videoconference; (4) had extreme low or high propensity scores (< 0.1 or > 0.9, Figure A.1). We also examined the potential influence of study attrition by (5) including participants who were lost to follow-up assuming all did not have the outcome in question.

We conducted all analyses using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). The study was approved by the Advarra Institutional Review Board and is registered with clinicaltrials.gov (NCT02513043).

3. Results

Sites mailed 503 TelAbortion packages during the analysis period (Fig. 1). We excluded 91 (18%) occurrences because participants did not provide a LMP date, did not take mifepristone, or did not have a recorded abortion outcome. Our final analysis included 287 no-test MA and 125 test-MA participants. The two groups differed in many characteristics (Table 1). For example, compared to test-MA participants, no-test MA participants were more likely to be aged ≥35 years, be non-Hispanic Black, have above high school education, and have GA ≤ 42 days. No-test MA participants were less likely than test-MA participants to live ≥ 150 miles from the study site and have GA > 63 days. The proportion of participants having no-test MA at each site ranged from 47.4%–84.3%. After weighting on propensity scores, the groups were balanced on all characteristics except urban/rural residence (Table A.1); therefore, we included urban/rural residence in multivariable logistic regression models of clinical and service delivery outcomes.

All 412 participants had outcome information on unplanned clinical encounters (Table 2). Two participants in the test-MA group were known to have had a clinical encounter, but sites were unable to obtain information on abortion outcome, blood transfusion, or hospitalization, thus they were excluded from analysis of those outcomes. Overall, 392of 410 (95.6%) participants had a complete MA with pills alone. Abortion was not complete with pills alone for more patients in the no-test than in the test-MA group (5.6% and 1.6%, respectively). In adjusted analysis, the likelihood of this outcome was significantly higher by 4.3 percentage points (95% CI: 1.5, 7.1) among no-test MA participants. Among the 18 participants who had an abortion that was not complete with pills alone (i.e., had a procedure intervention and/or ongoing pregnancy), 5 received care at an emergency room or urgent care center, 6 received care at an office or clinic not affiliated with the study site, and seven received care at a center affiliated with the study site. More patients in the no-test MA group (12of 274, 4.2%) than in the test-MA group (0of 123) had procedure interventions for reasons not specifically noted as ongoing pregnancy ($p < 0.01$, data not shown). We found no statistically significant difference between groups regarding ongoing pregnancy alone or likelihood of serious adverse events, and no ectopic pregnancies were detected. Among the 3 participants with serious adverse events (i.e., hospitalization and/or blood transfusion), two individuals in the no-test MA group received procedure interventions and blood transfusions during emergency room visits and one individual in the test-MA group was hospitalized due to fever and abdominal pain and later discharged after showing improvement on antibiotics and fluids. The proportion of participants who had unplanned clinical encounters after treatment was significantly higher (6.7%; 95% CI: 0.5, 13.1) in the no-test MA group than the test-MA group. Sensitivity analyses showed consistent re-

Table 1
Baseline characteristics of included U.S. TelAbortion study population, March 24 to September 15, 2020

Characteristic	No-test MA,N = 287n (%)	Test-MA,N = 125n (%)	*p*-value[a]
Age (years)			
<25	58 (20.2%)	40 (32.0%)	0.03
25 – 34	159 (55.4%)	63 (50.4%)	
≥35	70 (24.4%)	22 (17.6%)	
Race/ethnicity			
Non-Hispanic white	158 (55.1%)	84 (66.2%)	0.04
Non-Hispanic black	78 (27.2%)	15 (12.0%)	
Asian/pacific islander	8 (2.8%)	3 (2.4%)	
Hispanic	18 (6.3%)	9 (7.2%)	
Native American	11 (3.8%)	8 (6.4%)	
Other/multiple	8 (2.8%)	2 (1.6%)	
Unknown/did not say	6 (2.1%)	4 (3.2%)	
Education			
< High school	9 (3.1%)	3 (2.4%)	0.03
High school/GED	66 (23.0%)	33 (26.4%)	
> High school	207 (72.1%)	80 (64.0%)	
Unknown/missing	5 (1.8%)	9 (7.2%)	
Prior pregnancies			
0	55 (19.2%)	35 (28.0%)	0.14
1	56 (19.5%)	22 (17.6%)	
≥2	176 (61.3%)	68 (54.4%)	
GA by LMP at videoconference			
≤42 D	115 (40.1%)	24 (19.2%)	<0.01
43 – 63 D	167 (58.2%)	86 (68.8%)	
>63 D	5 (1.7%)	15 (12.0%)	
Urban/rural residence			
Urban	227 (79.1%)	90 (72.0%)	0.15
Rural	38 (13.2%)	26 (20.8%)	
Unknown/missing	22 (7.7%)	9 (7.2%)	
Distance to site			
≥150 miles	91 (31.7%)	64 (51.2%)	<0.01
Payment for abortion service			
Insurance used	75 (26.1%)	41 (32.8%)	0.17
Self-pay/abortion fund	212 (73.9%)	84 (67.2%)	
Study site			
Maine family planning	21 (7.3%)	4 (3.2%)	<0.01
Planned parenthood of the rocky mountains	36 (12.5%)	40 (32.0%)	
Carafe	150 (52.3%)	28 (22.4%)	
Planned parenthood of Montana	25 (8.7%)	28 (22.4%)	
Planned parenthood of north & central states	55 (19.2%)	25 (20.0%)	

GA, gestational age; LMP, onset of last menstrual period; No-test MA, no-test medication abortion; Test-MA, test medication abortion (i.e., pre-abortion ultrasound or pelvic exam).
[a] *p*-values calculated using chi-square test of association.

Table 2
Effect of no-test medication abortion on clinical and service delivery outcomes in U.S. TelAbortion study, March 25 to September 15, 2020

	No-test MA	Test-MA	Unadjusted analysis		Adjusted analysis[a]	
	n (%)	n (%)	Risk difference(95% CI)	*p* value	Risk difference(95% CI)	*p* value
Clinical outcomes	N = 287	N = 125				
Abortion not complete with pills alone[b,c]	16 (5.6%)	2 (1.6%)	4.0% (0.5, 7.4)	0.03	4.3% (1.5, 7.1)	<0.01
Ongoing pregnancy[c]	4 (1.4%)	2 (1.6%)	-0.2% (-2.8, 2.4)	0.86	0.5% (-1.3, 2.2)	0.59
Ectopic pregnancy	0	0	-	-	-	-
Hospitalization and/ or blood transfusion[c]	2 (0.7%)	1 (0.8%)	-0.1% (-2.0, 1.7)	0.90	0.3% (-1.4, 1.9)	0.76
Any unplanned clinical encounter	36 (12.5%)	10 (8.0%)	4.5% (-1.6, 10.7)	0.14	6.7% (0.5, 13.1)	0.03
Service delivery outcomes						
Interval from initial contact to package shipment	N=287	N=125				
>7 D	53 (18.5%)	49 (39.2%)	-20.7% (-30.4, -11.1)	<0.01	-21.2% (-33.4, -9.1)	<0.01
GA at mifepristone ingestion[d]	N=281	N=117				
>63 D	21 (7.5%)	22 (18.8%)	-11.3% (-19.1, -3.6)	<0.01	-6.2% (-12.6, 0.2)	0.06

CI, confidence interval; GA, gestational age; MA, medication abortion; No-test MA, no-test medication abortion; Test-MA, test medication abortion
[a] Estimates derived from logistic regression model that incorporates inverse probability of treatment weighting and the covariates study site, urban/rural residence, and gestational age at videoconference.
[b] Abortion not complete with pills alone defined as having a procedure intervention and/or diagnosis of ongoing pregnancy
[c] Two participants in the Test-MA group were not included in the analysis of abortion not complete with pills alone, ongoing pregnancy, or hospitalization and/or blood transfusion outcomes because they had a known planned clinical encounter but were subsequently lost to follow-up and the final determination of ongoing pregnancy and whether abortion was not complete with pills alone was unknown
[d] Analysis includes only participants with gestational age ≤63 days at first study contact. Adjusted model includes propensity score, study site, urban/rural residence, and gestational age at first contact.

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Table 3
Effect of no-test approach to medication abortion on acceptability outcomes in TelAbortion study, March 25 to September 15, 2020

	No-test MAn (%)	Test-MAn (%)	*p* value[a]
Satisfaction with TelAbortion service	N = 256	N = 112	
Very satisfied	228 (89.0%)	99 (87.5%)	$p = 0.50$
Satisfied	25 (9.8%)	14 (12.5%)	
Unsatisfied	0	0	
Very unsatisfied	3 (1.2%)	0	
Future preference	N = 255	N = 111	
In-person care	9 (3.5%)	5 (4.5%)	$p = 0.14$
TelAbortion	233 (91.4%)	105 (94.6%)	
No preference	13 (5.1%)	1 (0.9%)	

No-test MA, no-test medication abortion; Test-MA, test medication abortion.
[a] Fisher's exact test.

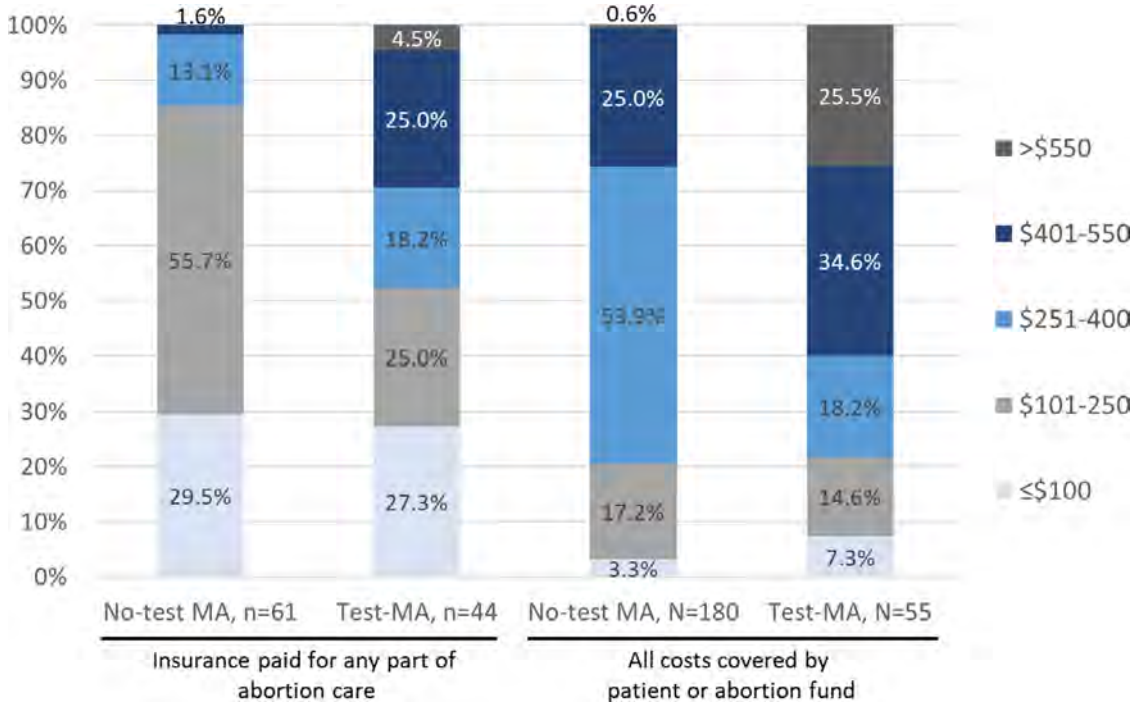

Fig. 2. Patient reported out-of-pocket costs by patients receiving no-test medication abortion (no-test MA) and those who had pre-abortion ultrasound or pelvic exam (test-MA) in the TelAbortion study.

sults, though the association of no-test MA and unplanned clinical encounters was not statistically significant when excluding participants with extreme propensity scores and including participants lost to follow-up (Figure A.2).

Our adjusted analysis of service delivery outcomes indicated significant or borderline significant differences between groups. Compared to test-MA participants, the proportion of participants who obtained their medications > 7 days after initial contact was 21.2 percentage points (95% CI: 9.1, 33.4) lower in the no-test MA group than the test-MA group (Table 2). Similarly, among participants with GA ≤ 63 days at first contact with sites, the proportion who took mifepristone at GA > 63 days was 6.2 percentage points (95% CI: -0.2, 12.6) lower in the no-test MA group than the test-MA group.

In the analysis population, 256 no-test MA and 112 test-MA participants completed exit questionnaires (Table 3), including 67 (26.2%) no-test MA and 16 (14.3%) test-MA via online survey. More than 98% of participants in both groups reported being very satisfied or satisfied with the TelAbortion service, and > 91% in both groups said they would prefer TelAbortion for a future abortion. Among the 340 participants who reported out-of-pocket costs, those who had no-test MA reported lower out-of-pocket costs whether or not they used insurance (Fig. 2). After controlling for insurance used and site-specific costs of the abortion service, significantly fewer no-test MA (47of 241, 19.5%) than test-MA patients (46of 99, 46.5%) reported out-of-pocket costs exceeding $400 ($p <$ 0.01, data not shown).

4. Discussion

This analysis of patients receiving MA via direct-to-patient telemedicine and mail shows both benefits and drawbacks of no-test MA. Over 94% of patients in both no-test MA and test-MA groups had a complete MA with pills alone, which is comparable to success rates previously reported of mifepristone and misoprostol regimens [12–14]. Self-reported patient satisfaction was excellent for both no-test MA and test-MA patients, and we show evidence that no-test MA may enable patients to access MA via telemedicine sooner and at lower cost. However, no-test MA patients were more likely to have unplanned in-person clinical encounters and an abortion that was not complete with pills alone.

Our analysis found no evidence that no-test MA leads to an increased risk of outcomes of particular clinical concern (i.e., ongoing pregnancy, hospitalization or blood transfusion, ectopic pregnancy); these results are consistent with other studies [5,15,16]. However, our findings show that approximately 4.3% more no-test MA patients may have an intervention compared to patients who have pre-abortion tests. This differs from results of a large retrospective cohort study from the United Kingdom that examined use of telemedicine MA with no-test MA which showed that patients who have no-test MA may have higher MA success rates compared to patients who have screening ultrasonography [5]. This discrepancy may be explained by differences in how information was gathered on abortion outcome; while the UK study used program data and clinical incident reports for abortion outcome determination, our analysis includes data collected prospectively with rigorous efforts to obtain outcome information from participants. In our study, it is possible that no-test MA patients had slightly higher intervention and encounter rates due to concerns and anxiety related to providers and patients adapting to the new clinical practice; there may have been differences in counseling that made no-test MA patients more likely to seek care, and study providers may have been more likely to encourage no-test MA patients to seek in-person evaluation during follow-up contacts.

Notably, patients who had pre-abortion screening tests had an intervention rate of 1.6% which is lower than the average rate of 3%to 7% reported in studies of first-trimester MA [12–14,17]. This could indicate a reduced likelihood of patients seeking care during the COVID-19 pandemic. Such tendencies in delays or avoidance of care-seeking due to COVID-19 concerns has been documented in the general U.S. population [18]. This impact of reduced care-seeking would apply to patients in both no-test MA and test-MA groups, with the higher rate of care-seeking and interventions observed in the no-test MA group occurring for reasons hypothesized above.

Our results also show benefits of no-test MA in facilitating provision of MA sooner through telemedicine and reducing the cost burden. Previous studies show that cost is an important barrier to abortion access, and this disproportionately impacts people in states where Medicaid and other insurance plans may not cover abortion care [19,20]. By reducing out-of-pocket costs, use of no-test MA could facilitate more equitable expansion of access to MA via telemedicine.

This analysis has limitations. First, patients were not randomized to receive no-test MA or test-MA and the two groups differed on factors that may affect outcomes. To address this, we used propensity score weighting with double robust estimation on key variables and we also conducted numerous sensitivity analyses that showed our results to be robust under various scenarios; however, there could be residual confounding. Second, our sample size of 412 patients from five clinical sites is rather small, especially considering the rare nature of some clinical outcomes. However it is notable that, despite our small sample size, we did document significant differences in the study groups for more common outcomes. Our analysis is strengthened by the prospective data collection, consistent study monitoring, and low loss-to-follow-up. The geographic diversity of the study population within the US increases generalizability.

The COVID-19 pandemic led to profound changes in MA service provision, including increased use of no-test MA within both telemedicine and in-person services [16,21,22]. Overall, our results support the continued use of no-test MA since treatment success rates remain high and we saw no increase in more serious outcomes in this population. Our analysis also shows that no-test MA patients may have more post-MA interventions than patients who had preabortion tests; this increase could be temporary as providers and patients become more comfortable with clinical protocol changes, as has been shown with use of telemedicine more broadly [23]. Additional rigorous research and evaluation of no-test MA would help further elucidate the consequences of these shifts in practices.

Declaration of Competing Interests

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Disclaimer

The findings and conclusions in this article are those of the authors and do not necessarily reflect the views of Planned Parenthood Federation of America, Inc.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.contraception.2021.07.108.

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Original research article

Clinical and service delivery outcomes following medication abortion provided with or without pretreatment ultrasound or pelvic examination: An updated comparative analysis☆,☆☆

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ABSTRACT

Objectives: This study aimed to compare medication abortion outcomes among people screened without or with ultrasound or pelvic examination.

Study design: We used data collected from March 24, 2020, to September 27, 2021, at five TelAbortion Project sites that provided medication abortion with mifepristone and misoprostol by mail. Using logistic regression weighted on propensity scores, we compared outcomes in participants who had neither ultrasound nor examination before treatment (No-Test group) or had such tests (Test group). We analyzed outcomes separately for participants screened early in the analysis period (before September 15, 2020) or later. Outcomes included procedural abortion completion or ongoing pregnancy, serious adverse events, and unplanned posttreatment abortion-related clinical visits.

Results: Among 416 participants in the early period, the No-Test group had a significantly higher risk than the Test group of procedural abortion completion or ongoing pregnancy (5.6% vs 0.9%, risk difference 4.6%, 95% CI 1.5%, 7.7%) and abortion-related clinical visits (13.3% vs 6.3%; risk difference 7.0%; 95% CI 1.1%, 12.8%). Among 364 participants screened later, the risk of procedural abortion completion or ongoing pregnancy did not differ by group, while unplanned abortion-related clinical visits were less common in the No-Test group (9.9% vs 20.5%; risk difference −10.6%; 95% CI −20.1%, −1.1%). The risk of serious adverse events did not differ by group in either period.

Conclusions: When providers first began omitting ultrasound or pelvic examination before medication abortion, the practice was associated with increased risks of failure of complete abortion and posttreatment clinical visits; however, these increased risks resolved over time.

Implications: Medication abortion without pretreatment ultrasound or examination is effective and safe. This model should be routinely offered to eligible patients.

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1. Introduction

In recent years, guidelines for first-trimester medication abortion (MA) with mifepristone and misoprostol have been updated to allow eligibility screening based on history alone without pretreatment sonography or pelvic examination [1,2]. A systematic review of 21 studies published in 2023 [3] as well as a large study published subsequently [4] concluded that effectiveness and complication rates were similar to rates reported in studies of patients who had pretreatment ultrasound. However, only two of the 22 studies compared outcomes in patients receiving MA with or without ultrasound contemporaneously in the same setting. One study [5], which included 327 patients treated in Hawaii in 2020, reported no differences in the unadjusted proportions of patients who required

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additional treatment to complete the abortion, who visited a hospital or emergency department, or who had significant adverse events. The second study [6] was an analysis that we performed using data from 412 people who received MA in 2020 through the TelAbortion Project [7–9], a set of two prospective, multicenter, case series studies that evaluated provision of MA by telemedicine and mail. After adjusting for baseline differences, we found that participants without pretreatment ultrasound were less likely to complete the abortion with medications alone (risk difference 4.3%, $p < 0.01$) and more likely to have unplanned posttreatment clinical visits (risk difference 6.7%, $p = 0.03$). However, 94% of participants who did not have pretreatment ultrasound had a complete MA without intervention, and we saw no evidence that screening ultrasound was associated with an increased risk of ongoing pregnancy, hospitalization, or transfusion.

Despite these supportive findings, many clinicians in the United States still have reservations about history-based screening [10–12]; indeed, as of September 2023, it was legally prohibited in some 16 states, including states where abortion is legal and available [13]. Additional evidence documenting its safety and effectiveness may be helpful. The TelAbortion Project enrolled hundreds of additional participants after the period of our study described above. Here, we present an update of the prior analysis that includes the additional data.

2. Materials and methods

As described previously [7–9], people seeking MA through the TelAbortion Project were screened for MA eligibility by study clinicians using videoconference. Sites mailed mifepristone 200 mg and misoprostol 1600 mcg to consenting eligible participants with instructions to take the mifepristone followed within 48 hours by misoprostol. Providers used their standard practice regarding misoprostol dose (800 or 1600 mcg) and route for individual participants. Sites followed participants until abortions were complete and adverse events resolved. Study 1 was conducted under an Investigational New Drug Application filed with the United States Food and Drug Administration (FDA) and ran from 2016 through April 2021. Study 2 was not filed with FDA and ran from late 2020 through September 2021. The overlap reflected the changing regulatory requirements for dispensing mifepristone at that time [14]. The studies were conducted at the same sites and were essentially identical except that the gestational duration (GD) limit for treatment was 63 days in Study 1 and 70 days in Study 2, and the Study 1 protocol included an explicit requirement for pretreatment ultrasound, whereas the Study 2 protocol did not. Despite the Study 1 ultrasound requirement, clinicians at some sites began in March 2020 to omit the ultrasound when deemed necessary for patient welfare during the coronavirus disease 2019 (COVID-19) pandemic. Study 2 did not provide specific criteria for confirming eligibility without ultrasound; each clinician followed their institution's abortion policies. Studies 1 and 2 were approved by the Advarra Institutional Review Board and Allendale Investigational Review Board, respectively, and were registered with clinicaltrials.gov (NCT02513043 and NCT04599725, respectively).

The present analysis followed the same general methods described in our prior paper [6]. Our aim was to compare clinical and service delivery outcomes of participants who had neither an ultrasound nor pelvic examination before treatment ("No-Test" group) and those who had such a test ("Test" group). We used final data from TelAbortion participants screened between March 24, 2020 (the screening date of the first participant after the onset of the COVID-19 pandemic who had a No-Test MA) and September 27, 2021 (the screening date of the last TelAbortion Project participant enrolled) at the five project sites that contributed to our prior paper [6]. These data differ slightly from those used in that paper because of new information obtained since that time. Three of the five sites were Planned Parenthood affiliates (Planned Parenthood of the Rocky Mountains, Planned Parenthood of Montana, and Planned Parenthood North Central States), and the other two were independent (Maine Family Planning, carafem). Collectively, they provided abortion in 10 jurisdictions: Colorado, Georgia, Illinois, Maine, Maryland, Minnesota, Montana, New Mexico, New York, and District of Columbia. We excluded data from the two other sites that did not provide no-test abortions during the time of our prior analysis because the focus of this update paper was to determine whether the findings of the prior paper changed over time. The two excluded sites performed only 26 no-test abortions. As in the prior paper, we excluded participants who did not report the onset date of the last menstrual period (LMP) or who did not ingest mifepristone. If a participant had multiple eligible abortions during the analysis period, we included only the first. We also excluded participants from outcome analyses if we or the site investigator determined that follow-up was insufficient for ascertainment of that outcome.

The clinical outcomes were (1) abortion completed by a procedure or an ongoing pregnancy diagnosed by ultrasound during follow-up; (2) diagnosis of ongoing pregnancy separately; (3) serious adverse events (hospitalization, blood transfusion, or death); and (4) any unplanned abortion-related in-person clinical visit. To ascertain the last of these, both authors independently reviewed data from every in-person posttreatment visit to a medical facility or laboratory and coded it as abortion related if it was motivated by a concern about a medical problem or symptom related to the abortion or it resulted in detection of an abortion-related problem requiring further evaluation or treatment. These criteria were similar to those used for the prior paper [6]. The service delivery outcomes were (1) interval > 7 days between the participant's initial contact with study staff and medication shipment and (2) mifepristone ingestion > 63 days after LMP. The latter analysis excluded participants whose LMPs began > 63 days before initial contact.

As in the prior paper, we estimated unadjusted and adjusted risk differences with 95% CIs to compare outcomes between the No-Test and Test groups. Because we noted different results in participants screened during the period of our previous analysis (on or before September 15, 2020) and those screened later, we analyzed the data separately from the two periods, which we here refer to as Periods 1 and 2, respectively. We generated adjusted risk differences and 95% CIs from logistic regression models with inverse probability of treatment weights to address the imbalance of baseline confounders between groups. First, we calculated propensity scores using logistic regression to model the probability of omitting pretreatment ultrasound or pelvic examination based on the following variables: age group, race/ethnicity, education, number of previous pregnancies (0, 1, ≥2), linear and quadratic terms for GD by LMP at videoconference, urban/rural residence (using US Census designation), distance from participant's residence to the study site (< 150 miles, ≥150 miles), insurance used to pay for the abortion), and study site. In Period 2, the propensity score calculations also included a measure of calendar time, specifically whether the screening date was on or before April 13, 2021, vs later; April 13, 2021, was the date the FDA announced that mailing mifepristone was permitted during the COVID-19 pandemic. Our logistic regression models of clinical outcomes were weighted on propensity scores using stabilized inverse probability of treatment weights. We used the same analysis method for service delivery outcomes, except that in the outcome of mifepristone ingestion > 63 days after LMP, we used GD by LMP at first contact with the site instead of GD at videoconference in propensity score estimation.

To explore temporal trends with more granularity and to better understand how changes in health-seeking behavior over the course of the pandemic may have impacted our results, we divided Period 2 into two subperiods (Periods 2a and 2b) using the April 13, 2021,

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cutoff date. We then used the propensity score weighting method described above to estimate adjusted proportions of participants with clinical outcomes in the No-Test and Test groups in each subperiod and created plots for each group showing the change in these proportions across Period 1 (March 24, 2020, to September 15, 2020, the period of the prior analysis), Period 2a (September 16, 2020, to April 13, 2021, the date of the FDA announcement), and Period 2b (April 14, 2021, to September 27, 2021, the screening date of the last participant enrolled in the study).

We conducted sensitivity analyses of clinical outcomes to examine whether results were robust after excluding participants who had abortion outcome determined based on history alone (i.e., without ultrasonography, serum human chorionic gonadotropin (HCG) measurement, or high-sensitivity urine pregnancy test). We also examined the influence of study attrition using multiple imputations with fully conditional specification to generate outcome values for people excluded due to loss-to-follow-up; we generated 20 data sets with missing outcomes imputed based on modeling the same variables used to calculate propensity scores, performed outcome analysis on each data set, and calculated pooled effect estimates.

We conducted analyses using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

The five study sites provided 1013 TelAbortions to participants screened from March 24, 2020, through September 27, 2021 (Fig. 1). Our analysis excluded 79 (8%) participants because the participant did not take mifepristone, did not report an LMP onset date, or had a previous abortion during the study period. We excluded an additional 154 (15%) participants because follow-up data on clinical outcomes were unavailable. The analysis population comprised 416 participants screened in Period 1 and 364 participants screened in Period 2, including 289 (62%) who had No-Test MA in Period 1 and 170 (47%) with No-Test MA in Period 2.

Pretreatment characteristics of the two groups differed by study group and period. In both periods, participants in the No-Test group were older and earlier in gestation (Table 1). In Period 1, No-Test participants were more likely to be non-Hispanic Black and to live within 150 miles from the study site, but these differences were not apparent in Period 2. Conversely, education did not differ significantly by group in Period 1, but the No-Test participants were more educated in Period 2.

Overall, 740 (95%) of 777 participants with known abortion outcomes had complete abortions without a procedure (Table 2). Complete abortions were confirmed by ultrasound, serum HCG tests, or urine pregnancy test in 654 (88%) of these 740 participants and by history alone in the rest. In the No-Test group, the proportion with test confirmation was significantly higher among participants screened in Period 1 than those screened in Period 2 (93% vs 83%, $p < 0.01$), but did not differ by period in the Test group. One participant in the No-Test group had scant bleeding after treatment and was found by ultrasound to have an ectopic pregnancy. The participant was hospitalized and had surgical treatment Three days after mifepristone ingestion. Two other participants were hospitalized for bleeding and discharged within One day.

Among participants screened in Period 1, the adjusted proportion of those who did not have complete abortions without a procedure was higher in the No-Test group than the Test group (5.6% vs 0.9%, risk difference 4.6%, 95% CI 1.5%, 7.7%, Table 3). The adjusted proportion of participants who had unplanned, abortion-related clinical visits was also higher in the No-Test group in Period 1 (13.3% vs 6.3%, risk difference 7.0%, 95% CI 1.1%, 12.8%). In contrast, in Period 2, we found no significant difference between groups regarding the adjusted proportion who did not have complete abortions without a

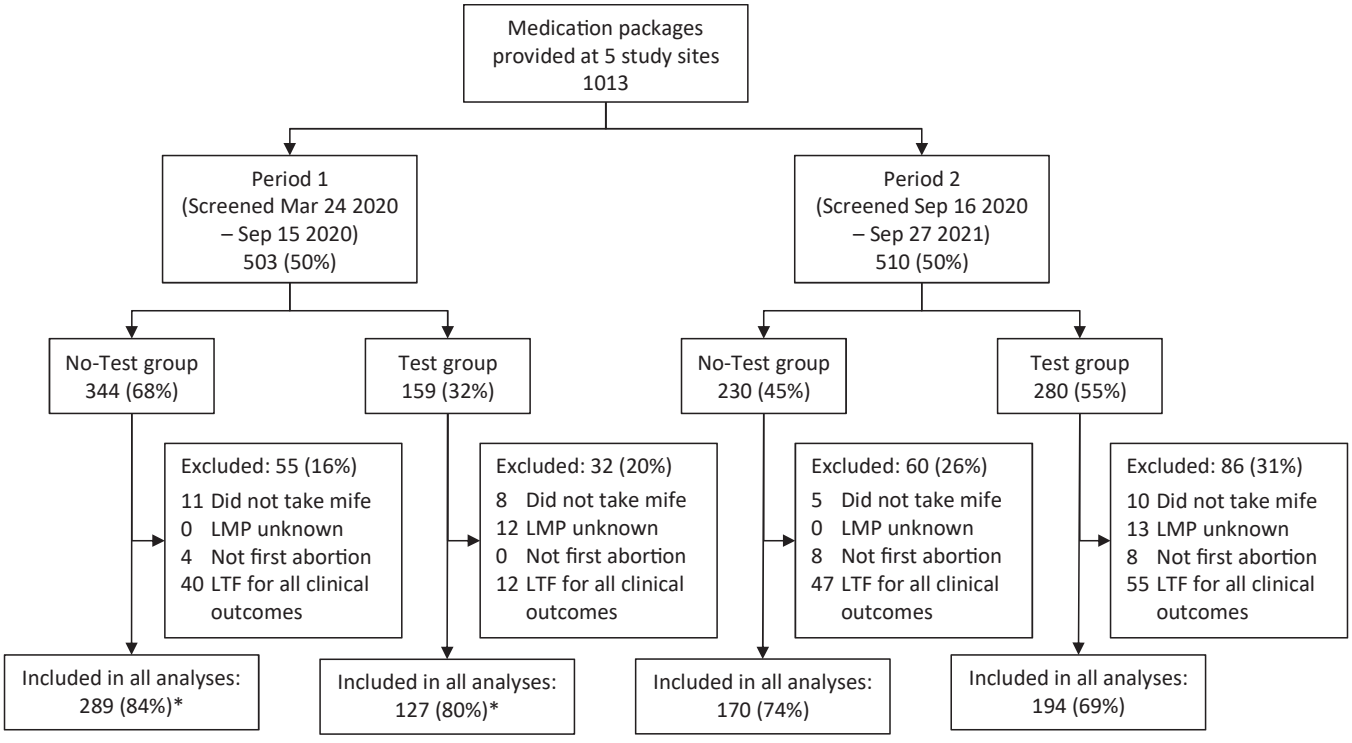

Fig. 1. Study population flowchart, United States, 2020–2021.
Percents are based on the number in the preceding box. The reasons for exclusion are hierarchical in the order listed; each excluded participant is counted only once.
*The numbers of participants in this time interval are more than the corresponding numbers in our prior paper (287 and 125 in the No-Test and Test groups, respectively) [5] because new information obtained after that paper indicated eligibility.
LMP, last menstrual period; LTF, lost to follow-up; mife, mifepristone.

Table 1
Baseline characteristics of analysis population, by study group, United States, 2020–2021, $N = 780$

Characteristic	Period 1 (screened March 24 to September 15, 2020)[a]					Period 2 (screened September 16, 2020, to September 27, 2021)				
	No-Test ($n = 289$)		Test ($n = 127$)		p-value†	No-Test ($n = 170$)		Test ($n = 194$)		p-value[b]
Age (y)					0.02					0.03
17–24	59	20%	41	32%		32	19%	59	30%	
25–34	160	55%	64	50%		97	57%	99	51%	
35–46	70	24%	22	17%		41	24%	36	19%	
Race/ethnicity[c]					0.04					0.24
Non-Hispanic White	159	55%	86	68%		115	68%	124	64%	
Non-Hispanic Black	78	27%	15	12%		17	10%	19	10%	
Hispanic	20	7%	9	7%		15	9%	33	17%	
Native American	11	4%	8	6%		5	3%	6	3%	
Asian/Pacific Islander	8	3%	3	2%		7	4%	6	3%	
Other/multiple	10	3%	5	4%		7	4%	5	3%	
Declined to answer	3	1%	1	1%		4	2%	1	1%	
Education					0.06					< 0.01
Less than high school	9	3%	3	2%		3	2%	2	1%	
High school/GED	66	23%	33	26%		31	18%	48	25%	
More than high school	208	72%	82	65%		123	72%	96	49%	
Unknown/missing	6	2%	9	7%		13	8%	48	25%	
Previous pregnancies					0.12					0.76
0	56	19%	36	28%		55	32%	70	36%	
1	56	19%	23	18%		29	17%	31	16%	
2–13	177	61%	68	54%		86	51%	93	48%	
GD by LMP at videoconference (d)					< 0.01					< 0.01
12–42	115	40%	24	19%		62	36%	30	15%	
42–63	169	58%	88	69%		90	53%	125	64%	
63–101[d]	5	2%	15	12%		18	11%	39	20%	
Urban/rural residence					0.16					0.38
Urban	229	79%	92	72%		121	71%	125	64%	
Rural	38	13%	26	20%		48	28%	68	35%	
Unknown or missing	22	8%	9	7%		1	1%	1	1%	
Distance to study site					< 0.01					0.82
< 150 miles	198	69%	61	48%		73	43%	81	42%	
≥150 miles	91	31%	66	52%		97	57%	113	58%	
Payment for abortion care					0.19					0.94
Insurance used	75	26%	41	32%		45	26%	52	27%	
Self-pay or abortion fund	214	74%	86	68%		125	74%	142	73%	
Date of first contact with site										
Mar 24, 2020, to Sep 15, 2020	289	100%	127	100%		0		0		
Sep 16, 2020 to Apr 13, 2021	0		0			66	39%	146	75%	
Apr 14, 2021 to Sep 27, 2021	0		0			104	61%	48	25%	
Study site					< 0.01					< 0.01
Maine Family Planning	21	7%	4	3%		32	19%	9	5%	
Planned Parenthood of the Rocky Mountains	37	13%	40	31%		40	24%	90	46%	
Carafem	150	52%	28	22%		15	9%	20	10%	
Planned Parenthood of Montana	25	9%	30	24%		43	25%	35	18%	
Planned Parenthood North Central States	56	19%	25	20%		40	24%	40	21%	

GED, General Education Development; GD, gestational duration; LMP, onset of last menstrual period.
[a] The number of participants in this time interval is four more than the number in our prior paper [5] because new information obtained after that paper indicated eligibility.
[b] p-values calculated using χ^2 test of association.
[c] Participants could choose multiple responses. We coded each participant as Hispanic if that choice was checked, and otherwise as indicated.
[d] GD at provision of medications ranged from 25 to 72 d after last menses onset in the No-Test group and from 33 to 78 d by ultrasound in the Test group.

procedure (risk difference −1.2%, 95% CI −5.0%, 2.7%). Those in the No-Test group were significantly less likely than those in the Test group to have unplanned, abortion-related clinical visits (9.9% vs 20.5%, risk difference −10.6%, 95% CI −20.1%, −1.1%). Risks of other clinical outcomes did not differ significantly by group in either period. Unadjusted results are presented in Appendix A Table 1. Sensitivity analyses that excluded individuals with abortion outcomes determined based on history alone and that used multiple imputation to estimate outcomes for those excluded due to loss-to-follow-up yielded similar results (data not shown).

Participants in the No-Test group were significantly more likely to have eligibility confirmed and abortion medications mailed within Seven days after screening; the adjusted risk differences were > 13 percentage points in both periods (Table 3). The adjusted proportion of participants who took mifepristone more than 63 days gestation did not differ significantly between groups. Based on all information obtained before and after treatment, no participant is known to have ingested mifepristone at > 80 days of gestation.

In the Test group, the adjusted proportion of participants who did not have complete abortions without a procedure and who had unplanned, abortion-related clinical visits both increased across the duration of the study, from Period 1 to Period 2a and to Period 2b (Fig. 2). In the No-Test group, the proportions of participants with these outcomes were highest in Period 1 when the no-test approach was new to sites, then declined in Period 2a and rose in Period 2b. These outcomes were more common in the No-Test group than in the Test group in Period 1, but in Period 2a and 2b, these outcomes were more common the Test group. The risk of these outcomes rose substantially in both groups over the course of Period 2.

4. Discussion

This updated analysis corroborates some key findings from our earlier paper [6]. Specifically, it confirms that providing MA to people selected using history alone, without pretreatment ultrasound or pelvic examination, was not associated with increased risks

Table 2
Clinical outcomes in analysis population, by study group, United States, 2020–2021, *N* = 779

Characteristic	Period 1 (screened Mar 24 to Sep 15, 2020)[a]				Period 2 (screened Sep 16, 2020, to Sep 27, 2021)			
	No-Test		Test		No-Test		Test	
	n	%	*n*	%	*n*	%	*n*	%
Abortion outcomes								
Total with known outcomes	289		125		169		194	
Complete abortion without procedure	273[a]	94	123	97	161	95	183[a]	94
Confirmed by test[b,c]	253	93	111	90	133	83	157	86
Confirmed by history alone[c]	20	7	12	10	28	17	26	14
Procedure to terminate pregnancy	15	5	1	1	8	5	11	6
Ongoing pregnancy	4	1	1	1	5	3	4	2
Ectopic pregnancy	0	0	0	0	1	1	0	0
Other reason	11	4	0	0	2	1	7	4
Ongoing pregnancy not aborted	1	< 1	1	1	0	0	0	0
Serious adverse events								
Total with known outcomes	289		125		169		194	
Hospitalization	0		1	1	1	< 1	1[d]	< 1
Transfusion	2	1	0		0		1[d]	< 1
Deaths	0		0		0		0	
Unplanned, abortion-related, in-person visits								
Total with known outcomes	288		126		170		193	
Visits	36	13	12	10	21	12	38	20
Emergency department visits	9	3	5	4	5	3	13	7

Two participants in the Test group in the earlier period and one in the No-Test group in the later period were excluded from the analyses of abortion outcomes and serious adverse events because they had insufficient follow-up. One participant in each group in the earlier period and one in the Test group in the later period were excluded from the visits analysis because they had insufficient follow-up.

[a] One participant in the No-Test group and three in the Test group received misoprostol not supplied by the study and thus may have taken more than 1600 mcg misoprostol in total.

[b] Complete abortion confirmed by ultrasound, serum HCG tests, or urine pregnancy test.

[c] Proportion is among those with complete abortion without procedure.

[d] One participant had both a hospitalization and a transfusion.

of failure to terminate ongoing pregnancy or of posttreatment serious adverse events. Moreover, No-Test group participants were more likely to receive treatment within a week after initially contacting the study site.

Importantly, our new results appear to mitigate the findings of possible drawbacks of No-Test MA reported in our prior paper [6]. Among participants screened in the period of the prior study, those in the No-Test group were significantly more likely than those in the Test group to require a procedure to fully complete the abortion and to have unplanned clinical visits for abortion-related reasons. However, these elevated risks did not persist: in the later study period, abortion outcomes were similar in the two groups, and the No-Test group was less likely to have unplanned abortion-related visits after treatment. This marked temporal change cannot be directly explained by our data, but we note that the earlier period included the initial months of the COVID-19 pandemic, during which

Table 3
Adjusted risk difference in clinical and service delivery outcomes between No-test and Test groups in TelAbortion study, United States, 2020–2021, *N* = 780

	Period 1 (screened Mar 24 to Sep 15, 2020)		Period 2 (screened Sep 16, 2020, to Sep 27, 2021)	
	n/*N* (adjusted %)	Risk difference (95% CI)	*n*/*N* (adjusted %)	Risk difference (95% CI)
Procedure intervention or ongoing pregnancy[a]				
No-Test	16/289 (5.6%)	4.6% (1.5%, 7.7%)	8/169 (3.4%)	−1.2% (−5.0%, 2.7%)
Test	2/125 (0.9%)		11/194 (4.6%)	
Ongoing pregnancy[a]				
No-Test	5/289 (1.6%)	0.7% (−1.3%, 2.7%)	5/169 (2.0%)	0.4% (−2.0%, 2.9%)
Test	2/125 (0.9%)		4/194 (1.6%)	
Hospitalization, transfusion, or death[a]				
No-Test	2/289 (1.0%)	0.1% (−2.1%, 2.4%)	1/169 (0.3%)	0.0% (−0.8%, 8.6%)
Test	1/125 (0.9%)		1/194 (0.3%)	
Unplanned in-person abortion-related clinical visit[b]				
No-Test	36/288 (13.3%)	7.0% (1.1%, 12.8%)	21/170 (9.9%)	−10.6% (−20.1%, −1.1%)
Test	12/126 (6.3%)		38/193 (20.5%)	
> 7 d from first contact to shipment				
No-Test	54/289 (19.6%)	−19.4% (−31.5%, −7.3%)	21/170 (16.1%)	−13.8% (−25.9%, −1.6%)
Test	49/127 (39.0%)		73/194 (29.9%)	
GD at mifepristone ingestion > 63 d[c]				
No-Test	22/283 (9.0%)	−6.2% (−14.5%, 2.2%)	7/154 (10.7%)	−0.3% (−11.0%, 10.4%)
Test	22/118 (15.2%)		28/168 (10.9%)	

GD, gestational duration.

Proportions and risk differences are adjusted using inverse probability of treatment weighting (IPW) with stabilized weights. Propensity scores in IPW models were generated based on modeling the likelihood of having a No-Test MA based on age group, race/ethnicity, education, number of previous pregnancies, GD, urban/rural residence, distance from participant's residence to the study site, insurance used to pay for the abortion, and study site. Propensity score generation in the later period also incorporated screening date (≤April 13, 2021, vs ≥April 14, 2021).

[a] Two participants in the Test group in the earlier period and one in the No-Test group in the later period were excluded because they had insufficient follow-up for this outcome.

[b] One participant in each group in the earlier period and one in the Test group in the later period were excluded because they had insufficient follow-up.

[c] Analysis includes only participants with GD ≤63 d by LMP at first study contact. Model includes GD at first contact instead of GD at time of videoconference.

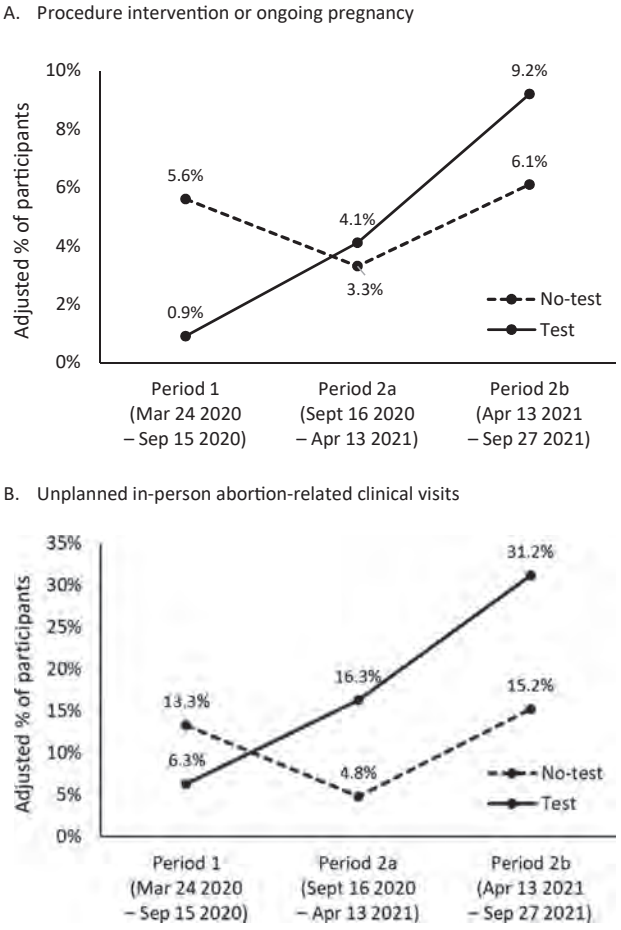

Fig. 2. Adjusted proportion* of participants with selected outcomes by study group over time, United States, 2020–2021, $N = 780$. A. Procedure intervention or ongoing pregnancy. B. Unplanned in-person abortion-related clinical visits.
*Adjusted proportions calculated from logistic regression models with inverse probability of treatment weighting (IPW). Propensity scores in IPW models were generated based on modeling the likelihood of having a No-Test MA based on age group, race/ethnicity, education, number of previous pregnancies, gestational duration, urban/rural residence, distance from participant's residence to the study site, insurance used to pay for the abortion, screening date, and study site.

physical distancing was strongly recommended to minimize infection risk [15]. We postulate that this recommendation may have resulted in a transient reduction in the frequency of in-person visits for nonserious problems in the Test group. However, because the no-test approach was novel in the United States in 2020 [16], unfamiliarity with the protocol may have led providers to encourage participants in the No-Test group to seek follow-up in person despite the pandemic. Subsequently, as pandemic concerns waned, participants in the Test group may have resumed a more typical pattern of in-person care for posttreatment concerns. In contrast, in the No-Test group, as experience with the no-test protocol grew, participants and their providers may have become more comfortable managing problems without in-person evaluation. Moreover, people who choose to have abortions without pretreatment tests may in general be inclined for many reasons to forgo in-person health care unless critically needed. These explanations are supported by our visual analysis of temporal trends and suggest that the favorable findings of the new data should reflect the expected pattern going forward.

The strengths of this study include prospective collection of data according to a standardized protocol, geographic diversity, the fairly high follow-up rate of 83% for all outcomes, and confirmation of complete abortion using objective tests in 88% of participants with that outcome. The study was not randomized, but we used robust methods to adjust for baseline differences between groups. However, the sample size was relatively small. Furthermore, abortions were provided by telemedicine and mail; the results may not apply to patients who have in-person care.

Currently, the FDA-approved label for mifepristone [17] lacks clarity regarding the advisability of using clinical history alone, without ultrasound or physical examination, to assess eligibility for provision of the drug. Although this screening approach can, in rare cases, result in treatment of someone with undetected advance gestation or ectopic pregnancy [18], our analysis strengthens the substantial evidence supporting the safety and effectiveness of this practice [3], as well as its benefit in accelerating treatment provision. We hope that these findings help prompt mifepristone manufacturers to submit and FDA to approve a label revision that explicitly reflects this evidence. Meanwhile, providers should routinely offer the no-test option to suitable patients following evidence-based guidelines [1,2,19].

Author contributions

H.A.A.: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. E.G.R.: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.contraception.2024.110552.

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Miles and days until medical abortion via TelAbortion versus clinic in Oregon and Washington, USA

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ABSTRACT

Background Medical abortion provided via telemedicine is becoming more widely available, potentially decreasing travel time for in-person abortion evaluation.

Methods We conducted a retrospective chart review of all outpatient medical abortions from October 2016 through December 2019 at our academic medical centre in Portland, Oregon, USA. Using mifepristone administration logs, we identified patients who underwent abortion via direct-to-patient telemedicine or in clinic. Both groups had pre-abortion ultrasound examination. We extracted patient characteristics and geographic data to compare travel distance to clinic, ultrasound facility, and nearest advertised abortion clinic. We compared time from first contact until mifepristone ingestion and gestational age at mifepristone ingestion.

Results Median distance from mailing address to clinic for 80 telemedicine and 124 clinic medical abortions was 95 (range 4–377) and 12 (range 0–184) miles (p<0.01). Distance travelled to ultrasound facility was shorter for telemedicine patients (median 7 miles, range 0–150 vs 12 miles, range 0–184; p<0.01) excluding outliers >200 miles. Distance to nearest advertised abortion clinic was equal between groups (median 7 miles, p=0.4). Time to mifepristone administration (ingestion) was longer (11 vs 6 days; p<0.01) and median gestational age was higher (49 vs 44 days; p=0.01) for telemedicine.

Conclusions Telemedicine increases the reach of abortion providers and provides care to more geographically distant patients. Patients chose telemedicine abortion even when they had an equidistant option, suggesting that patients value telemedicine for reasons other than geographic convenience. This telemedicine delivery model that included ultrasound testing prior to abortion resulted in up to a 5-day delay in abortion initiation, which was not clinically significant.

Key messages

- Telemedicine expands geographic access to abortion in Oregon and Washington and does not result in clinically significant delayed care even when requiring ultrasound examination.
- Patients may choose to undergo abortion via telemedicine, even when an abortion clinic is geographically convenient.

INTRODUCTION

Compared with other regions of the United States (US), abortion is relatively accessible in the Pacific Northwest: in Oregon and Washington combined, there are more than 50 abortion clinics with regularly available appointments.[1] Despite the abundance of providers, most abortion clinics are located in urban centres, with 10% of reproductive-aged women in Washington and 23% in Oregon living in a county without an abortion clinic.[1] The provision of medical abortion is also limited by the US Food and Drug Administration (FDA), including an explicit requirement for dispensing mifepristone in a medical office or hospital and prohibition of pharmacy dispensing.[2] This requirement limits the ability to provide medical abortion via telemedicine, even while use of telemedicine is a rapidly expanding mode of healthcare administration globally.

In 2016, the TelAbortion Study began offering medical abortion via direct-to-patient telemedicine, dispensing mifepristone via mail under an Investigational New Drug application.[3] Patients complete pre-screening tests at local facilities, meet with a provider via videoconference, and receive the medication via mail.[3]

Currently, the TelAbortion Study is the only legally recognised way patients in the US can access medical abortion without entering a physical abortion clinic.[4] Telemedicine alleviates barriers to medical abortion such as the need to secure childcare or take time off work, and improves access for geographically remote patients by decreasing travel time and cost.[5–9]

We sought to compare demographic and geographic characteristics between patients choosing TelAbortion (telemedicine) versus clinic medical abortion at our urban, academic Family Planning Clinic in the Pacific Northwest. We questioned whether distance from an abortion clinic was farther for those undergoing TelAbortion and whether those choosing TelAbortion experienced later care due to a multistep process when ultrasound is a pre-abortion requirement.

METHODS

Study design

We performed a retrospective chart review of all medical abortions initiated at the Family Planning Clinic at Oregon Health & Science University (OHSU) between 1 October 2016 and 31 December 2019 to compare patient and procedural characteristics by method of care delivery: telemedicine or clinic.

Comparison groups

During the study period, our site provided medical abortion both via TelAbortion (telemedicine) and in clinic, self-selected by the patient.[3] Patients interested in telemedicine accessed a TelAbortion website and hotline to begin the study screening process, which included a requirement to be in Oregon or Washington for the videoconference and to receive medications via mail. They completed a gestational dating ultrasound at the facility of their choice. We accepted both formal and informal reports, given there was documentation of the ultrasound date, finding of intrauterine pregnancy, and gestational size. Unless Rhesus (Rh)-type was known, patients completed Rh-testing at the location of their choice. Patients visited with a provider through videoconference and received standard pre-abortion counselling and consent. After confirming eligibility and enrollment, we mailed abortion medications directly to the patient. Patients who called the main Family Planning Clinic phone number requesting medical abortion were scheduled in clinic. The clinic scheduler did not routinely offer TelAbortion, but referred patients to the study as requested. Patients presenting in clinic for medical abortion received ultrasound, Rh-typing, and mifepristone while on site. We sent additional prescriptions, including misoprostol, to the patient's chosen pharmacy.

During the study period, TelAbortion operated under two different billing models. From October 2016 to June 2018, TelAbortion patients underwent a video evaluation visit and obtained all medications at no cost, and received US$50 for study completion. Patients who called the main clinic telephone number were not informed that TelAbortion was available for no cost. After July 2018, the TelAbortion study transitioned to routinely billed care where patients or their insurance were responsible for all costs associated with medical abortion: ultrasound, Rh-typing and follow-up tests, as well as the video evaluation visit and medications. This change aligned the TelAbortion payment model with the clinic payment model.

For inclusion in this chart review, we used research and clinic mifepristone dispensing logs to identify eligible cases of induced medical abortion at <10 weeks' gestation, excluding patients aged <18 years, or without confirmed intrauterine pregnancy or non-viable pregnancies. These criteria matched the inclusion criteria of the TelAbortion study. We then compared patient characteristics and distance to care between those who initiated medical abortion via telemedicine versus in clinic. The Institutional Review Board at OHSU approved a waiver of consent.

Data collection

We collected variables from the electronic health record and entered data directly into REDCap (Research Electronic Data Capture).[10] Variables included age, race, ethnicity, mailing address, ultrasound facility address, gravidity/parity and gestational age based on ultrasound. We also collected time variables such as: date of first contact, defined as the first time the patient specifically requested abortion services, date of mifepristone delivery as determined from postal tracking, and self-reported date of mifepristone administration (ingestion). Gestational age was calculated by ultrasound or by last menstrual period if gestational age on ultrasound was non-specifically documented. We did not collect insurance data since many TelAbortion patients did not provide their primary insurance information when choosing to self-pay. For repeat abortions, we only included the first abortion. We included patients who were lost to follow-up in all analyses except those related to unknown mifepristone ingestion date.

For distance calculations, we used the patient mailing address listed in the electronic health record at the time of chart review. We marked addresses as 'confirmed' for the abortion date if the patient did not have a repeat visit in our healthcare system after their abortion, as addresses are confirmed or updated as necessary at every visit. Address data for patients without repeat visits are more reliable, as their documented address could not have been updated since the time of abortion. We categorised mailing addresses by county and as urban or rural as defined by 2010 Census Urbanized Areas or 2010 Census Urban Clusters.[11]

We identified abortion clinics by searching Google Maps for 'abortion clinic'. Abortion providers at our institution reviewed this list carefully for known clinics and we excluded clinics that did not advertise abortion on their website.

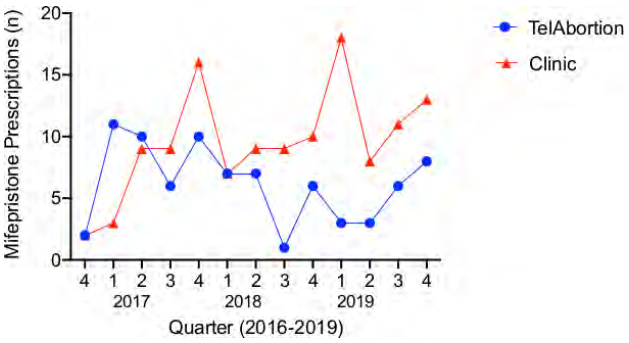

Figure 1 Mifepristone prescriptions written per quarter from October 2016 through December 2019 by method of delivery: TelAbortion (n=80) or clinic (n=124). This figure includes 21 TelAbortion patients with unknown dates of mifepristone ingestion (21/80, 26.3%). All clinic patients had known dates of mifepristone ingestion. There was not a significant difference in trend between either delivery method over time.

Statistical analysis

The primary outcome was the proportion of patients traveling ≥25 miles for abortion care based on method of care delivery: TelAbortion versus clinic. We selected this cut-off because a 25-mile radius from our clinic covers the Portland metro area. Based on case numbers over time at our Family Planning Clinic, in this convenience sample we estimated needing approximately 50% TelAbortion patients compared with clinic patients (60 vs 120) to be able to see at least a 15% difference between groups for the proportion travelling more than 25 miles for their abortion care.

We exported collected data to STATA Version 16.1 for analysis (StataCorp LP, College Station, TX, USA). We compared TelAbortion versus clinic groups using t-tests for continuous variables, chi square for categorical variables, and Wilcoxon rank sum tests to compare medians for non-parametric distributions. We considered a value of $p<0.05$ a significant result.

Distances were calculated using the 'georoute' programme in STATA which uses the HERE application programming interface to calculate the driving distance between two locations.[12] We compared median distances using the Wilcoxon rank sum test. We defined distance to care differently for the two groups. For TelAbortion patients, we measured distance to care as distance from mailing address to their respective ultrasound facility. We did not include distance to a laboratory since not all TelAbortion patients required testing and many were able to obtain this at a similar location to the ultrasound. For clinic patients, we measured distance to care as distance from mailing address to our Family Planning Clinic. We planned to exclude patients from this distance analysis if they did not have a mailing address listed or if they travelled more than 200 miles for care. We recognised that significantly large distances occurred in unique situations, such as obtaining an ultrasound while travelling out of state.

We also compared median distance from the patient's mailing address to the nearest advertised abortion clinic. We further used this list of advertised abortion clinics to determine the proportion of patients with a mailing address in a county without an abortion clinic.

Secondary outcomes included patient and procedure characteristics, including time from first clinic contact to mifepristone ingestion date.

RESULTS

From October 2016 through December 2019, 204 medical abortions were performed at OHSU through the Family Planning Clinic: 80 via TelAbortion (38.9%) and 124 in clinic (61.1%). There was a gap in service delivery of TelAbortion at the time of transition from free to billed visits in the third quarter of 2018, but otherwise there was not a significant difference in trend between either delivery method over time (figure 1).

Demographic outcomes

On average, patients in both groups were 30 years old and had a mailing address in an urban area. While overall demographic characteristics between the two groups were similar, there were some notable differences in race. The TelAbortion group had a higher proportion of White/Caucasian patients and the clinic group had a higher proportion of Asian patients (table 1). Patients undergoing TelAbortion were more likely to have a prior induced abortion (table 1). Mean time from first contact for scheduling to mifepristone administration was longer for TelAbortion (11 vs 6 days; $p<0.01$). Over three-quarters of TelAbortion patients received mifepristone via mail within 2 days of prescription signature (61/80, 76.3%, range 1–8). Median time from mifepristone delivery to mifepristone ingestion for TelAbortion patients was 2 (range 1–8) days. Date of mifepristone ingestion was not reported by 21 TelAbortion patients (26.3%). All clinic patients ingested mifepristone on the date of prescription signature. Median gestational age was clinically similar at mifepristone ingestion (49 vs 44 days; $p=0.01$). A similar proportion of TelAbortion and clinic patients initiated abortion after 63 days' gestation.

Geographic outcomes

We excluded four TelAbortion patients and three clinic patients from distance analyses, as their distance to care was greater than 200 miles. We excluded one additional clinic patient from these analyses due to missing address (total excluded: 5.0% vs 3.2%). Excluding these patients, median distance from address to our Family Planning Clinic was 95 (range 4–377) miles for TelAbortion and 12 (range 0–184) miles for clinic patients ($p<0.01$). However, median distance travelled for care was only 7 (range 0–150) miles for TelAbortion versus 12 (range 0–184) for clinic patients ($p<0.01$). Fewer TelAbortion patients had to travel ≥25 miles for their abortion care (5/76, 6.6% vs 26/120, 21.7%;

Table 1 Demographic characteristics of patients undergoing medical abortion via TelAbortion or in clinic in our retrospective study of care delivery method (n=204)

Demographic	TelAbortion patients (n=80)	Clinic patients (n=124)	P value
Age at consent (years)	30.9±6.1	30.3±7.1	0.54
Location of patient mailing address			
Oregon	44 (55.0)	115 (92.7)	<0.01
Washington	36 (45.0)	7 (5.7)	
Other	0	2 (1.6)	
Address classification*			
Urban	67 (83.8)	104 (83.9)	0.63
Rural	67 (83.8)	15 (12.1)	
Not classified	1 (1.3)	4 (3.2)	
No address listed	0	1 (0.8)	
Race			
White/Caucasian	67 (83.8)	84 (67.7)	0.01
African American/Black	4 (5.0)	5 (4.0)	
Asian	1 (1.3)	18 (14.5)	
Native Hawaiian/Pacific Islander	0	3 (2.4)	
Native American/Alaska Native	1 (1.3)	0	
Multiracial	2 (2.5)	8 (6.5)	
Unknown	5 (6.3)	6 (4.8)	
Ethnicity			
Hispanic/Latina	12 (15.0)	8 (6.45)	0.12
Not Hispanic/Latina	66 (82.5)	111 (89.5)	
Unknown	2 (2.5)	5 (4.1)	
New patient			
Yes	76 (95.0)	107 (86.3)	0.05
No	4 (5.0)	20 (13.7)	
Address confirmed†	62 (81.6)	68 (56.7)	<0.01
Gravidity			
First pregnancy	22 (27.5)	47 (37.9)	0.13
Prior pregnancies	58 (72.5)	77 (62.1)	
Prior induced abortion	31 (53.5)	20 (26.0)	0.01
Rhesus (Rh)- type			
Positive	72 (90.0)	106 (85.5)	0.26
Negative	6 (7.5)	17 (13.7)	
Unknown	2 (2.5)	1 (0.8)	
Gestational size on date of mifepristone administration (days)‡§	49(42–58)	44(41–52)	0.01
≤42	15 (25.4)	54 (43.6)	0.08
43–49	16 (27.1)	28 (22.6)	
50–56	10 (17.0)	23 (18.6)	
57–63	12 (20.3)	13 (10.5)	
64–70	6 (10.2)	6 (4.8)	

Data are mean±SD, n (%) or median (IQR).
*As defined by 2010 Census Urbanized Areas or 2010 Census Urban Clusters.
†Address marked 'confirmed' if patient did not have a repeat visit in our healthcare system after abortion, as addresses are confirmed or updated as necessary at every visit.
‡Excludes 21 participants with unknown mifepristone administration dates.
§Gestational size based on ultrasound measurements or last menstrual period if unmeasured.

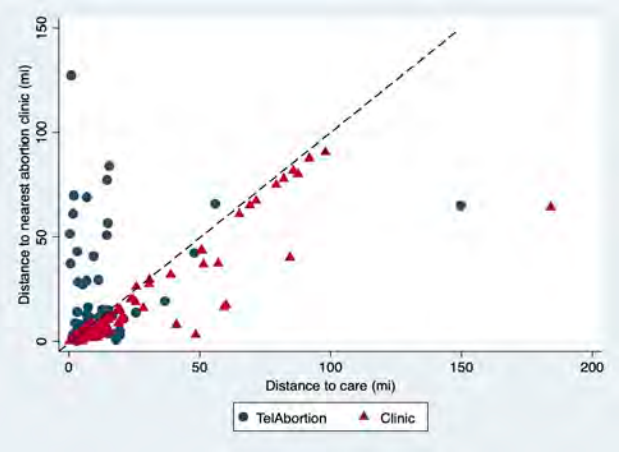

Figure 2 Distance to care versus distance to nearest abortion clinic, excluding four TelAbortion patients and three clinic patients who traveled >200 miles for care, and one clinic patient with unknown address. TelAbortion (n=76) and clinic patients (n=120) live similar distances to the nearest abortion clinic, but TelAbortion patients travelled a shorter distance to receive abortion care. The dashed line provides a reference for where abortion care chosen and nearest abortion clinic are equidistant. Points above the reference line represent individuals who are located farther away from an abortion clinic than the distance they travelled for abortion care. Points below the reference line represent individuals whose nearest abortion clinic is farther away than the distance they travelled for abortion care.

p=0.01). Median distance from mailing address to the nearest advertised abortion clinic was 7 (range 0–127) miles for TelAbortion and 7 (range 0–91) miles for clinic patients (p=0.4) (figure 2). Figure 2 depicts the relative distance to care versus distance to nearest abortion clinic for each individual.

TelAbortion patients were more likely than clinic patients to live in a county without an advertised abortion clinic (19/76, 25.0% vs 19/120, 15.8%; p=0.11). Similarly, more TelAbortion patients than clinic patients had a mailing address ≥25 miles from an abortion clinic (19/76, 25.0% vs 20/120, 16.7%; p=0.15).

Of the 76 TelAbortion patients included in distance analyses, 49 (64.5%) had free telemedicine visits and recived US$50 TelAbortion study compensation and 27 (35.5%) underwent routinely billed care or self-pay with no compensation. These two groups had similar distances to care. We also found similar distance results when analysing data only from patients with confirmed addresses.

DISCUSSION

In our cross-sectional study comparing characteristics and geographic location of medical abortion patients in Oregon and Washington, we found that patients who underwent TelAbortion had mailing addresses farther away from our Family Planning Clinic than patients who underwent medical abortion in person. This finding supports previous hypotheses that telemedicine may increase the reach of abortion providers and provide care to more geographically distant patients.[3]

Interestingly, TelAbortion patients and clinic patients were located similar distances from their nearest advertised abortion clinic, suggesting that distance from an abortion clinic may not be the primary reason patients opt for care via telemedicine, at least in this region. More than 90% of TelAbortion patients did not have to travel more than 25 miles for an ultrasound, demonstrating that ultrasound is a geographic option for most patients.

Telemedicine patients lived similar distances to an abortion clinic as their clinic counterparts, yet they still chose telemedicine. Although our results come from a single site, our findings demonstrate that TelAbortion offers something appealing to patients beyond simple geographic convenience, such as confidentiality, anonymity or facility hours that are more convenient.

We hypothesise that direct-to-patient care may reduce the need for childcare and lower additional abortion-related expenses, thus removing significant barriers for some patients. Patients may prefer flexible timing for mifepristone administration or ultrasound examination. Patients may also feel an increased sense of privacy meeting with their provider from their home, avoiding protestors and limiting exposure to COVID-19. Cost may be a further deciding factor for many patients. Telemedicine creates new financial options by allowing women without abortion coverage to use their insurance for ultrasound and laboratory tests. Alternately, patients may not decide where to undergo abortion based on full knowledge of the process specifics, such as appointment length, ultrasound requirements or cost. Full transparency about these details can help patients make an informed choice.

A limitation of this study is our inability to confirm that the mailing address listed in the electronic health record was the patient's physical address at the time of the abortion. However, repeat analyses including only patients whose addresses could be confirmed yielded similar results. It is also possible that we underestimated distance, as we did not include distance to a laboratory in our analyses and excluded those >200 miles from care. Due to limitations of a chart review, we were unable to collect further socioeconomic data to determine if TelAbortion improves abortion access for specific groups. We could not determine if patients choosing TelAbortion could have accessed in person care if telemedicine was not available, and we did not assess reasons for choosing a particular method.

Our TelAbortion study site followed the same workflow for both telemedicine and clinic patients. Appointments were available after a similar intake process, with the same providers, during the same hours, and with the same after-hours resources. Despite needing to coordinate multiple steps and wait for mifepristone to arrive via mail, TelAbortion patients only had a 5-day delay in abortion initiation. We could not determine if patients would have experienced further delays without this option. We do not think this 5-day difference is clinically significant, but assessment of timeliness of access is important in future studies. While ultrasound may be geographically feasible for women in our region, requiring an ultrasound may contribute to the delay and create a medically unnecessary emotional, social or financial burden for patients. Programmes should not require ultrasound examination for documentation of gestational age for most patients, as medical abortion can be performed safely without ultrasonography.[13–15]

TelAbortion increases abortion availability by creating another option that may be more acceptable and satisfactory to some patients than physically presenting to a nearby clinic. Despite close proximity to an abortion clinic, patients still chose TelAbortion, even when it meant travelling farther for care and experiencing a 5-day delay in abortion initiation. Further research should investigate reasons for choosing telemedicine and barriers to choosing telemedicine, as these factors may help shape policy and provide guidance for increasing equitable access to abortion.

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Patient consent for publication Not required.

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"It Was So Easy in a Situation That's So Hard": Structural Stigma and Telehealth Abortion

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Abstract

For decades, sociological research has examined the role of stigma in contributing to health disparities, yet such research seldom grapples with the interplay between individuals and structures. There is a particular paucity of research on abortion that concurrently examines individual experiences with stigma and structural barriers. In this article, we use telehealth abortion as a case, which now accounts for one in five abortions in the United States. We conducted 30 interviews and approach the data using a structural stigma framework in tandem with conceptualizations of felt, internalized, and enacted stigma. Findings advance a sociological theory of structural abortion stigma: a combination of structural barriers, internalized beliefs, and interpersonal shame. Telehealth reduces structural barriers to abortion and mitigates internal and interpersonal experiences of stigma. The latter is achieved by the ability to avoid the traditional abortion clinic, which many interviewees view as the site where stigma is produced and experienced.

Keywords

abortion, inequality, reproduction, stigma, telehealth

> For the regular [American Medical Association] AMA physicians, the limitation of abortion became one way of asserting their own professional domination over other medical practitioners. In their crusading, these physicians had translated the social goals of cultural and professional dominance into moral and medical language. They lobbied long and hard to convince legislators of the danger and immorality of abortion. (Conrad and Schneider 1980:12)

Abortion in the United States is a highly common medical experience, and yet it has been subject to a unique stigmatization process. This stigma has translated to decades of anti-abortion legislation, which came to a tipping point in 2022 after the *Dobbs v. Jackson Women's Health Organization* Supreme Court decision overturned *Roe v. Wade*. Abortion has largely been overlooked by sociologists as a site of theoretical exploration despite representing a growing structural problem with major implications for social inequality and health disparities. Specifically, only seven articles on abortion have been published in top sociological journals since the year 2000 (Kimport and Kreitzer 2023). And yet, analyzing abortion care provides a critical case for exploring key questions within sociology regarding stigma as well as medicalization,

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cultural norms, gender and sexuality, social movements, and structural inequality.

In fact, in a now canon text in sociology, Conrad and Schneider (1980) utilize the case of abortion to develop a theory on medicalization and deviance—two central themes in sociology. As their work argues, abortion became moralized in the mid-nineteenth century United States to professionalize medicine and assert dominance over alternative healers and midwives. This history clashes with a common assumption in the cultural imaginary that "[a]bortion was always defined as deviant and illegal in America prior to the Supreme Court's landmark decision in 1973" (Conrad and Schneider 1980:11) The assumption that abortion has always been (and thus will always be) defined as deviant has allowed for abortion care to be marginalized by two key social institutions: medicine and the law. Abortion care in the United States has long been siloed to a limited number of freestanding clinics that are frequented by protestors, which further denotes abortion as separate from "ordinary" gynecological and reproductive health care. Abortion is incredibly common; 25% of pregnancies end in abortion (Jones 2024). However, abortion training is largely left out of medical school curriculums: Half of medical schools offer no formal training on abortion or only a single lecture (Burns and Shaw 2020). The lack of training in tandem with the stigma and violence against abortion providers for doing "dirty work" have led to decreased numbers of providers over time (Joffe 2010). Legislation is also regularly passed to limit access to abortion via politically motivated abortion bans, the closing of physical clinics, and the exclusion of abortion from insurance plans and Medicare (Cohen and Joffe 2020). Taken together, individual beliefs about abortion being immoral or worthy of stigma become codified structurally such that abortion is continually medically inaccessible and under legislative attack.

However, most sociological work on abortion focuses on the individual level, including examinations of the ideological underpinnings of abortion stigma (Kumar, Hessini, and Mitchell 2009; Luker 1984) and analyses of abortion patients' internalized feelings of shame (Becker 2019; Cockrill and Nack 2013), fear of being stigmatized (Hanschmidt et al. 2016), and secrecy behaviors (Cowan 2017). This work is largely separate from work on the structural barriers to abortion, which primarily come from the field of public health and focus on barriers to care (Biggs et al. 2020; Upadhyay, Cartwright, and Grossman 2022; Upadhyay, McCook et al. 2021). In this article, we advance a sociological theory on "structural abortion stigma," which refers to the ways in which the stigmatization of abortion operates on the macro (state- and nation-wide legislation) level and in turn manifests in the meso (medical institutions, interpersonal interactions) and micro (individual) levels. In the process, this article provides a sociological framework for how cultural norms and stigma around abortion coalesce to create structural inequity to abortion access. As we argue, the social conditions, organizations, systems, and policy around abortion produce the individual-level phenomena that scholarship on abortion stigma tend to focus on. Moreover, by focusing on telehealth abortion as a case, we demonstrate how telehealth—a practice that is becoming an increasingly established norm in health care—can mitigate the effects of stigma across other cases.

BACKGROUND

Barriers to Abortion Care

Barriers to abortion care are manifold because its provision is often constrained by ideological political decisions rather than driven by scientific evidence. Patients in need of abortion care must often travel for care—whether to the other side of the city or across state lines—because its provision is excluded from the formal health care system (Kimport and Rasidjan 2023). Therefore, access hinges on a patient's socioeconomic status given limitations in many states on private insurance coverage for abortion and the Hyde Amendment, which bars abortion coverage for patients in many states on Medicare and Medicaid (Dennis, Blanchard, and Cordova 2011). Beyond paying for the abortion itself, other costs arise in the form of travel, time off work, the cost of childcare and dependent care, and the cost of lodging, particularly for those living in states with waiting periods, which require 24 to 72 hours in between an initial clinic visit and the abortion itself (Upadhyay, Cartwright, and Grossman 2022). Gestational limits are also a substantial barrier, particularly for those experiencing pregnancy complications at later gestations, and few clinicians provide abortions at later gestations (Foster, Dobkin, and Upadhyay 2013). Moreover, abortion medications are under intense legal scrutiny, including the recent Supreme Court case *U.S. Food and Drug Administration v. Alliance for Hippocratic Medicine* (2024), which experts had anticipated would severely limit access to mifepristone, the first of two medications typically used in a

medication abortion. Lastly, after the *Dobbs* decision that overturned *Roe v. Wade*, abortion bans in various states have led to the criminalization of abortion for patients, providers, or both. This criminalization carries over to self-managed abortion. The criminalization of abortion, in part, distinguishes structural stigma of abortion from structural barriers. Using structural stigma as a lens elucidates the ways that these various barriers to care are a codification of stigma, which ultimately further perpetuate abortion stigma. Although sweeping legislation and increased public education are key for reducing barriers and stigma at the individual level, this article will indicate the ways that telehealth abortion mitigates and disrupts various manifestations of structural abortion stigma.

Telehealth Abortion as a Case

We develop a theoretical framework of structural abortion stigma by using telehealth abortion—in which the entire medication abortion process occurs remotely—as a case. Key cultural, technological, and legislative changes in the past three years have led to increased salience of telehealth abortion. First, the onset of the COVID-19 pandemic necessitated and normalized innovations in remote health care, allowing fully remote telehealth models to expand. Next, at the height of the pandemic, the U.S. Food and Drug Administration permanently lifted restrictions on in-person dispensing of mifepristone (Belluck 2021). These changes permitted the formation of virtual clinics—abortion clinics without an affiliated brick-and-mortar facility—whereas previously, only some brick-and-mortar clinics offered telehealth. Additionally, despite previous regulations, new data collected during this time showed that telehealth medication abortion provision is equally safe and effective as in-clinic medication abortion, including telehealth abortion without an ultrasound or other form of in-person test (Anger et al. 2021; Upadhyay, Koenig et al. 2024; Upadhyay, Koenig, and Meckstroth 2021; Upadhyay, Raymond et al. 2022).

Moreover, the reversal of *Roe v. Wade* in 2022 resulted in many states outright banning abortion, leading to the closing of clinics in those states and longer wait periods in protected-access states, leading to an increased demand for abortion care beyond brick-and-mortar clinics (Society of Family Planning 2023). With these various sociocultural and legislative changes in motion, growing proportions of patients are expected to rely on telehealth abortion in the coming years (Aiken and Upadhyay 2022). From April 2022 to December 2022, for instance, there was a 137% increase in the number of virtual clinic abortions (Society of Family Planning 2023). Presently, one in five abortions are provided via telehealth (Society of Family Planning 2024). Furthermore, in past work, we found that telehealth allowed patients before the *Dobbs* decision to avert a median of 10 miles and 25 minutes of round-trip driving and 1 hour 25 minutes of round-trip public transit time (Koenig et al. 2023). After *Dobbs*, entire regions of the country are now abortion deserts (Cartwright et al. 2018), and travel time to the nearest abortion facility is significantly greater, with Black, Indigenous, and other people of color experiencing the greatest increases in travel time to abortion facilities (Rader et al. 2022).

Sociological scholarship has failed to grapple with the increasing salience of telehealth. Medical and public health literature has long discussed the capacity for telehealth to produce better health outcomes for patients, gather better data, and reduce health expenditures (Edwards et al. 2014; Toole 2013; WHO Global Observatory for eHealth 2011). However, sociological work tends to critique the meaning of telehealth and other digital health technologies, focusing on how telehealth changes the provision of health care and extends the medical gaze and surveillance into patient homes (Lupton 2013, 2014; Lupton and Maslen 2017). We conceive of telehealth at a unique intersection of medicalization and demedicalization (Halfmann 2012; Torres 2014; Zola 1972) given that it involves interacting with a licensed medical provider while simultaneously circumventing the physical clinic. Abortion via telehealth challenges central assumptions about how abortion needs to be provided—in a clinic, after ultrasounds and other tests, often after a waiting period—and provides a hybrid experience of medicalized and demedicalized care: the privacy and comfort of demedicalized at-home care with the supervision and direction of medicalized care.

In this article, we fill a critical gap in sociology scholarship through our focus on the use of telehealth for a stigmatized health practice. We argue that telehealth is a way to mitigate stigma. We find that obtaining abortion care by telehealth aids patients in managing the various cultural, societal, and policy-based manifestations of abortion stigma by circumnavigating the need to enter a clinic—a space that can heighten feelings of stigma for some—and by reducing the barriers to care that we argue are the product of stigma. Telehealth largely eliminates disruptions to one's schedule and associated cost and allows patients to feel more in control and experience a greater degree of privacy. As such, by examining the benefits

of telehealth abortion, we advance a sociological framework for structural abortion stigma—the ways that structural barriers coalesce with abortion stigma to produce structural inequality and a structural stigmatization of abortion.

Stigma

The stigmatization of health behaviors is a complex social process that can lead to poor health outcomes and lower quality of health care provision (Hatzenbuehler, Phelan, and Link 2013; Link and Phelan 2001; Norris et al. 2011). Although stigma has been applied to various realms of medicine, including mental illness and sexually transmitted disease, abortion stigma continues to be undertheorized (Hanschmidt et al. 2016). This lacuna in the literature leaves questions regarding the effects of abortion stigma and how individuals navigate and manage abortion stigma. In particular, there is a paucity in examinations of the structural manifestations of abortion stigma, which Kumar et al. (2009) introduced. Instead, there is substantial focus on stigma on the individual level, with little theoretical connections made between barriers to access and the codification of stigma on a structural level and between the individual and institutions.

In a special issue on structural stigma, Hatzenbuehler and Link (2014:2) defined structural stigma as "societal-level conditions, cultural norms, and institutional policies that constrain the opportunities, resources, and well-being of the stigmatized." In this article, we apply this theoretical framework to the realm of abortion—a highly stigmatized health care treatment—to advance social scientific literature on stigma. Abortion fits squarely within the study of structural stigma because cultural norms and policies not only constrain the well-being of and resources for abortion patients but also "[create] environments that have increased threat, punishment" (Richman and Lattanner 2014:95) for patients and providers alike. Although abortion is relatively simple to provide and demonstrably safe, the societal and cultural conditions have transformed access to abortion into what Cohen and Joffe (2020) refer to as "an obstacle course."

Moreover, we apply Hatzenbuehler and Link's (2014) conceptualization of structural stigma in tandem with Herek, Gillis, and Cogan's (2009) three levels of stigma: enacted, felt, and internalized levels of stigma. Enacted stigma refers to "overt behavioral expressions" (Herek et al. 2015:21), which in the case of abortion stigma can include the targeted violence and harassment ubiquitous across physical abortion clinics. Felt stigma refers to an individual's "expectations about the probability" (Herek et al. 2015:20) of being the target of the overt expressions of enacted stigma. This level of stigma has a particular bearing on people's behaviors because it causes individuals to engage in coping strategies to avoid or reduce the risk of discrimination. In the case of abortion, this can manifest as keeping an abortion secret or seeking to avoid a physical clinic through self-managed abortion or telehealth. The final level of stigma in Herek et al.'s (2009) framework is internalized stigma, which occurs when an individual accepts the beliefs underpinning stigma as part of their own value system. In the case of abortion, internalized stigma could manifest as shame or guilt.

Although the prevailing trend in abortion stigma literature fails to account for the way that structures and individuals interact, there are notable exceptions. In the first, Kimport and Rasidjan (2023) describe the emotional burden on individuals when forced to travel for an abortion to surpass local restrictions. In the context of Ireland, Broussard (2020) expounds on the way that structural abortion stigma manifests in peoples' embodied experiences with abortion, with the barriers to care manifesting as internalized stigma. Moreover, Coleman-Minahan et al. (2021) argued that "multilevel" abortion stigma is reinforced by the judicial bypass process, required in Texas of young people seeking abortion without parental consent. Abortion stigma also inhibits the quality of care received by patients, as found in a scoping review conducted by Sorhaindo and Lavelanet (2022), and can lead people to unsafe abortion methods to maintain keeping the procedure a secrecy (Cárdenas et al. 2018). Lastly, various researchers have examined how abortion stigma can lead to subpar and judgmental care from providers in various non-U.S. contexts, including Peru, Nepal, Senegal, and South Africa (Favier et al. 2018; Palomino et al. 2011; Puri et al. 2012; Suh 2018). In this present article, we build on this nascent work by using telehealth abortion as a case to advance a theory on structural abortion stigma while elucidating the way telehealth mitigates structural stigma for individual patients.

DATA AND METHODS

We conducted 30 in-depth interviews with individuals who had a telehealth medication abortion between May 31, 2021, and January 17, 2022. Participants were purposively sampled from the California Home Abortion by Telehealth Study, a

longitudinal evaluation of the safety, effectiveness, and acceptability of telehealth abortion care provided by three U.S. virtual clinics: Abortion on Demand, Choix, and Hey Jane (Koenig et al. 2023, 2024; Upadhyay, Koenig et al. 2024). These services offer fully remote, synchronous and/or asynchronous medication abortion care. Although the eligibility criteria differed slightly among the three providers, patients were generally eligible for medication abortion care if they lived in an approved state and their pregnancy duration was less than 70 days (assessed by date of last menstrual period or by ultrasound).[1] The services ranged in price from $199 to $289. Once their eligibility was approved by a licensed medical provider, patients received abortion medications via a mail-order pharmacy. Patients also received follow-up messages via secure text message or phone after receiving the medications. At the time of this study, Abortion on Demand, Choix, and Hey Jane served a combined 20 states and Washington, D.C., across the continental United States, primarily in the West and Northeast but with 2 states in the Midwest and 5 in the South.

Sample

We recruited 30 individuals (Table 1) who had a telehealth medication abortion with one of the three participating virtual clinics to participate in semistructured interviews. In a previous stage of the study, we conducted three longitudinal surveys with 1,600 individuals: a baseline survey at abortion intake, a second survey approximately one week after intake, and a final survey four weeks after intake. Individuals were eligible to participate in an interview if they had completed the series of longitudinal surveys and agreed to be contacted again in the future regarding an interview, resulting in a subsample of 1,260 individuals. We then used a purposive sampling method to account for a diverse interview sample in terms of race and ethnicity and age and to include those who required additional medical care after taking the abortion medications.

Interview participants ranged in age from 16 to 39, with an average age of 27, and 5 participants were adolescents (19 years or younger). In terms of race and ethnicity, 9 identified as non-Latinx White, 6 as Asian, 5 as non-Latinx Black, 5 as Latinx, and 5 as multiracial. Three participants reported requiring additional medical care after taking abortion medications. Participants were recruited from 11 states (CA, CO, GA, IL, MA, MN, NY, NJ, PA, RI, VA), representing all four regions in the country—West, Northeast, Midwest, and South. In terms of abortion history, 18 participants reported 0 prior abortions on the intake survey, and 12 reported 1 or more prior abortions.

Table 1. Sample Characteristics ($N = 30$).

Characteristics	Participants
Age (years)	
Range	16–39
Average	27
Race-ethnicity	
White	8
Black	5
Latinx	5
Asian	6
Multiracial	5
Complications	3

Procedures

Interviews were conducted remotely via Zoom by the first, second, and third authors between July and September 2022. The in-depth interviews followed a semistructured interview guide of 20 questions. The questions addressed the factors that contributed to participants' decisions to choose telehealth medication abortion and their overall experience of telehealth abortion. Sample questions included: "How did you first hear about telehealth abortion?" "What appealed to you about this service?" "Did you consider or call a brick-and-mortar clinic first?" "Can you tell me about your experience taking the abortion medications?" and "What kinds of things did you like and not like about the telehealth service?" The interviews lasted between 40 and 90 minutes. Patients provided informed consent for participation in the interview and audio recording. Interviews were audio recorded via Zoom and transcribed verbatim. Participants were compensated with a $50 electronic debit card for their participation. All procedures were reviewed and approved by the University of California, San Francisco's institutional review board.

Analysis

The data were coded by the first and second authors using a flexible coding approach on Dedoose. Flexible coding is a rigorous method of qualitative data analysis that uses both deductive and inductive approaches to coding and theory development (Deterding and Waters 2018). During the first stage

of data analysis, the authors began by developing a codebook that categorized broad topics that were addressed in the interviews (e.g., "reason for abortion," "reason for telehealth," "feelings about abortion"). To allow for flexibility, the authors also identified emergent codes from the text and refined existing codes based on ongoing analysis. Once the overarching theme of "structural abortion stigma" was selected, the first and second authors conducted axial coding to identify key subthemes (e.g., "financial barriers," "fear of the clinic," "internalized stigma"). Divergences in coding were discussed by the research team to ensure congruence across coding during the entire process of data analysis.

RESULTS

To utilize telehealth abortion as a case for advancing a theory on structural abortion stigma, we present the findings in the following two sections. First, we review the ways that telehealth mitigates structural barriers to abortion care—how telehealth removes travel to potentially distant physical clinics and, in the process, reduces logistical and financial hurdles. These findings build on a growing body of work on the benefits of telehealth and a long-standing literature on structural barriers to abortion care. Next, we present novel findings on how telehealth manages various manifestations of stigma—internalized, felt, and enacted—by circumnavigating the physical clinic and the visibility of being an abortion patient. Taken together, these findings contribute to a theoretical framework for structural abortion stigma.

How Telehealth Mitigates Structural Barriers

For many participants, telehealth medication abortion services increased access to needed health care. Structural barriers to accessing abortion care were mitigated by being able to obtain medication abortion through telehealth, from reduced waiting times and more affordable prices to the eliminated need to travel. Telehealth felt "convenient" and "easy" for participants, often resulting in positive abortion experiences.

Participants emphasized how telehealth reduced barriers to accessing abortion by offering fast and convenient care. Unlike brick-and-mortar clinics, participants felt that telehealth services more quickly accommodated their appointments and shipped medications. For example, Rachel, an 18-year-old White woman living in Illinois, explained the barriers she faced while looking for care at physical clinics:

> So when I had called Planned Parenthood, I had to have a first appointment, which would've been in a month, I think, and then a second appointment after that. And…I didn't want to wait that long. And also it was very expensive to go there. So that was mostly why I didn't go with that one. And then I called around to other clinics too, like OBs, and they either said that they didn't deal with that kind of stuff or that they didn't take my insurance.

Long wait times for appointments at physical clinics were a major barrier to accessing care for participants. Telehealth mitigated this barrier by offering the ability to quickly schedule appointments. Elaine, a 27-year-old multiracial law student in New Jersey, felt that telehealth removed multiple barriers to care, particularly those related to wait times and travel. She explained:

> Well, I really do think it kind of just boiled down to the difficulty of, not that I couldn't get somewhere, but finding somewhere that had an appointment available and having an appointment to pick because most of them didn't have appointments anytime soon. It was weeks away, month away, month and a half, whatever. And then trying to figure out what classes do I have that day? Do I have something else going on? Do I have something I have to do the next day? Well, if I need the car, does my boyfriend have work that day? Things like that. Telehealth was like, I could just take care of it. I didn't even have to go anywhere…it was so much easier.

Many participants also appreciated how telehealth mitigated other logistical barriers to accessing abortion care, such as taking time off work or finding childcare. Sara, a 34-year-old White woman living in Massachusetts, succinctly explained: "Honestly, I liked the fact that I didn't have to take any time off work. I didn't have to go anywhere. Didn't have to worry about all that." Similarly, Tess, a 39-year-old White woman who lives in Rhode Island with her husband and son, shared how the telehealth model provided a much more convenient way to complete her abortion at home:

> Having to take an extra day off would have added such a massive hindrance to the whole procedure. Being able to do this on my time, on

> my schedule, from my home, so I didn't have to get childcare coverage or take time off from work. So the convenience of it was huge. . . . It was easy. There were no hoops to jump through. It was: Google search, set up an appointment, pay for it, get the stuff done. Not: find the clinic, go make the appointment, have somebody take you to the appointment, find childcare to cover while you're going to the appointment. So the convenience, the ease of telehealth was good.

Telehealth also removed another critical structural barrier: traveling to a physical clinic. For many participants, the ease of accessing abortion care through telehealth was not simply a convenience; rather, it was a necessity. This was the case even in patients living in legal, protected states. Whether participants lacked reliable transportation or lived in abortion deserts, the telehealth model aided participants in accessing needed care from home. Had Alyssa, a 24-year-old Black woman, not lived in New York—where abortion care is generally more accessible—completing her abortion would have been "impossible." She explained:

> It's something that I could just do right on my phone. So I feel like for a lot of people, especially someone like myself, I didn't have a car, which I was in New York at the time. But if I was in another state, that probably would've made things a lot harder for me or made it impossible for me to go to a clinic. So I feel like that's a good option for people who maybe don't have reliable transportation, are able to get to an actual clinic.

Similarly, Michelle, a 36-year-old Black woman living in New Jersey, shared her experience:

> The area where I live, there are literally no abortion providers whatsoever. And I did not have the actual time to travel to the area where they do have actual abortion providers in person . . . and at the time, I was working. Some weeks, it was seven days a week. And myself, I didn't physically have the time to get [to the nearest abortion clinic]. But I was, "If I have to take sick time, I'll do it. And I'm going to have to go far."

Although Michelle may have been willing and able to travel to a clinic to receive care, the telehealth model removed the burden of travel and made abortion care more accessible.

This accessibility was crucial given that many other participants were simply unable to travel. In particular, participants living in rural areas faced numerous structural barriers to accessing abortion care. Katie, an 18-year-old White woman in rural Minnesota explained: "The closest [abortion clinic] was in [the nearby city], and that's probably a two-and-a-half-hour drive. I didn't want to go alone, so it would've just been harder to have to figure out me and my mom's schedule to be able to both go together." Similarly, Adriana, a 15-year-old Latina living in central California, described the difficulties she faced when trying to access abortion care: "The nearest clinic that was open was two hours away. There used to be [a clinic in my town], but there hasn't been one in a while." Further complicating her experience, Adriana also mentioned that she had not told her parents about the pregnancy or abortion. Thus, being too young to drive herself coupled by a lack of transportation or family support, "to find an excuse and a way to go that far [to a clinic] was just too hard."

Another recurring theme across all interviews was the affordability of telehealth medication abortion. Cost is one of the greatest barriers to abortion care and a key reason why many participants sought out telehealth as opposed to medication abortions at physical clinics. Participants felt surprised by the affordability of telehealth services. Rebeca, a 19-year-old Latina in New York, explained: "I felt like it was affordable because I've heard that abortions could be up to $800 . . . but I was like, '$250? That's not bad. I'll do that. I'll pay for it.' To me it felt like a good price. It's realistic." Similarly, Angelica, a 38-year-old White woman in California, described her shock at learning the cost of an abortion at her local in-person clinic, leading her to explore telehealth options:

> Compared to having to go to a clinic and meet someone in person, [telehealth] was a lot cheaper. Because . . . I think it was about $800 or maybe even a little more [at the local clinic]. So that kind of shocked me. I didn't think it would be so much. I didn't know. So I can't remember exactly how much it was with [the telehealth service]—maybe a couple of hundred or something—so, by comparison, it was a lot cheaper. And I didn't mind paying it because you're paying for the convenience of it and just being able to be at home.

For Annie, a 28-year-old Asian woman in California, the affordability of telehealth was particularly

important because she did not have health insurance at the time of her abortion. She explained:

> I felt like, compared to [other options] in the area, it was very affordable…[and] the closest [abortion] clinic was an hour away from me. And even then, the earliest appointment that I could get was probably two weeks. There was no guarantee that when I got there I wouldn't have to wait longer as well…I feel like time-wise, it was very effective for me. And also, cost-wise, it was as well. It was very expensive at [another health clinic]. I don't remember the exact price, but having to pay for the consultation and then having to pay for the medication, as well. And at the time, I didn't have health insurance to be doing something like that.

The affordability of telehealth abortion was critical given that many participants cited financial hardship as a key reason they wanted the abortion. For example, Sara, the 34-year-old White woman living in Massachusetts, succinctly noted: "One of the main reasons we aren't having another child right now is because we're broke. So I mean, [telehealth] was a few hundred bucks compared to [a more expensive in-clinic procedure]."

To understand the ways in which telehealth mitigated financial burdens, consider Maya, a 20-year-old multiracial woman in California. When Maya found out she was pregnant, she was already working two jobs to make ends meet. Due to these financial hardships and lack of family support, Maya knew that having a child "would be a huge struggle." Although she knew abortion was the right decision, she noted the cost of abortion care as a significant barrier. She explained:

> When I first found out that I was pregnant, I wasn't in the right financial means to have the child. And I knew even if I did choose to have it, it would be a really hard struggle for me. And so, then when I decided to go through with [the abortion], I was considering going to [an abortion clinic], but then when I went over there for the prices and stuff, I was just kind of iffy about it.

After working "long hours just trying to be able to get the money," Maya was able to pull together enough funds to pay for the telehealth medication abortion. Without telehealth, Maya would have likely encountered even more delays in care in order to afford a more expensive in-clinic procedure. These participants' experiences demonstrate how telehealth mitigates structural barriers by reducing logistical and financial burdens, affording them the ability to have the abortions they wanted and needed.

Avoiding the Clinic, Managing Stigma

In addition to structural barriers, many participants discussed the benefit of telehealth as a way of avoiding interpersonal and individual experiences of stigma by avoiding physical abortion clinics, which many participants view as the primary site where abortion stigma is experienced. In these accounts, entering the physical clinic represents facing abortion stigma across various levels—from having to drive to a different city or state or to a remote part of town to encountering anti-abortion protesters outside to physically being in a room as an abortion patient and requesting abortion pills face-to-face. Having a telehealth option circumnavigated these various facets of abortion care. As such, in addition to telehealth as a means of navigating costs, travel, and logistics, avoiding the physical clinic also allows one to manage internalized, felt, and enacted abortion stigma—together comprising structural abortion stigma. This adds insight into the ways that individuals' feelings of shame about a stigmatized health procedure can be mitigated by removing a primary place where abortion stigma is experienced.

As an example of how telehealth allows for the managing of abortion stigma across these various levels, consider Tess, the 39-year-old White woman who lives in Rhode Island with her husband and son mentioned previously. She was able to schedule and have her abortion while balancing her two-hour daily commute to work and being the primary caregiver to her son. In addition, access to telehealth aided in managing or avoiding internalized, enacted, and felt stigma. For instance, despite identifying as "pro-choice," she holds shame in choosing an abortion for herself. When probed about what she meant about her abortion evoking "hard feelings," she said the following through tears:

> I had to confront a lot of internal biases that I didn't really even know that I had, where I didn't deserve an abortion because financially, I could afford another child. I had to confront this internal bias that I had that abortions are for people on hard times…and that, as an intelligent person, I feel like I should have known better. I should have made smarter choices, and these are consequences that come up from them. So, that's hard…because this was a life.

While Tess was sifting through these complicated emotions—or internalized abortion stigma—she felt certain that an abortion was the correct choice for her and her family. The telehealth model aided in Tess managing these feelings and reducing additional layers of abortion stigma. She mentioned being comforted by the ability to avoid the physical clinic and potential protestors in making "an uncomfortable situation somewhat less uncomfortable."

> I didn't want to face the idea of there being protestors…you see all the footage of people standing outside and harassing people, and I'm already dealing with a super hard decision. I don't need people screaming in my face. I was nervous about that. So when I Googled and I found out that you can just do this via web interview, over the phone, I was like, I'm here for it.

Indeed, many participants mentioned anticipating stigma by having to confront protestors and anti-abortion signage outside of the clinic, with the severity of anti-abortion vitriol impossible to predict. Lindsey, a 30-year-old Asian American woman living in Colorado who had a previous in-clinic abortion in Louisiana—where abortion has long been highly restricted—said the following about the benefits of telehealth abortion:

> Just imagine living in a red state, and people are screaming and yelling at you and showing you these photoshopped pictures of babies being vacuumed out of women's wombs. That could be terrifying. And not having to experience that and being able to do an abortion in the comfort of your own home and your own space and being private about it and having, I guess, the choice to be private, I think that's great.

As Lindsey indicates in this excerpt, telehealth allows for a greater degree of privacy and comfort by being able to have the abortion process from one's home—specifically, "the choice to be private." In addition, Lindsey's quote indicates that telehealth mitigates both felt and enacted stigma by avoiding the feeling of anticipating being stigmatized when accessing a physical clinic and avoiding the enacted stigma in the form of protestors.

In addition to the presence of protestors, many participants mentioned that simply entering the physical clinic sparked negative emotions from the physicality of the space itself. For instance, consider Emily, a 24-year-old Asian American woman living in California. Earlier on in our interview, she mentioned that the ability to have the process remotely, and particularly the option to use the secure messaging feature, caused "less guilt" about the abortion. When asked to elaborate, she said the following about avoiding the physical clinic:

> If you go to a clinic then there's people that are outside of it with signs saying that it's bad and I don't have to deal with that or be confronted with it. It helped me in the process of not having to go to a clinic…and just having to be in the clinic is kind of just very depressing just in itself…I don't know. It just feels weird because there's putting names to faces and they know why I'm there rather than just doing it online. And you have someone that's there for you if you need help, but you're not sitting there looking at someone. So there's kind of less guilt into it.

As this quote indicates, for Emily and others in the study, being physically in the clinic, embodying "the abortion patient," conjures negative feelings due to multiple factors in addition to having to confront protestors. In such cases, receiving abortion care mediated through a phone or computer screen lessens internalized stigma or other negative feelings associated with an abortion because being seen in person by providers, other patients, and any potential onlookers seems to increase feelings of stigma.

In addition, as participants explained, having a telehealth option allows a greater degree of secrecy regarding the abortion, allowing patients increased control about who to disclose the abortion to. This, in turn, mitigates feelings of stigma. Rebeca, the 19-year-old Latina living in New York, for instance, said she appreciated telehealth because "I wouldn't want people to know that I'm having an abortion at the time. It's still something I'm not really proud of, so I would want it to be as secretive as possible." In this case, secrecy helps manage internalized stigma. The desire for privacy and secrecy is particularly the case for those living in small towns or rural areas. Take, for instance, Katie, the 18-year-old living in Minnesota. In addition to managing having an abortion while being a teenager living with her parents, Katie was also managing the fear of being seen and recognized at a location that provides abortions. As she said:

> When I go to the clinic, I know a lot of the nurses, the office people, so I just didn't want them to know what I was doing. And then, potentially, I know they can't say anything, but I mean you never really know, and I didn't want to

> be viewed different, I guess. So, that's why I wanted to keep it more confidential and not have to worry about someone seeing or hearing or saying something about it.

Indeed, anonymity and being in one's home were repeatedly mentioned as the benefits of telehealth. As Lindsey recounted:

> Just being able to do it in the safety of your own home and being absolutely 100% anonymous. They don't know what you look like. I mean, they know your name and they know your information, but they're not going to see you out on the street and be like, "Hey, she got an abortion." You know?

Advances in telehealth therefore disrupt stigma processes by removing the embodied element of receiving stigmatized health care, which could have implications beyond abortion, including other types of sexual and reproductive health or even mental health.

Additionally, although sociological literature on structural barriers and on stigma tend to be separate, many participants alluded to the structural barriers themselves being a source of stigma. This contributes to a sociological theory of structural abortion stigma by demonstrating a cycle in which abortion stigma leads to structural barriers, which then implicitly lead to abortion stigma. In the following excerpt, Michelle describes the connection between the reduction in structural barriers and the reduction in stigma, both of which telehealth provides.

> I don't think that it would be such a devastating process if Abortion on Demand or services like it were easily available and accessible to women. Because it destigmatized it a lot for me. Destigmatized it to the point where I've actually recommended it…ever since then, I'm, "You should go to this Abortion on Demand site…" Because it was such an easy process. It made it, like I said, like you can go get this done without it being an epic poem of emotion and having to figure out, am I going to be able to walk through the doors of some place? And it was so easy. I don't even know how many other people know about it. And that's why I want people to know. It's a safe place to get something done that could very well be very unsafe if you don't know that you have this option.

As Michelle describes, it is often the structural barriers of abortion that cause receiving this health care to be "a devastating process" or even "an epic poem of emotion." The process itself of having to find a physical clinic, plan a trip, and anticipate and/or encounter protestors fuels feelings of shame and sadness given the marginalization of the procedure. In fact, in the following excerpt, Michelle describes feeling surprised by her lack of negative emotions despite initially feeling very guilty about not continuing the pregnancy.

> I worried often, for the time during and afterwards, that I wasn't more emotionally connected to the process. Why am I not crying? Why am I not sad? Why am I not feeling like a bad person? And the answer is, because I didn't have to feel like a bad person. I didn't have to seek thousands of miles or millions of dollars' worth of care in order to get this thing done. And when I got it done, I felt physically safe. I felt physically taken care of.…But the fact that I don't have to deal with the mental consequences thereafter, that is probably where I place most of the value here. Because a lot of women that I have talked to are, "I feel so guilty that I've done this years later." And I sometimes have forgotten that I've done it. And I don't mean to sound callous, but this was not a pregnancy that I was ever going to be able to carry to term healthfully.

As this findings section demonstrated, there is a need for a theory of abortion stigma that combines structural barriers with internal and interpersonal experiences of stigma. The barriers themselves are a result, or codification of, individual-level abortion stigma, and the barriers then lead to feelings of abortion stigma for individuals receiving this care (in addition to providers, although the present study does not speak to this element of abortion stigma).

DISCUSSION

Our findings demonstrate the importance of understanding experiences with a telehealth model for abortion care. More broadly, this article makes important contributions to social scientific literature on stigma and health inequality. We found that a telehealth model aided patients not only in accessing abortion via reduced costs, time, and logistical hurdles but also in the managing of internalized, enacted, and felt stigma. Using telehealth abortion as a case, we connect barriers to care with the individual and interpersonal experiences of stigma to advance the theoretical concept of structural abortion stigma—a combination of structural barriers,

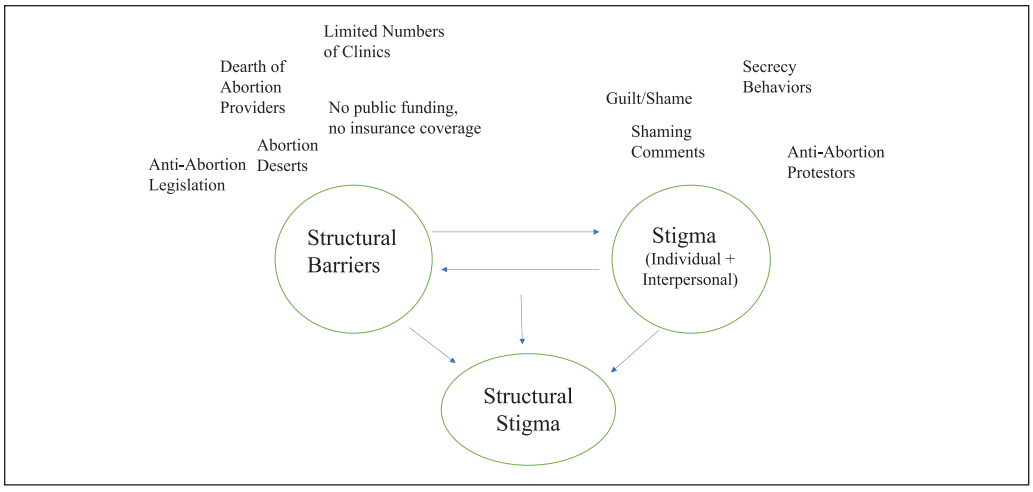

Figure 1. Structural Abortion Theoretical Model.

internalized beliefs, and interpersonal shame (see Figure 1). The findings may help direct future policy on expanding access to telehealth abortion, especially in the wake of the reversal of *Roe v. Wade*, which has and will continue to exacerbate long-standing inequities in abortion access.

Interview data point to a telehealth abortion model as a way of reducing structural abortion stigma that we define by modifying Hatzenbuehler's (2014) structural stigma framework. Structural abortion stigma is the product of cultural norms, societal-level conditions, and policies around abortion that constrain the opportunities, resources, and well-being of abortion patients. Due to geographic variation in abortion acceptance across the country, abortion stigma has been structurally codified via abortion deserts and states without abortion access—also referred to as spatial stigma (Kelaher et al. 2010). Abortion stigma has also been codified via policies that silo abortion care to freestanding abortion clinics where the presence of protestors has been normalized and via policies—including the Hyde Amendment—that render abortion financially unfeasible for many.

These various structural manifestations of stigma, in turn, exacerbate individual-level stigma. Being forced to surpass these various obstacles created by the structural marginalization of abortion care—particularly the need to travel—increases feelings of shame and exclusion and of being deviant or "abnormal" (Kimport and Rasidjan 2023). By continuing to explore the interplay between structures and the individual in the study of stigma, our findings build on a growing, relatively nascent body of work in sociology that can be applied to various stigmatized elements of health and health care—including mental health, sexually transmitted illness, and gender-affirming care for trans populations.

Our study indicates that telehealth abortion aids patients in managing the various cultural, societal, and policy-based manifestations of abortion stigma by circumnavigating the need to enter a physical clinic—where patients may encounter stigmatizing actors inside and outside of the clinic—and by reducing the barriers to care that we argue are the product of stigma. Most of the sample pointed to the ease and convenience of telehealth in seamlessly fitting the abortion in their schedule. This includes accommodating job schedules and child and elderly care, eliminating the need to travel, reducing the cost of the abortion itself, and reducing associated costs, such as lost wages, childcare, travel, and accommodations. This supports prior research on telehealth abortion as both a patient-centered model and a potent tool for reducing barriers to care, including by drastically reducing cost barriers (Endler et al. 2019; Kerestes et al. 2021; Raymond et al. 2019; Upadhyay, Koenig et al. 2024; Upadhyay, Schroeder et al. 2024).

As telehealth becomes increasingly part of U.S. health care models post-COVID-19, it is critical for sociologists to continue to theorize how this model disrupts long-standing social inequities. Moreover, it is long overdue for the field of sociology to seriously grapple with abortion as a site of theoretical exploration, interconnected as it is within the fields of health, gender, stigma, the family, and technology studies and perennially unresolved tensions

between structures and agency. This study therefore constitutes a key step in addressing the exclusion of abortion from mainstream sociological theorization while contributing key findings that could aid in paving the way for patient-centered health models both within abortion care and beyond.

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NOTE

1. Choix provided medication abortion care to some adolescents ages 16 and older, following specific state laws.

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EXHIBIT B-2

APPENDIX TO PETITIONER GENBIOPRO, INC.'S CITIZEN PETITION DATED JULY 3, 2025[1]

Source	Appendix Starting Page
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Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curaçao

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ABSTRACT

Objective To evaluate the efficacy and safety of home administration of buccal misoprostol after mifepristone for medical abortion up to 70 days' gestation in a general practice in Curaçao, where induced abortion is severely restricted by law.

Methods In a prospective study 330 women received 200 mg mifepristone and were instructed to take four tablets (800 μg) of misoprostol via the buccal route 24–36 h later, at home. One week later, follow-up took place.

Results The outcome could be evaluated in 307 of the 330 women. The efficacy of the mifepristone-buccal misoprostol procedure was 97.7% (300/307). In seven women vacuum aspirations for continuing pregnancy or incomplete abortion following treatment were required. Success rates at 64–70 days' gestation were the same as for gestations of less than 64 days duration. The main adverse effects were nausea and diarrhoea.

Conclusion Home administration of buccal misoprostol 24–36 h after mifepristone is a safe and effective method of medical abortion up to 70 days. It could be applied in a general practice in Curaçao, where induced abortion is legally restricted.

KEYWORDS Medical abortion, Mifepristone, Buccal misoprostol, Home abortion, Caribbean

INTRODUCTION

In Curaçao, a Caribbean island, part of the Kingdom of the Netherlands, induced abortion is rigorously restricted by law. Nevertheless, induced abortion on request of a woman is performed by a small number of general practitioners (GPs) and both the Health Inspectorate and the Public Prosecutor's office are

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aware of that. The Public Prosecutor stipulated a tolerance policy in 1999 and the Inspectorate supervises correct compliance. In this tolerance policy the health personnel involved in abortion care is protected from prosecution and since 1999 GPs carrying out abortions have no longer been prosecuted. Women having an abortion are not protected, but none of them has been prosecuted because of an abortion since then. In our practice we provide medical abortion and although this is done clandestinely we can continue because of the tolerance policy. Induced abortion on medical indication can only be performed in the main (Roman Catholic) hospital after approval of the institution's ethical board. A change in law still seems far away because of the strong influence of the Roman Catholic Church and, for most policy makers, abortion is still a highly sensitive subject.

Because of the illegal nature of abortion, women may delay seeking assistance for abortion as well as seeking care in case of complications. During one year the 11 GPs carrying out abortions at the request of women registered their results. Compared to countries where induced abortion is legal, there were more complications (Boersma AA, Alberts JF, Meyboom-de Jong B, Kleiverda G. Termination of pregnancy in Curacao: Need for improvement of sexual education and reproductive healthcare. Unpublished.) In the Caribbean islands estimates of induced abortion are around 300,000 a year with a high hospitalisation rate for complications[1]. In most countries in the region induced abortion is prohibited. Since use of misoprostol for medical abortion in countries where induced abortion is illegal has increased, morbidity and mortality rates are declining[2].

Most studies on medical abortion are conducted in clinical settings in countries where abortion is legal. The combination of mifepristone and misoprostol is more effective and results in a higher rate of complete abortions (97–98%) than when either methotrexate and misoprostol (92–95%) or misoprostol alone (70–90%)[3] are used. Home abortion is preferred by most women[4,5]. In Curaçao, methotrexate was used in the past because mifepristone was not available[6].

To perform this study the import of mifepristone was allowed under stringent conditions of the Health Inspection. Women had to be informed about the fact that mifepristone was not registered and had to give written consent. A proper follow-up was also a condition.

Medical abortion at home is mostly reported to have been carried out at gestational ages of 63 days or less. Although there is evidence that medical abortion is safe up to 83 days – and even later – in clinical settings, hardly any studies have described medical abortion in the home situation at a gestational age exceeding 63 days[7–10].

In Curaçao, due to its illegal status, abortion on request is not available in a clinical setting. Therefore, it was decided to enroll women with pregnancies of a maximum of 70 days of amenorrhoea in our study of home treatment. We decided to use buccal misoprostol, as the bioavailability of the prostaglandin analogue in such cases is higher than after vaginal and oral administration[11]. In more advanced pregnancies, success rates of oral misoprostol diminish with increasing gestational age[12]. Buccal administration has the advantage that no residues can be found as with vaginal treatment. In countries with a restrictive abortion law this may be important.

We investigated whether in Curaçao, where induced abortion is legally restricted, medical abortion can safely be carried out in a general practice. Further, we assessed whether, to this end, home administration of buccal misoprostol after mifepristone is an effective and safe method of medical abortion up to 70 days' gestation.

METHODS

This study was conducted from 1 April 2009 until 1 April 2010. It involved women requesting induced abortion at a gestational age of up to 70 days, who presented in a general practice in an underprivileged neighbourhood in the old centre of Willemstad, the capital of Curaçao. The women concerned were patients registered at this general practice, had been referred by other GPs or were passers-by who had heard of the possibility of having a medical abortion in this practice. Most patients were of Afro-Caribbean origin. All were informed about the small risk of ongoing pregnancy and were strongly advised to proceed with a surgical procedure, if the medical abortion failed. Women received written information about the procedure, and written consent for medical treatment was obtained. The gestational age was confirmed by abdominal ultrasound; if there was no amniotic sac visible at a gestational age of less than 42 days, the pregnancy was confirmed by a urine test.

All women were offered 200 mg mifepristone orally at the first visit in the clinic and four tablets of 200 μg misoprostol for home administration 24–36 h later. Women were instructed to place two tablets of misoprostol (200 μg each) in each cheek for 30 min and then to swallow any remaining pill fragments with some water. Acetaminophen or ibuprofen was advised for pain relief. If bleeding did not occur within 48 hours, misoprostol was used again in the same dosage and via the same route. After an unsuccessful second attempt, an instrumental abortion was performed in the general practice. Follow-up consisted of either an abdominal ultrasound one week after termination of the pregnancy, or a telephone conversation after two weeks. On this occasion three questions were asked by the principal investigator: 'Did you have a bleeding of several days duration?', 'Did you lose the pregnancy?', and 'Do you feel that you are no longer pregnant anymore?'. The endpoints were effectiveness of treatment to achieve complete abortion, and safety. Treatment was considered to have failed if instrumental evacuation was needed because of ongoing pregnancy or incomplete abortion.

Approval for the study was obtained from the Medical Ethical Committee of Curaçao. The Fisher exact test was used to analyse categorical data and the Z-test was used to compare the proportions of two different groups. The level of statistical significance was defined as a p-value of <0.05.

RESULTS

A total of 331 women with first trimester pregnancies were treated. In one woman an ectopic pregnancy was detected after medical abortion was attempted; surgical removal was carried out. Of the remaining 330 women, 42 (13%) were registered in our practice, 182 (55%) were referred by other GPs, and 106 (32%) were passers-by.

The mean gestational age was 49 days (range 29–70 days). Most women (199; 60%) were 49 days pregnant or less, 105 (32%) were between 50 and 63 days, and 26 (8%) between 64 and 70 days of amenorrhoea.

At the time of the pregnancy, the mean age of the women was 26 years with a range of 14–45 years. Almost half of the patients (148) were between 21 and 30 years old, more than a quarter (92) was aged more than 30 years, and a quarter (87) was younger than 20 years. Of three women the age was unknown. Nearly one third (105; 32%) were nulliparous, 89 (27%) had one child, 82 (25%) had two children, and 54 (16%) had three or more children.

Follow-up was in most cases (237; 72%) with ultrasound and in 70 (21%) it consisted of a telephone conversation. If the answers to the three questions were positive the treatment was considered successful. Twenty-three women (7%) were lost to follow-up. The gestational ages in 13 of them were 49 days or less, in eight between 50 and 63 days, and in two between 64 and 70 days.

The available results show a success rate of 97.7% (300/307). Two women presented two days after the first visit with an ongoing pregnancy, and three with an incomplete abortion after one week (gestational age 41–59 days). After a second dose of 800 μg buccal misoprostol four of them had a complete abortion within 48 h. The fifth one, with an incomplete abortion, had a vacuum aspiration as had six other women, with ongoing pregnancy (2) or incomplete abortion (4) within two weeks after the first dose of misoprostol (gestational age 41–64 days). These six women chose vacuum aspiration after administration of mifepristone and one dose of misoprostol. Suction curettage rates for pregnancies between 50 and 63 days and between 64 and 70 days of amenorrhoea (4.2% and 3.8%, respectively) were not significantly higher than in those with a gestational age of 49 days or less. (1.1%) ($p=0.24$, Fisher Exact test) (Table 1). Nulliparity was not associated with a significantly greater risk of failure of abortion (Table 2). Of the five women with incomplete abortion who needed surgical intervention, two were admitted to the department of gynaecology with pain and heavy bleeding. The most frequently mentioned side effects were nausea and diarrhoea.

DISCUSSION

Induced abortion is still highly restricted by law in Curaçao. While mifepristone for medical abortion is used legally in most parts of Europe and in the United States, this compound is not registered in Curaçao. But with the assistance of the Health Inspectorate it was made available. This made medical abortion easier to perform compared to the method which had been applied during the previous ten years in Curaçao and which consisted in administering methotrexate intramuscularly, followed by intravaginal misoprostol

Table 1 Outcome, by gestational age, of medical abortions induced by oral administration of 200 mg mifepristone followed by 800 μg misoprostol via the buccal route

Duration of pregnancy	*Only one dose of misoprostol required*	*Second dose of misoprostol required*	*Suction curettage (after one or two treatments*)*	*Total*
≤49 days	182	2	2 (1.1%)	186
50–63 days	89	2	4 (4.2%)	95
64–70 days	25	0	1 (3.8%)	26
				307

*Six after administration of one dose of misoprostol, and one after two doses.

Table 2 Outcome of medical abortion according to age and parity

	Successful outcome group (n = 300)	*Failed outcome group (n = 7)*	*p-value*
Mean age (years)	26.0	26.6	NS
Nulliparity (%)	32	14	NS

NS: not significant.

three to five days later. The success rate in the current study is higher. Moreover, in accordance with the literature, the women participating in this study found the ingestion of mifepristone followed by home administration of buccal misoprostol to be more convenient: not only were the results better, but also the expulsion of the products of conception (POCs) was faster and women had less complaints[6,13–15]. In addition, the procedure was also less time-consuming: women had to come back to the practice just once instead of three times with the methotrexate-vaginal misoprostol procedure.

In 2005 the first trial comparing buccal with vaginal misoprostol, after intake of mifepristone, was published[16]. Since then more publications have appeared and, in all, the results obtained with buccal misoprostol were similar to those observed after vaginal administration of that prostaglandin analogue and better than after its oral administration[12,13,17,18].

In our study only seven of the 307 women for whom complete data are available needed a vacuum aspiration. Two of these went to the Emergency Department and were admitted because of pain, but did not mention the previous medical abortion because of fear of retaliatory measures of the hospital staff due to the illegal status of abortion. A wait-and-see policy might have allowed for complete expulsion of the POCs and would have made the results even better.

Four of the five women who took a second dose of misoprostol had a complete abortion thereafter and only one woman had a vacuum aspiration. Results of repeat doses of misoprostol have not systematically been evaluated in the literature, because mifepristone combined with a *single* dose of (buccal) misoprostol is already highly effective. Therefore, the effectiveness of repeat doses of misoprostol after mifepristone is not established[19].

The introduction of mifepristone was allowed by the Health Inspection under binding conditions, among which was a mandatory follow-up. Women received explicit instructions and 72% returned for an ultrasound. The gestational age of the 23 women lost to follow-up did not differ notably from that of the other women. This makes the impact of the cases lost to follow-up small. Fourteen of these women were passers-by and nine had been referred by other GPs. All women registered at our general practice came back. Routine follow-up may be a burden for some women and its necessity has been questioned[20]. The main reasons for this control are to exclude continuing pregnancy, on the one hand, and ectopic pregnancy after early medical abortion when an intrauterine gestational sac had not been visualised on ultrasound prior to this, on the other hand.

The efficacy and safety of mifepristone-misoprostol regimens for medical abortion in clinical settings have

been proven for gestational ages of up to 91 days[8]. Different studies about home abortion show that safety and acceptability are high; most women value home abortion because it allows greater autonomy and privacy, and preserves personal integrity[9,21,22]. Home administration of misoprostol for medical abortion at a gestational age between 64 and 70 days has not been reported previously. Our findings indicate that buccal misoprostol remains equally effective up to and beyond 63 days' gestational age, while success rates of oral misoprostol diminish with increasing gestational age towards 63 days[12].

Its very low failure rate seems to make home administration of buccal misoprostol, after intake of mifepristone, suitable for medical abortion up to 70 days, in a general practice. When compared with literature data, our success rate was high[3,12,16,17,23,24]. In other studies, maternal age and parity have been cited as prognostic factors for failure of pregnancy termination with mifepristone and misoprostol[25–27]. In this series, this was not confirmed. The effect of more advanced gestational age was not apparent due to the small number of failures.

Home abortion is safe. We should be able to convince the Health Authorities of the lack of evidence for routine follow-up after this procedure. Instead women should be encouraged to contact qualified health personnel after a medical abortion *if* they feel a need for it or *if* there are symptoms suggestive of an ectopic pregnancy, an incomplete abortion or ongoing pregnancy. Legalisation of abortion is desirable in order to allow women to terminate their unwanted pregnancy in optimal circumstances and, for those with complications, to seek assistance openly.

The strength of this study is the high follow-up rate in a country where abortion is illegal. A weakness of this study is that the number of participants with gestational ages varying from 64 to 70 days was limited. Our findings reflect the effectiveness and the safety of mifepristone followed by home administration of buccal misoprostol up to 70 days' amenorrhoea in a general practice. Future research should address larger groups to confirm the efficacy and safety of home abortion up to 70 days' amenorrhoea.

In conclusion, home administration of buccal misoprostol 24–36 hours after oral mifepristone is a safe and effective method of medical abortion up to a gestational age of 70 days. The method was successfully applied in a general practice in Curaçao, where induced abortion is legally restricted.

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Contribution to authorship

A. Boersma collected and analysed the cases and wrote the manuscript. G. Kleiverda and B. Meyboom-de Jong were involved in the interpretation of the data and the critical review of the manuscript. All authors approved the final version.

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Original research article

A two-pill sublingual misoprostol outpatient regimen following mifepristone for medical abortion through 70 days' LMP: a prospective comparative open-label trial☆☆,★,★★

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Abstract

Objective: To test the effectiveness and acceptability of an outpatient medical abortion protocol with 200 mg mifepristone and 400 mcg sublingual misoprostol at 64–70 days' last menstrual period (LMP) and compare it to the already known efficacy of the 57–63 days' LMP gestational age range.

Study Design: We conducted a prospective, comparative open-label trial in six hospitals and clinics in Ukraine, Georgia, India and Tunisia. We enrolled 714 reproductive age women with pregnancies 57 to 70 days who presented requesting abortion. Medical abortions were managed with the current service delivery protocol (200 mg oral mifepristone followed in 24–48 h by 400 mcg sublingual misoprostol). Data on safety, efficacy and acceptability were collected. The main outcome measure was complete abortion without surgical intervention at any point.

Results: A total of 703 cases were analyzable for efficacy. Success rates did not differ significantly in the two groups [57–63-day group: 94·8%; 64–70-day group: 91.9%; Relative Risk (RR): 0.79 (0.61–1.04)]. Ongoing pregnancy rates also did not differ significantly (57–63 days: 1.8%; 64–70 days: 2.2%; RR: 1.10 (0.65–1.87)].

Conclusion: A medical abortion regimen of 200 mg mifepristone followed in 24–48 h by 400 mcg sublingual misoprostol is effective through 70 days' gestation and may be offered within existing outpatient abortion services.

Implications: A regimen of 200 mg mifepristone followed in 24–48 h by 400 mcg sublingual misoprostol is effective up to 70 days' LMP. The findings have important implications for expanding access to outpatient medical abortion services in settings where the cost of misoprostol is of concern or a two-pill misoprostol regimen is the standard of care.

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Keywords: Termination of pregnancy; Mifepristone; Misoprostol

☆☆ Authors: Expanding Access to Outpatient Medical Abortion Research Group.

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1. Introduction

Mifepristone–misoprostol is used widely for early abortion and recommended for outpatient use through 63 days from the last menstrual period (LMP) [1–3]. Earlier studies demonstrated the effectiveness of medical abortion after 9 weeks' LMP, but most protocols required repeat dosing and inpatient care [4–10]. New evidence has shown that the most common outpatient protocol for early medical abortion in the United States (200 mg mifepristone followed by 800 mcg buccal misoprostol) is effective and acceptable for ending pregnancies 64–70 days from LMP and can be offered without altering existing outpatient services [11].

The first regimens of medical abortion introduced in most countries used 400 mcg oral misoprostol following mifepristone for medical abortion through 49 days' gestation [12,13]. Evidence has since shown that medical abortion is also safe and effective at increasing gestational ages, particularly using other in-the-mouth routes (buccal and sublingual) or with higher doses of misoprostol [1,14–18]. An alternative outpatient protocol of 200 mg mifepristone followed by 400 mcg sublingual misoprostol is used through 63 days' LMP [16,19] and is the standard of care in Tunisia, Georgia and Moldova, among other countries that have historically used two-pill misoprostol regimen since the method's introduction. The higher-peak misoprostol plasma concentration and greater bioavailability associated with sublingual administration allow for a lower dose of misoprostol when compared to buccal administration [20]. Although generally an inexpensive drug, the cost of misoprostol is subject to local market variability and may be difficult to access or expensive in some settings. In addition to a potentially reduced cost, lower doses of misoprostol are associated with fewer side effects [19,21,22]. Our study sought to estimate the efficacy and acceptability of a 400-mcg sublingual misoprostol regimen following 200 mg mifepristone through 70 days' LMP and to compare outcomes between women with pregnancies of 64–70 days' duration and women with pregnancies in the range of 57–63 days.

2. Materials and methods

This open-label prospective study was conducted between July 2009 and March 2012. Enrollment was planned at seven facilities in four countries: Zhordania Institute of Human Reproduction (Tbilisi, Georgia), Central District Maternity House (Odessa, Ukraine); Maternity Hospital No. 2 (Simferopol, Ukraine); Naval Nursing Home (Solapur, India); Government Medical College (Nagpur, India); La Rabta Maternity Hospital (Tunis, Tunisia); and Family Planning Center of Nabeul (Nabeul, Tunisia). One site was found to have an excessive amount of incomplete data and unanswerable queries on primary outcome data. Enrollment was discontinued, and none of the data from that site ($n=60$) was included in the analysis. The protocol was approved by the institutional review board at each facility. The study was registered with ClinicalTrials.gov, NCT00997347.

Women seeking abortion services were screened for eligibility and asked to participate in the study. Eligible women were 18 years or older, in good health and assessed to have a pregnancy greater than 56 days and less than 71 days from LMP based on the standard gestational age assessment practice at each site (ultrasound and/or clinical exam and history). Participants had to be willing and able to sign consent forms and agree to comply with the study procedures and visit schedule. All women gave informed consent to participate.

On day 1, women received 200 mg oral mifepristone and were given the option of administering 400 mcg sublingual misoprostol either in the clinic or at home 24–48 h later. Women were instructed to place two pills under the tongue for 30 min and swallow any remaining fragments. Each participant received analgesic medication and/or a prescription for analgesia, antidiarrheal and antiemetics as per individual clinic protocol. Women were also provided with a daily home study card to record bleeding days, time and date of misoprostol administration, and information on where to call with questions or concerns.

Women were asked to return to the clinic 7–14 days after mifepristone administration for follow-up to determine abortion outcomes. Outcome was determined by clinical assessment, including ultrasonography as needed. Women with an ongoing pregnancy were offered a surgical evacuation. Women with nonviable pregnancies (e.g., sac or other evidence of conception, but no growth in the gestation or cardiac activity on ultrasound) were given treatment options per the clinic's standard protocol including expectant management, an additional dose of misoprostol or a surgical evacuation. A short semistructured interview was conducted once the abortion was complete. Women were asked about the incidence and severity of side effects, and the acceptability of the overall process, side effects and bleeding. If a participant failed to return to the clinic, the assessment of abortion status and interview could be conducted via phone. If a woman failed to return or contact the clinic, study sites attempted to contact the woman three times before she was considered lost to follow-up.

The primary purpose of the trial was to assure that an outpatient medical abortion regimen could be used in gestations 64–70 days from LMP and achieve a success rate of at least 90%, which would characterize a clinically acceptable regimen. Three hundred thirty-four women per group were needed to detect a 5% or greater lower efficacy than the hypothesized 95% success rate in the 57–63 days group, based on previously published reports ($\alpha=0.05$, $1-\beta=0.8$, using a one-tailed test) and would allow us to estimate a success rate of 90% with a confidence interval (CI) of ±3.2% [13,18]. Data were analyzed using SPSS 15.0. An independent data and safety monitoring committee reviewed the interim results for safety and efficacy after 50% of the data were available.

The primary outcome was complete abortion without surgical intervention at any point, regardless of the number of misoprostol doses used. Secondary outcomes included side effects and days of heavy bleeding. Acceptability data will be presented in a separate publication. One tailed p<.05 was considered to indicate statistical significance. Fischer's exact test was used to determine differences in proportions and Student *t*-test to determine differences in means of continuous variables. The analysis of the primary outcome was intent to treat.

3. Results

A total of 714 women were enrolled: 389 women in the 57–63 days group and 325 women in the 64–70 days group. Gestational age was confirmed by ultrasound in approximately three-quarters of all cases [57–63 days: 72.2% (281/389); 64–70 days: 77.5% (252/325); p=.12]. Five women in the 57–63 day group and 4 women in the 64–70 day group were lost to follow-up. In the 57–63 day group, 8.2% of women (32/389) were followed up by phone compared to 6.7% of women in the later gestational age group (22/325). Two women in the 57–63 days group discontinued participation in the study on or before the follow-up visit. The final efficacy analysis included 703 women: 382 in the earlier gestational age group and 321 in the later gestational age group. The sociodemographic characteristics (mean age, parity, abortion history, level of education) of the two groups were similar (Table 1).

The success rate was 94.8% (or 362/382) in the 57–63 days group and 91.9% (or 295/321) in the 64–70 days group [Relative Risk (RR): 0.79 (0.61–1.04)] (Table 2). Two percent of women in each group received a surgical evacuation for an ongoing pregnancy [57–63 days: 1.8% (7/382); 64–70 days: 2.2% (7/321); RR: 1.10 (0.65–1.87)]. There was a significant difference between the two groups in rates of surgical evacuation for excessive or prolonged bleeding [57–63 days: 0.5% (2/382); 64–70 days: 2.5% (8/321); RR: 1.77 (1.29–2.44)].

Almost all women took the misoprostol according to protocol [57–63 days: 98.7% (384/389); 64–70 days: 97.5% (317/325)]. Most women elected to take the misoprostol at home [57–63 days: 78.9% (307/389); 64–70 days: 72.6% (236/325); p=.05]. Significantly more women in the later gestational group received one additional dose of 400 mcg sublingual misoprostol at the follow-up visit for management of bleeding or a retained sac [57–63 days: 5.7% (22/386); 64–70 days: 10.5% (34/325); p=.03].

Two women did not take the misoprostol at all (1 in 57–63 days group and 1 in the 64–70 days group) and failed to expel the ongoing pregnancy. Four women took misoprostol more than 48 h after mifepristone administration (i.e., 72–74 h after mifepristone administration). Of these, three women in the 64–70 days group had a successful medical abortion and one woman in the 57–63 days group underwent a surgical evacuation for a persistent nonviable sac.

Four women in the 64–70 days group used an alternate route of misoprostol administration. One woman administered the pills buccally and had a successful outcome. Three women administered the tablets orally. Two had a successful outcome, and one woman underwent a surgical evacuation and was hospitalized and received a blood transfusion as treatment for prolonged bleeding. A per-protocol analysis excluding cases who failed to administer the misoprostol or

Table 1
Participant characteristics

	57–63 days (*n*=389)	64–70 days (*n*=325)	p-Value[a]
Age (y), mean (SD) (range)	27.7 (5.7) (18–46)	28.1 (6.4) (18–47)	.36
Gravidity[b]			.88
1	69 (17.7)	80 (18.5)	
2	96 (24.7)	72 (22.2)	
3	78 (20.1)	65 (20.0)	
4+	146 (37.5)	128 (39.4)	
Previous abortion[b]	173 (44.5)	150 (46.2)	.71
Previous medical abortion[b]	68 (17.5)	55 (16.9)	.92
Education[b]			.81
No formal education	11 (2.8)	8 (2.5)	
Less than high school	47 (12.1)	48 (14.8)	
High school	183 (47.0)	150 (46.2)	
University or postgraduate	147 (37.8)	117 (36.0)	
Unknown	1 (0.3)	2 (0.6)	

[a] Two-tailed p-value; Student *t*-test for difference in means; Fischer's exact test for difference in proportions.
[b] Values are presented as n (%).

Table 2
Medical abortion outcome, n (%)[a]

	57–63 days (*n*=382)	64–70 days (*n*=321)	RR (95% CI)
Success	362 (94.8)	295 (91.9)	0.79 (0.61–1.04)
Failure[b]	20 (5.2)	26 (8.1)	
Ongoing pregnancy	7 (1.8)	7 (2.2)	1.10 (0.65–1.86)
Persistent nonviable pregnancy/sac	5 (1.3)	3 (0.9)	0.82 (0.33–2.01)
Substantial debris in uterus[c]	4 (1.0)	6 (1.9)	1.32 (0.79–2.21)
Excessive/prolonged bleeding	2 (0.5)	8 (2.5)	1.77 (1.29–2.44)
Woman's request	1 (0.3)	1 (0.3)	1.10 (0.27–4.40)
Other	1 (0.3)	1 (0.3)	1.10 (0.27–4.39)
Major adverse events			
Received blood transfusion	1 (0.3)	1 (0.3)	1.10 (0.27–4.39)
Hospital admission	2 (0.5)	1 (0.3)	0.73 (0.15–3.62)

[a] Excludes women lost to follow-up (57–63 days: 5; 64–70 days: 4) and women who withdrew from the study (57–63 days: 2).
[b] Includes 2 women who did not take misoprostol (57–63 days: 1; 64–70 days: 1) and 8 women who did not administer the misoprostol per protocol (57–63 days: 1; 64–70 days: 7).
[c] Substantial debris was subjectively defined and differed by local practice.

administered the misoprostol by an alternative route (buccal or oral) or more than 48 h after mifepristone yields slightly higher success rates, which were still not significantly different [57–63 days: 95.0% (361/380); 64–70 days: 92.7% (290/313); p=.21].

Three women in the study (including the protocol violation mentioned above) were hospitalized due to bleeding during the study period [57–63 days: 0.5% (2/382); 64–70 days: 0.3% (1/321); RR: 0.73 (0.15–3.62)]. One woman in the earlier gestational age group and one woman in the later gestational age group received a blood transfusion (p=1.000).

Ultrasound was performed at the follow-up visit in approximately two-thirds of cases [57–63 days: 61.1% (214/350); 64–70 days: 67.9% (197/290); p=.08]. Among women who returned to the clinic for follow-up, women in the later gestational age group were assessed as incomplete (i.e., persistent gestational sac or substantial debris as diagnosed by ultrasound) at the follow-up visit at a higher rate than women in the earlier gestational age group [57–63 days: 6.5% (21/350); 64–70 days: 9.7% (29/298); RR: 1.29 (1.00–1.66); p=.08]. Most women with incomplete expulsion were treated with additional misoprostol [57–63 days: 52.3% (11/21); 64–70 days: 75.9% (22/29); p=.13]. Of those women who received an additional dose of misoprostol, most went on to have a successful abortion [57–63 days: 90.9% (10/11); 64–70 days: 86.3% (19/22); p=.35].

Self-reported side effects experienced by women in both groups were similar. Over one-third of women in both groups reported no side effects [57–63 days: 38.2% (145/380); 64–70 days: 35.4% (111/314); RR: 1.07 (0.90–1.27)]. Reported rates of diarrhea, nausea, vomiting, chills, headache, dizziness and weakness were not significantly different in the two study groups (Table 3). Reports of fever were slightly fewer in the lower gestational age group [57–63 days: 9.2% (35/380); 64–70 days: 14.0% (44/314); RR: 0.79 (0.64–0.98)].

Table 3
Side effects [n (%)]

	57–63 days (*n*=380)	64–70 days (*n*=314)	RR (95% CI)
None	145 (38.2)	111 (35.4)	1.07 (0.90–1.27)
Diarrhea	35 (9.2)	39 (12.4)	0.84 (0.67–1.06)
Nausea	139 (36.6)	118 (37.6)	0.98 (0.83–1.16)
Vomiting[a]	54 (14.2)	56 (17.9)	0.87 (0.71–1.06)
Fever	35 (9.2)	44 (14.0)	0.79 (0.64–0.98)
Chills	65 (17.1)	63 (20.1)	0.90 (0.74–1.10)
Headache	61 (16.1)	51 (16.2)	0.99 (0.80–1.24)
Dizziness	70 (18.4)	69 (22.0)	0.89 (0.73–1.08)
Weakness	133 (35.2)	121 (38.5)	0.92 (0.78–1.09)
Heavy bleeding	*n*=350	*n*=302	p=.05
Days of heavy bleeding	1.89±1.37 (0–9)	2.10±1.39 (0–7)	
Median days of heavy bleeding	2	2	

[a] The 64–70 days group (*n*=313).

Data on bleeding were collected on a diary completed at home. Almost all women (93.2%, or 655/703) completed the diary. The median duration of all bleeding (i.e., spotting, moderate and heavy bleeding) was slightly longer in the later gestational age group (57–63 days: 10 median days; 64–70 days: 11 median days), although the mean difference in bleeding was not statistically significant (57–63 days: 9.8±3.0; 64–70 days: 10.2±3.0; p=.07). The mean difference in duration of heavy bleeding between the two groups approached significance (p=.05), with women in the 64–70 days group reporting slightly more days of heavy bleeding than their counterparts in the lower gestational age group (Table 3).

Approximately half of women in both groups used nonsteroidal anti-inflammatory drugs for pain management [57–63 days: 47.6% (182/382); 64–70 days: 53.6% (172/321); p=.13]. Rates of narcotic use were low and not significantly different between groups [57–63 days: 18.3% (70/382); 64–70 days: 17.8% (57/321); p=.92]. Mean days of any pain medication was not significantly different between the two study groups (57–63 days: 2.0 mean days; 64–70 days: 2.2 mean days; p=.35).

4. Discussion

Medical abortion with an outpatient regimen of 200 mg mifepristone followed 24–48 h later by 400 mcg sublingual misoprostol is effective in women 57 to 70 days from LMP. Our results are consistent with other studies of outpatient medical abortion regimens to 70 days' LMP [11,23]. Winikoff et al. [11] found a success rate of 92.8% (95% CI: 89–95) with a regimen of 200 mg mifepristone and 800 mcg buccal misoprostol in women with gestational ages 64–70 days from LMP. Rates of ongoing pregnancy in this group were also consistent across studies; the rate of ongoing pregnancy in this study (2.2%) was slightly lower than reported rate in the study of the 800 mcg buccal regimen (3.0%).

This study did show a statistically significant difference in the rate of surgical intervention for excessive/prolonged bleeding between the two study arms (0.5% in 57–63 days vs. 2.5% in 64–70 days). The rate of intervention in the higher gestational age group (2.5%) was also higher than the reported rate for a regimen of 200 mg following in 24–48 h by 800 mcg buccal misoprostol (1.0%, or 3/304) [11]. Most interventions for prolonged bleeding (8/10) occurred at two hospital study sites. The differences in rates of intervention for management of bleeding may reflect variations in provider practice for management of incomplete abortion. Still, women in the 64–70 days group may have also experienced slightly more bleeding. Women at the more advanced gestational age group did report experiencing more median days of bleeding (57–63 days: 10 median days; 64–70 days: 11 median days). The difference in mean duration of heavy bleeding between groups did approach significance

(57–63 days: 1.89 mean days; 64–70 days: 2.1 mean days; p=.05) but was similar to the rate reported for the 800 mcg buccal outpatient regimen (57–63 days: 2.5 mean days; 64–70 days: 2.3 mean days) [11].

Only fever was significantly more likely to be reported by women in the higher gestational age group. Relatively few women reported this side effect (57–63 days: 9.2%; 64–70 days: 14.0%). The difference, while statistically significant, may not be clinically relevant. The incidence of fever reported in this study is slightly lower than prior studies of this regimen (28.1% and 25.0%) [16,19]. Reports of chills (57–63 days: 17.3% and 64–70 days: 20.1%) are also lower than reports of chills/shivering from prior studies of 400- and 800-mcg regimens (38% and 52.9% of women reported experiencing chills/shivering up to 3 h after misoprostol administration, respectively) [21]. Fever and chills are commonly reported side effects associated with sublingual misoprostol administration, and the effect may be a result of the higher misoprostol plasma concentrations after sublingual administration [17,18].

This study was not powered to detect a difference in adverse events because these outcomes (e.g., hospitalization or need for transfusion) are rare. This study also suggests that such events occur infrequently with no evidence of a difference by gestational age. The study was conducted in sites where ultrasound is not used routinely for gestational age dating, but gestational age was confirmed by ultrasound in over three-quarters of cases in both groups. It is possible that some women could have been misclassified into study groups based on variability in woman's report of LMP or clinical assessment. Even so, the findings may help to reassure providers that medical abortion may be safely provided up to the 70 days' LMP without relying exclusively on ultrasonography for gestational age dating. Access to ultrasonography may be limited in many places where improved access to first trimester abortion services is greatly needed.

One limitation of the study is that the study was not blinded and two categories of failure (excessive bleeding and substantial debris in the uterus) are dependent upon subjective evaluation. As indicated above, interventions for excessive bleeding were primarily confined to two study sites. Rates of intervention for substantial debris in the uterus also varied with slightly higher rates in Tbilisi and Odessa (2.2% and 2.3%) compared to the sites in India and Tunisia (0–1%), where ultrasound use was less frequent.

In conclusion, the study findings show that a regimen of 200 mg mifepristone followed in 24–48 h by sublingual misoprostol is effective. The study results demonstrate that it is possible to expand access to outpatient regimens to 70 days' LMP using mifepristone plus a two-pill misoprostol regimen.

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ORIGINAL ARTICLE

Randomized Trial of Very Early Medication Abortion

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ABSTRACT

BACKGROUND

Medication abortion, with a combination of mifepristone and misoprostol, is highly effective and safe. However, there is insufficient evidence on efficacy and safety at very early gestations before a pregnancy can be visualized with ultrasonography.

METHODS

We conducted a multicenter, noninferiority, randomized, controlled trial involving women requesting medication abortion at up to 42 days of gestation with an unconfirmed intrauterine pregnancy on ultrasound examination (visualized as an empty cavity or a sac-like structure without a yolk sac or embryonic pole). Participants were randomly assigned to either immediate start of abortion (early-start group) or standard-care treatment delayed until intrauterine pregnancy was confirmed (standard group). The primary outcome was complete abortion. The noninferiority margin was set at 3.0 percentage points for the absolute between-group difference.

RESULTS

In total, 1504 women were included at 26 sites in nine countries and were randomly assigned to the early-start group (754 participants) or the standard group (750 participants). In an intention-to-treat analysis, a complete abortion occurred in 676 of 710 participants (95.2%) in the early-start group and in 656 of 688 (95.3%) in the standard group; the absolute between-group difference was −0.1 percentage points (95% confidence interval, −2.4 to 2.1). Ectopic pregnancies occurred in 10 of 741 participants (1.3%) in the early-start group and in 6 of 724 (0.8%) in the standard group, with one rupture before diagnosis (early-start group). Serious adverse events occurred in 12 of 737 participants (1.6%) in the early-start group and in 5 of 718 (0.7%) in the standard group (P=0.10); the majority were uncomplicated hospitalizations for treatment of ectopic pregnancy or incomplete abortion.

CONCLUSIONS

Medication abortion before confirmed intrauterine pregnancy was noninferior to standard, delayed treatment with respect to complete abortion. (Funded by the Swedish Research Council and others; VEMA EudraCT number, 2018-003675-35; ClinicalTrials.gov number, NCT03989869.)

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*The members of the VEMA Study Group are listed in the Supplementary Appendix, available at NEJM.org.

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CME

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Medication abortion with a combination of mifepristone and misoprostol is a highly effective and safe method of first-trimester induced abortion.[1,2] As compared with procedural abortion, medication abortion has the advantage that the provision, treatment, and outcome assessment can be managed by the patient.[1] Although medication abortion is recommended by both national and international organizations, there is limited evidence regarding its efficacy when provided at very early gestations before a pregnancy can be visualized on ultrasound examination. Therefore, many clinical guidelines refrain from specific recommendations on clinical management for induced abortion before confirmed intrauterine pregnancy.[1,3-5]



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Where medication abortion is available and barriers such as mandatory waiting times and provider referrals are removed, an increasing proportion of women present to abortion services even before an intrauterine pregnancy can be visualized with ultrasonography.[6-8] In services that routinely use ultrasonography before abortion, this scenario can lead to the labeling of a pregnancy as having an unknown location (positive pregnancy test but no ultrasonographic evidence of intrauterine pregnancy) or as being a probable intrauterine pregnancy (a sac-like intrauterine structure without a yolk sac or embryonic pole).[9] Providers may then delay treatment or recommend a diagnostic uterine aspiration owing to concerns that the pregnancy may be ectopic.[10,11] However, observational studies have shown that with assessment of human chorionic gonadotropin (hCG) levels before and after abortion, the time to diagnosis of pregnancy location does not increase (as compared with delaying abortion treatment until pregnancy location is confirmed).[5,12,13]

Evaluating provision of very early abortion is particularly important given recent legal changes in some U.S. states that limit access to abortion at gestations of more than 6 weeks.[14] A small number of observational studies of medication abortion performed before ultrasonographic confirmation of an intrauterine pregnancy suggest treatment efficacy ranging from 85 to 100%.[5,12,13,15-18] However, these studies differed in inclusion criteria for maximum gestational length, ultrasound criteria for unconfirmed intrauterine pregnancy, and definitions of failed abortion.[19] We conducted a multicenter, multinational, noninferiority, randomized, controlled trial to evaluate the efficacy and safety of early as compared with delayed start for women seeking medication abortion before confirmed intrauterine pregnancy.

Method

Trial Design

The VEMA (Very Early Medication Abortion) trial took place at 26 sites in nine countries (1 site in Austria, 1 in Australia, 2 in Denmark, 1 in Finland, 7 in Nepal, 1 in New Zealand, 1 in Norway, 2 in Scotland, and 10 in Sweden) from March 2019 through April 2023. The original protocol included 11 sites, but owing to slow recruitment, we added trial sites. The trial protocol (available with the full text of this article at NEJM.org) was approved by the Swedish Ethical Review Authority and local ethics committee at each trial site or in each country. (Trial sites are listed in the Supplementary Appendix, available at NEJM.org.) Participants were included after providing written informed consent. An external monitor and data and safety monitoring board were appointed. The data and safety monitoring plan is included in the Supplementary Appendix. Blinding with respect to trial-group assignments was not deemed to be feasible.

The trial funders did not have any involvement in or influence on the trial protocol or trial conduct. The first author wrote the first draft of the manuscript. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Trial Participants

Women seeking medication abortion with a maximum estimated gestational length of 42 days and an unconfirmed intrauterine pregnancy on vaginal ultrasound examination were screened for inclusion. We used the definition of an unconfirmed intrauterine pregnancy as either pregnancy of unknown location or probable intrauterine pregnancy.[9] For women with irregular menstrual cycles or an unknown date of the last menstrual period, enrollment was at the discretion of the local investigator. Women were eligible if they were 18 years of age or older, spoke English or a local language, and consented to participate after receiving written and oral information about the trial. Exclusion criteria were symptoms or signs of pathologic pregnancy (e.g.,

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bleeding or unilateral abdominal pain), risk factors for ectopic pregnancy (previous ectopic pregnancy or the presence of an intrauterine device), or any contraindications to medication abortion (see the Supplementary Appendix). Baseline data on age, body-mass index, and previous and current pregnancy, as well as baseline ultrasound findings and hCG level, were collected for all the participants; data were not collected on race, ethnic group, and gender.

TRIAL PROCEDURES

Participants were randomly assigned, by means of block randomization with varying block size and stratification according to center, in a 1:1 ratio to receive either early treatment (early-start group) or delayed treatment (standard group). Participants in the early-start group initiated medication abortion on the day of or the day after trial inclusion. We delayed treatment for participants in the standard group until a repeat ultrasound examination on trial day 7 (with a window of ±2 days) visualized an intrauterine pregnancy. If an intrauterine pregnancy was still not confirmed, participants in the standard group had a third ultrasound evaluation at trial day 14 (with a window of ±2 days). If an intrauterine pregnancy could still not be confirmed, the participant was considered to have a pathologic pregnancy. Participants with a pathologic pregnancy that was diagnosed at any time during the trial were treated according to local clinical practice but followed for assessment of outcome and adverse events.

All the participants received the World Health Organization–recommended protocol for medication abortion: mifepristone at a dose of 200 mg orally, followed 24 to 48 hours later by misoprostol at a dose of 800 μg administered vaginally, sublingually, or buccally according to local standard practice.[1] An additional dose of misoprostol (400 μg) was administered if bleeding had not started within 3 hours (except in Australia).[4] Oral analgesia was offered according to local clinical routine with a combination of nonsteroidal antiinflammatory drugs and paracetamol with repeat doses or oral opioids (or both) if needed. The level of serum or plasma hCG was assessed at all preabortion visits for both groups (with the exception of Nepalese sites, where it was assessed only before intrauterine pregnancy had been confirmed). If the baseline hCG level was more than 5000 IU per liter, the participant was evaluated by a gynecologist for possible ectopic pregnancy before continuing in the trial.

Assessment of treatment outcome in the early-start group was by means of hCG measurements at mifepristone intake and on day 7. The treatment was deemed to be successful if a decrease of at least 80% was seen.[20] Additional clinical assessments were performed if there were signs or symptoms of complications or ongoing pregnancy. Assessment of treatment in the standard group was according to local clinical routine, including either blood or urine hCG levels (at home or in the clinic) or ultrasound examination.

All the participants were followed up at 4 weeks after abortion, by telephone or in person. If participants could not be reached for follow-up, medical records were retrieved and assessed.

OUTCOME MEASURES AND ADVERSE EVENTS

The primary outcome was complete abortion, with no ongoing intrauterine pregnancy and no need for surgical intervention for incomplete abortion within 30 days after treatment.[21] Adverse events were defined as complications related to the abortion treatment or trial conduct (e.g., pelvic infection, uterine perforation or other complications of surgery, side effects of mifepristone or misoprostol, and prolonged or heavy bleeding). Serious adverse events were defined as all conditions resulting in hospitalization (for ≥24 hours) or hemorrhage resulting in blood transfusion. Detailed data on all ectopic pregnancies were collected, including status at diagnosis (ruptured or unruptured) and type of treatment.

Secondary outcomes included incomplete abortion, additional medical treatment for incomplete abortion, infections treated with antibiotics, unscheduled telephone contacts, unscheduled visits, and acceptability measures including days with bleeding and maximum pain (assessed by means of a numerical rating scale, with scores ranging from 0 to 10 and a score of >7 classified as severe pain) as well as satisfaction with assigned treatment (assessed by means of the Likert scale, with scores ranging from 0 to 6 and a score of ≥5 classified as satisfied) and preferred and recommended treatment (early or standard treatment) (see the Supplementary Appendix). For data management, we used Research Electronic Data Capture (REDCap) software.[22]

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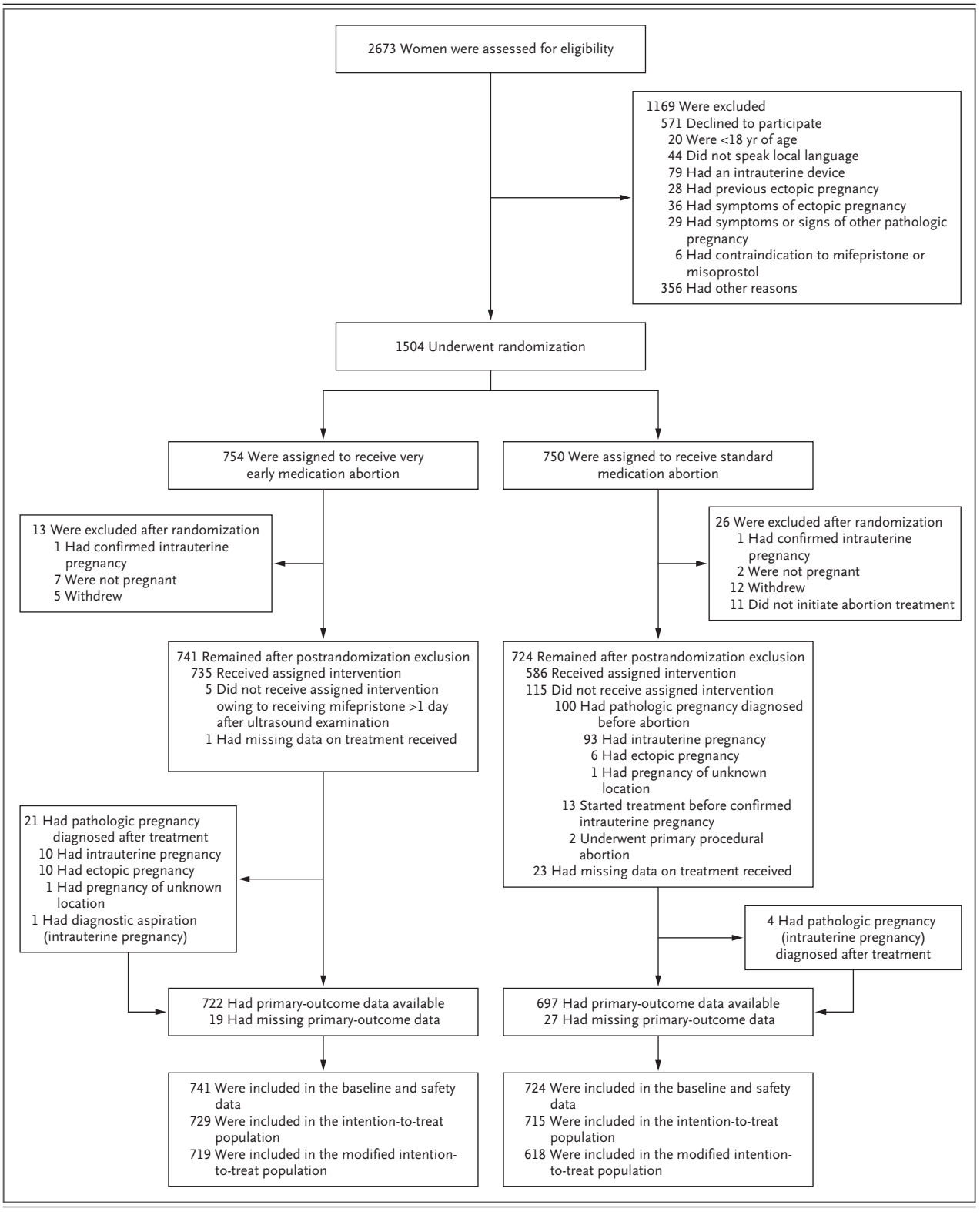

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Figure 1 (facing page). Enrollment, Randomization, Received Treatment, and Follow-up.

Among the women assessed for eligibility, exclusion data were missing from one site in Stockholm, and linear approximation was used for exclusion data from Helsinki before February 17, 2022. The intention-to-treat population included participants who started medication abortion, excluding those with ectopic pregnancy, primary procedural abortion, diagnostic aspiration, or a final diagnosis of pregnancy of unknown location. The modified intention-to-treat population included participants who started medication abortion, excluding those with a pathologic pregnancy, primary procedural abortion, or a final diagnosis of pregnancy of unknown location.

STATISTICAL ANALYSIS

We calculated that 1360 participants were needed to show noninferiority of early as compared with standard treatment with a power of 90%. The calculation was based on an estimated efficacy of 97% in both groups, on the basis of previous studies of very early medication abortion, and calculated by the construction of a two-sided 95% confidence interval for the difference in efficacy between the two groups.[5] The noninferiority margin was set at 3.0 percentage points, because this was deemed to be clinically relevant. Power calculation was done with the use of R software, version 3.3. To compensate for a 10% loss to follow-up (including participants with pathologic pregnancies diagnosed), we planned to include a total of 1500 participants.

The confidence interval for the primary-outcome analysis was constructed with the use of the proportion test for calculating the absolute between-group difference. According to our initial statistical analysis plan, a modified intention-to-treat analysis would include participants who started medication abortion and had a known outcome, excluding participants with pathologic pregnancies. We had anticipated a combined incidence of loss to follow-up and pathologic pregnancies of 10%. This calculation was exceeded in our standard group with 104 pathologic pregnancies (14.4%), as compared with 21 (2.8%) in the early-start group. To avoid selection bias, we opted to use a strict intention-to-treat approach that included participants with intrauterine pathologic pregnancies. Pathologic intrauterine pregnancies included early pregnancy loss and molar pregnancy, which can be treated with mifepristone or misoprostol (or both) or uterine aspiration in a fashion similar to induced abortion.[23,24] A modified intention-to-treat analysis and a per-protocol analysis were also performed as additional analyses of the primary outcome. Sensitivity analyses also included multivariate logistic regression with adjustment for country and ultrasound findings in the intention-to-treat population. According to our statistical analysis plan, adjustments were planned at the site level, but owing to the large number of sites (some of which had no failed abortions), we adjusted instead at the country level. Adjusted between-group differences were calculated as marginal means from a logistic-regression model.

The only prespecified subgroup analysis for the primary outcome was according to baseline ultrasound finding (pregnancy of unknown location or probable intrauterine pregnancy). Post hoc exploratory analyses included subgroups defined on the basis of baseline hCG level (≤1000, 1001 to 5000, or >5000 IU per liter) and gestational length in weeks according to the last menstrual period. All between-group differences for subgroup analyses were calculated as marginal means from a logistic-regression model that included interaction terms for the analyzed subgroup.

Secondary outcomes were analyzed in the modified intention-to-treat population. Risk ratios were calculated for binary outcomes. Confidence intervals around risk ratios for these outcomes were not adjusted for multiplicity and should not be used for hypothesis testing. For the main analysis of primary and secondary outcomes, the complete case analysis was used. As a sensitivity analysis, we imputed missing data using multiple imputation with chained equations.[25] All analyses were performed with the use of Stata software, version 17 (StataCorp).

RESULTS

PARTICIPANTS

In total, 2673 women were assessed for eligibility, of whom 1169 were excluded and 1504 were included in the trial (Fig. 1). We randomly assigned 754 participants to the early-start group

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Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Early Start (N=741)	Standard (N=724)
Age — yr	29.6±6.4	29.7±6.5
Body-mass index†	24.9±4.8	24.9±4.9
No. of pregnancies, including current pregnancy — no. (%)		
1	167 (22.5)	179 (24.7)
2	132 (17.8)	116 (16.0)
≥3	442 (59.6)	429 (59.3)
Nulliparous — no. (%)	254 (34.3)	247 (34.1)
Previous miscarriage — no. (%)	141 (19.0)	145 (20.0)
Previous ectopic pregnancy — no. (%)‡	2 (0.3)	3 (0.4)
Previous abortion — no. (%)	328 (44.3)	324 (44.8)
Last menstrual period — no. (%)		
Certain	650 (87.7)	634 (87.6)
Uncertain	91 (12.3)	90 (12.4)
Median length of gestation (IQR) — days§	37 (33–40)	36 (33–40)
Ultrasound finding — no./total no. (%)		
Pregnancy of unknown location	241/741 (32.5)	261/723 (36.1)
Probable intrauterine pregnancy	500/741 (67.5)	462/723 (63.9)
Median serum hCG level (IQR)¶	2220 (747–5200)	1850 (707–5900)
Pathologic pregnancy — no. (%)‖	21 (2.8)	104 (14.4)
Early pregnancy loss	9 (1.2)	96 (13.3)
Molar pregnancy	1 (0.1)	1 (0.1)
Pregnancy of unknown location	1 (0.1)	1 (0.1)
Ectopic pregnancy	10 (1.3)	6 (0.8)

* Plus–minus values are means ±SD. All the participants had requested medication abortion up to 42 days of gestation, with an unconfirmed intrauterine pregnancy on ultrasound examination. Participants in the early-start group were assigned to immediate start of abortion, and those in the standard group were assigned to standard-care treatment delayed until intrauterine pregnancy was confirmed. Shown are data from all randomly assigned participants without inclusion failure. The term hCG denotes human chorionic gonadotropin, and IQR interquartile range.
† The body-mass index is the weight in kilogram divided by the square of the height in meters. Data were missing for 5 participants in the early-start group and 14 participants in the standard group.
‡ These participants were enrolled by mistake. They are included in the intention-to-treat and modified intention-to-treat analyses but not in the per-protocol analysis.
§ Shown is the number of days since the last menstrual period, if known. One participant in the early-start group and five participants in the standard group had values for the last menstrual period that were outside a reasonable range (0 to 100 days).
¶ Data were missing for 3 participants in the early-start group and 11 participants in the standard group.
‖ Shown are data for pathologic pregnancies that were diagnosed after trial inclusion.

and 750 to the standard group. After randomization, 13 participants in the early-start group and 26 in the standard group were excluded owing to not meeting inclusion criteria. A total of 7 participants were erroneously enrolled in the trial (5 had a previous ectopic pregnancy and 2 had an intrauterine device in situ during this pregnancy). These participants received trial interventions and are included in the analysis. More participants in the early-start group than in the standard group received their assigned treatment (735 vs. 586), mainly owing to the diagnosis of 100 pathologic pregnancies in the standard group before abortion (93 intrauterine pregnancies [including 92

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Table 2. Complete Abortion (Primary Outcome).*

Population and Outcome	Early Start (N = 729)	Standard (N = 715)	Primary Analysis†		Multiple-Imputation Analysis	
	no./total no. (%)		Difference (95% CI)	Risk Ratio (95% CI)	Difference (95% CI)	Risk Ratio (95% CI)
			percentage points		*percentage points*	
Intention-to-treat population‡						
Complete abortion§	676/710 (95.2)	656/688 (95.3)	−0.1 (−2.4 to 2.1)	1.00 (0.98 to 1.02) ¶	−0.2 (−2.4 to 2.0)	1.00 (0.98 to 1.02)
Ongoing pregnancy	21/710 (3.0)	1/688 (0.1)	2.8 (1.5 to 4.1)	20.35 (2.74 to 150.87) ‖		
Surgical intervention for incomplete abortion**	13/710 (1.8)	31/688 (4.5)	−2.7 (−4.5 to −0.8)	0.41 (0.21 to 0.77) ‖		
Per-protocol population						
Complete abortion§	664/693 (95.8)	546/574 (95.1)	0.7 (−1.6 to 3.0)	1.01 (0.98 to 1.03)		

* Shown are unadjusted between-group differences and risk ratios in the intention-to treat population (participants who started medication abortion, excluding those with ectopic pregnancy, primary procedural abortion, diagnostic aspiration, or a final diagnosis of pregnancy of unknown location) and the per-protocol population (participants who met all inclusion criteria and no exclusion criteria; adhered to the protocol, including the timing of assigned treatment [early start or standard]; and had a known outcome). Data on unadjusted and adjusted between-group differences in the modified intention-to-treat population are provided in Table S4 in the Supplementary Appendix.

† Shown are complete case analyses without data imputation.

‡ Outcome data were missing for 19 participants in the early-start group and 27 participants in the standard group.

§ Complete abortion was defined as both no ongoing pregnancy and no need for surgical intervention for incomplete abortion (including surgical intervention for spontaneous abortion and missed abortion) within 30 days after abortion.

¶ P = 0.90 for superiority.

‖ Analyses were not adjusted for multiplicity and should not be used for hypothesis testing.

** Includes surgical intervention for spontaneous abortion and missed abortion, but not for ongoing pregnancy.

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Table 3. Secondary Outcomes in the Modified Intention-to-Treat Population.*

Outcome	Early Start (N=719)	Standard (N=618)	Risk Ratio or Median Difference (95% CI)†	
			Primary Analysis	Multiple-Imputation Analyses
Additional abortion treatment — no./total no. (%)‡	49/700 (7.0)	52/591 (8.8)	0.80 (0.55 to 1.16)	0.82 (0.56 to 1.19)
Surgical	17/700 (2.4)	28/591 (4.7)	0.51 (0.28 to 0.93)	
Misoprostol	24/700 (3.4)	29/591 (4.9)	0.70 (0.41 to 1.19)	
Mifepristone and misoprostol	15/700 (2.1)	3/591 (0.5)	4.22 (1.23 to 14.51)	
Median no. of bleeding days (IQR)§	5 (3 to 7)	6 (4 to 8)	−1 (−1.6 to −0.4)	−1 (−1.6 to −0.4)
Severe pain — no./total no. (%)¶	125/622 (20.1)	131/528 (24.8)	0.81 (0.65 to 1.01)	0.80 (0.64 to 1.01)
Infection treated with antibiotics — no./total no. (%)	11/646 (1.7)	25/543 (4.6)	0.37 (0.18 to 0.74)	0.40 (0.20 to 0.80)
≥1 Unscheduled telephone contact — no./total no. (%)	114/648 (17.6)	98/543 (18.0)	0.97 (0.76 to 1.25)	1.02 (0.87 to 1.33)
≥1 Unscheduled visit — no./total no. (%)	85/646 (13.2)	65/543 (12.0)	1.10 (0.81 to 1.49)	1.18 (0.86 to 1.63)
Satisfaction with treatment — no./total no. (%)‖	568/612 (92.8)	446/521 (85.6)	1.08 (1.04 to 1.13)	1.08 (1.04 to 1.13)
Preference — no./total no. (%)				
Standard	11/619 (1.8)	161/528 (30.5)		
Early start	570/619 (92.1)	277/528 (52.5)		
Unsure	38/619 (6.1)	90/528 (17.0)		
Recommendation — no./total no. (%)**				
Standard	9/615 (1.5)	150/520 (28.8)		
Early start	524/615 (85.2)	241/520 (46.3)		
Unsure	82/615 (13.3)	129/520 (24.8)		

* The modified intention-to-treat population included participants who started medication abortion, excluding those with a pathologic pregnancy, primary procedural abortion, or a final diagnosis of pregnancy of unknown location.
† Risk ratios are shown for all outcomes except median number of bleeding days, for which median differences are shown. Risk ratios and median differences were not adjusted for multiplicity and should not be used for hypothesis testing.
‡ Shown are additional treatments for ongoing pregnancy or incomplete abortion. Participants could receive a combination of additional treatments.
§ Data were missing for 103 participants in the early-start group and 96 participants in the standard group.
¶ Maximum pain was assessed by means of a numerical (integer) rating scale, with scores ranging from 0 to 10 and a score of more than 7 classified as severe pain.
‖ Satisfaction with treatment was assessed by means of a Likert scale, with scores ranging from 0 (dissatisfied) to 6 (very satisfied). Shown are participants with a score of 5 or 6.
** Shown is which treatment would be recommended to a friend.

early pregnancy losses and 1 molar pregnancy], 6 ectopic pregnancies, and 1 pregnancy of unknown location). Pathologic pregnancies that were diagnosed after treatment were followed for outcome and safety assessments. Primary-outcome data were not available for 19 participants in the early-start group and 27 in the standard group.

Baseline characteristics were similar in the two groups other than diagnosed pathologic pregnancies (Table 1 and Table S1 in the Supplementary Appendix). The demographic characteristics of the background population seeking induced abortion are shown in Table S2.

OUTCOMES

In an intention-to-treat analysis using complete data, the efficacy of medication abortion with respect to complete abortion was 95.2% (676 of 710 participants) in the early-start group and 95.3% (656 of 688 participants) in the standard group. The between-group difference was −0.1 percentage points (95% confidence interval [CI], −2.4 to 2.1), a finding consistent with noninferiority of early start to standard treatment (prespecified margin, 3.0 percentage points). Results were materially unchanged in analyses of the per-protocol population, the modified intention-

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to-treat population, and the intention-to-treat population with missing data imputed and in analyses adjusted for country and baseline ultrasound finding (Table 2 and Table S4).

Failed abortion included either ongoing pregnancy or surgical intervention for incomplete abortion; the reasons for failure differed between the two groups. The number of ongoing pregnancies was 21 (3.0%) in the early-start group and 1 (0.1%) in the standard group (risk ratio, 20.35; 95% CI, 2.74 to 150.87); surgical interventions for incomplete abortion were performed in 13 of 710 participants (1.8%) in the early-start group and in 31 of 688 (4.5%) in the standard group (risk ratio, 0.41; CI, 0.21 to 0.77) (Table 2).

Results of subgroup analyses, including subgroups stratified according to baseline ultrasound finding (pregnancy of unknown location or probable intrauterine pregnancy), hCG levels, and gestational length, are shown in Figure S1. These analyses were not adjusted for multiplicity, but they suggest a possible advantage of standard (over early) treatment for pregnancies of unknown location or with an hCG level of less than 1000 IU per liter, as compared with a possible advantage of early treatment for probable intrauterine pregnancy and when the hCG level was more than 5000 IU per liter.

Results of secondary-outcome analyses are shown in Table 3. In both groups, responses to questions about preference for future treatment and which treatment one would recommend to a friend favored early treatment.

There were 10 ectopic pregnancies (1.3%) in the early-start group and 6 (0.8%) in the standard group (Table 1), with one rupture occurring before diagnosis (early-start group). Clinical details are shown in Table S5. Serious adverse events were reported in 12 of 737 participants (1.6%) in the early-start group and in 5 of 718 (0.7%) in the standard group (P=0.10); most were uncomplicated hospitalizations (for ≥24 hours) for treatment of ectopic pregnancy or incomplete abortion (Table 4 and Table S6).

Table 4. Safety Outcomes.*

Event	Early Start (N=741)	Standard (N=724)	P Value
Adverse events†			
Any event — no./total no. (%)	15/737 (2.0)	35/718 (4.9)	0.003
Type of event — no. of participants			
Bleeding	0	10	
Pain	2	1	
Allergy	2	1	
Infection	11	23	
Other	1	5	
Serious adverse events‡			
Any event — no./total no. (%)	12/737 (1.6)	5/718 (0.7)	0.10
Type of event — no. of participants			
Blood transfusion	1	1	
Bleeding, no blood transfusion	3	0	
Infection (inpatient)	1	2	
Laparoscopy	6	2	
Laparotomy	0	1	
Uterine aspiration (inpatient)	3	0	
Medical treatment (inpatient)	0	1	

* Shown are data for all randomly assigned participants without inclusion failure. Data were missing for four participants in the early-start group and six participants in standard group.
† Serious adverse events are not included and are presented separately.
‡ Details regarding serious adverse events are provided in Table S6 in the Supplementary Appendix.

DISCUSSION

In this large, multicenter, randomized, controlled trial involving women with a maximum estimated gestational length of 42 days, we found that early start of medication abortion before confirmed intrauterine pregnancy was noninferior to delayed treatment after confirmed intrauterine pregnancy with respect to completing abortion. Reasons for failed abortion differed between the two groups, with a higher incidence of surgical intervention for incomplete abortion after standard treatment and a higher incidence of ongoing pregnancy after early start.

Our results are consistent with findings from the largest observational study on very early medication abortion[5], which included 2643 patients and showed a similarly high incidence of complete abortion for treatment with and without confirmed intrauterine pregnancy. Yet more recent observational studies on medication abortion that were limited to pregnancy of unknown location showed a lower efficacy of early treatment than delayed treatment.[12,13] Our trial was not powered to detect noninferiority within this subgroup. However, subgroup analyses involving our large population with pregnancy of unknown location suggested the possibility of an advantage of

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delayed treatment in this subgroup (unlike in the subgroup with probable intrauterine pregnancy).

Findings for some secondary outcomes, such as postabortion infections, days with bleeding, satisfaction with assigned treatment, and preferred treatment, appeared to favor early start over standard treatment. However, the absence of adjustment for the multiplicity of testing precludes firm conclusions about these outcomes.

In this trial, as well as in previous observational studies, early diagnosis of an ectopic pregnancy was possible regardless of whether abortion treatment was started early or delayed.[5,12,13,18] Making this diagnosis requires adherence to follow-up with hCG assessment, ultrasonography, or both.

Limitations of our trial should be recognized. Women with pregnancy of unknown location and those with probable intrauterine pregnancy were included, and the trial was not designed to evaluate these groups separately. In addition, participants who received a diagnosis of a pathologic pregnancy were not followed for secondary outcomes such as bleeding, pain, and acceptability of assigned treatment. Because we had underestimated the prevalence and imbalance of diagnosed pathologic pregnancies between the groups, we have unbalanced groups for these analyses. Moreover, treatment outcome was assessed with the hCG level in the early-start group and according to local clinical practice in the standard group. In Nepal, the routine use of ultrasonography for participants in the standard group might have led to "unnecessary" uterine aspirations for this group. To control for this possibility and for other potential differences in clinical practice, we adjusted for country in our sensitivity analysis of the primary outcome and found consistent results.

Whereas participants in our trial were included on the basis of ultrasound findings, there has been a shift toward selective use of ultrasonography only for those at high risk for pathologic pregnancy or with uncertain gestational length.[1,4] Nevertheless, we consider our results to be relevant to women with early pregnancy regardless of whether an ultrasound examination was performed. In our trial, we determined success in the early-start group on the basis of the decrease in blood hCG levels over a period of 7 days. It would be of value to evaluate whether this could be determined with urine hCG levels or could be determined sooner, especially for settings where abortion is restricted after 6 weeks of gestation.[12,13,26] In addition, we did not include procedural abortion, which has shown potential to offer rapid diagnosis of pregnancy location and to be highly effective.[13] Finally, we did not collect data on race or ethnic group in our trial population and hence cannot address the generalizability of our findings according to these characteristics (Table S3).

The results of this large multicenter trial indicate the noninferiority of the early start of medication abortion before confirmed intrauterine pregnancy, as compared with the standard approach of delaying abortion until an intrauterine pregnancy is confirmed.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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Original research article

Can women determine the success of early medical termination of pregnancy themselves?☆,☆☆,★

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Abstract

Objective: To determine the outcome of early medical termination of pregnancy (TOP) among women who choose a "self assessment" follow up comprising a self-performed low sensitivity urine pregnancy test with instructions on signs/symptoms that mandate contacting the TOP service.
Study design: A retrospective review of computer databases of 1726 women choosing self-assessment after early medical TOP (<9 weeks) in the UK. The main outcome measures were (a) number of women choosing self-assessment, (b) contact rates with TOP service and (c) time to presentation with an ongoing pregnancy (failed TOP).
Results: Ninety-six percent of women having an early medical TOP and going home to expel the pregnancy chose self-assessment. Two percent of women made unscheduled visits to the TOP service. One hundred and eighty-eight women (11%) telephoned the service about concerns related to complications or the success of treatment. There were eight ongoing pregnancies (0.5%; 95% confidence interval 0.2–0.9%). Four were detected within 4 weeks of treatment; the remainder were not detected until one or more missed menses after the procedure.
Conclusions: Most women having an early medical TOP, who go home to expel the pregnancy, choose self-assessment. Relatively few women make unscheduled visits or telephone the TOP service. Most ongoing pregnancies are recognized at an early stage, although late presentation (as with all methods of follow up) does still occur.
Implications statement: If women are given clear instructions on how and when to conduct a urine pregnancy test and on signs/symptoms that mandate contacting the TOP service, then they can confirm the success of early medical TOP themselves. Late presentation due to failure to recognize an ongoing pregnancy is rare.
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Keywords: Medical abortion; Mifepristone; Misoprostol; Low sensitivity pregnancy test

1. Introduction

It is estimated that one in three women will have a termination of pregnancy (TOP) at some point in their lives [1]. Increasingly in Great Britain, early TOP (up to 9 weeks gestation) is being conducted medically; 87% and 61% of those at less than 9 weeks gestation were conducted medically in Scotland and England/Wales, respectively, in 2013 [2,3]. The medical regimen at less than 9 weeks gestation usually consists of a single oral dose (200 mg) of mifepristone followed 24–48 h later by 800 mcg of misoprostol (usually administered vaginally) [4]. In most countries where early medical TOP is legal (e.g., USA, Sweden, France and Portugal), women are able to administer the second part of this treatment regimen (misoprostol) at home, and this has been shown to be safe and preferred by women [5]. In Great Britain, legal restrictions mandate that misoprostol must be administered on licensed premises, although women may then go home to expel the pregnancy [6,7]. This has sometimes been termed *early medical discharge*. With early medical

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TOP, the risk of ongoing pregnancy is small—approximately 0.5–1% [4]. For women in whom expulsion of the pregnancy has not been confirmed by a clinician before, follow-up traditionally has involved a routine clinic visit for ultrasound. While ultrasound will reliably exclude an ongoing pregnancy, its use can lead to unnecessary medical or surgical intervention due to detection of blood clot or products of conception that are visible but not clinically important [8,9]. Reliance on ultrasound is also costly and requires highly skilled staff, and for some services, the volume of repeat appointments may limit the number of new referrals that can be seen. Observational studies report high loss to follow up when women are scheduled for a routine clinic follow-up, which is a waste of resources [6,10]. The most studied alternative method of follow up to exclude ongoing pregnancy is that of a telephone follow-up from the TOP provider combined with a self-performed pregnancy test conducted by the woman herself at home [11,12]. Although telephone follow-up has been shown to be an acceptable method of follow-up [11,12], a survey of women showed that more than half would have preferred no routine telephone call but rather simply to contact the service themselves if there was a problem [11].

The TOP service in Edinburgh, which is part of the National Health Service (NHS) Scotland and provides free treatment, introduced telephone follow as routine in 2011. However, by 2012, staff of the TOP service, reported that there were increasing requests from women not to receive a routine call, and that several attempts had to be made before most women were successfully contacted. Furthermore, staff reported that women had often forgotten to perform the pregnancy test on the day of the scheduled call necessitating a second call at a later date for results of the pregnancy test. In response to this in April 2012 the TOP service introduced "self assessment," permitting women having early medical TOP and going home to expel the pregnancy, to opt out of receiving this routine telephone call provided that they understood how to conduct and interpret the urinary pregnancy test and signs and symptoms that indicated the need to contact the TOP service. The quality improvement team for gynecology for the region approved the new service.

We wished to evaluate the self-assessment option in terms of (a) proportion of women choosing this, (b) contact rates with the TOP service and (c) time to presentation with an ongoing pregnancy (failed TOP).

2. Methods

2.1. Self-assessment

All women attending the TOP service in Edinburgh had an ultrasound to assess gestational age, and the medical TOP regimen used was 200 mg mifepristone followed 24–48 h later with 800-mcg misoprostol. From September 2012, clinics for women requesting a TOP were held both in a hospital outpatient clinic and a city centre community sexual and reproductive health (SRH) clinic, 3 mi away. The same clinical lead was responsible for both sites, and the same clinic protocols were used at both NHS sites. Women were provided with a low sensitivity pregnancy (LSUP) test (detection limit 1000 IU Human Chorionic Gonadotrophin) at the clinic visit for administration of misoprostol and were instructed by clinic staff on when and how to conduct the LSUP test (Baby Duo, Quadratech diagnostics, UK). This was supplemented with both written and pictorial instructions on how to perform and interpret the test together with and signs/symptoms that might indicate an ongoing pregnancy [13] and for which they should contact the service on the dedicated number provided. All women who chose to have self-assessment were required to sign a form stating that they wished to opt out of receiving a routine telephone call, that they accepted the responsibility for contacting the TOP service if the pregnancy test was positive or invalid or they were not certain of the result or that even if the LSUP test was negative that they should still contact the service if they had less than 4 days of bleeding, had persisting symptoms of pregnancy or if their next period failed to arrive by 1 month after treatment (Fig. 1). In this way, ongoing pregnancy should in theory be detected at the latest when the next menses following treatment were missed (after 4 weeks).

The TOP service also provided free ongoing contraceptive supplies (pills, patch, ring) to women to start on the day that they received misoprostol. Progestogen-only injectables and implants were also administered/inserted at this visit before the woman was discharged home. Women wishing intrauterine contraception (intrauterine device or system) were given an appointment for insertion at a later date at the SRH service [14].

A retrospective review of the TOP service databases was conducted for all women choosing self-assessment during the period of study. Demographics that are routinely recorded include reproductive history, deprivation category based upon Scottish postcodes [15], body mass index (BMI) and method of contraception supplied to women at discharge from the service. For all women, the regional hospital computerized database was also checked to determine if women made an unscheduled visit to either the hospital or SRH site with a complication of treatment within 3 months of TOP or to the maternity service with an ongoing pregnancy. The TOP service telephone call registers were also checked to determine if women made telephone contact and reason for this. The chair of the local ethics committee confirmed that formal ethical committee approval was not required for this retrospective database review.

2.2. Statistical analysis

Statistical analysis was conducted using International Business Machines (IBM) Statistical Package for Social Sciences (SPSS) software Version 18 (SPSS, Chicago, IL, USA). Descriptive statistics were performed for demographics, and groups were compared by chi-squared test of significance.

I understand that:
• I am accepting responsibility to perform a 'self assessment' to exclude the possibility of an ongoing pregnancy (1 in 100 risk of ongoing pregnancy)
• I will not receive the telephone call at 2 weeks
Signs that treatment may not have worked and that I still may be pregnant, are: • **do not bleed within 24 hours of receiving misoprostol** • **less than 4 days of bleeding** • **still 'feel' pregnant at the end of one week or have symptoms of pregnancy such as sore breasts, sickness, tummy growing etc.** In such circumstances I should contact the clinic immediately, as I may require more treatment.
• Need to perform the urine pregnancy test that I have been given, 2 weeks after treatment
• The urine test must be performed using only my first morning urine
• If the pregnancy test is positive, or invalid, or I am not sure, that I should contact the clinic as soon as possible to arrange for an appointment, as I might still be pregnant
• If the pregnancy test is negative, that I could still be pregnant, if my next period does not come by one month after the treatment.
• If the treatment fails and I am still pregnant, that doctors cannot guarantee that the pregnancy will be healthy

Fig. 1. Details of the form that women sign if they choose self-assessment and wish to opt out of receiving a routine telephone call.

Ninety-five percent confidence intervals (CIs) for proportions and multiple logistic regression were conducted where appropriate. Statistical significance was taken as a p of <0.05.

3. Results

Between April 2012 and October 2013 (18 months), a total of 1791 women had an early medical TOP and chose to go home to expel the pregnancy. In 1726 cases (96%), the planned method of follow-up was self-assessment. All women from the SRH site opted for self-assessment, but 42 women (4%) attending the hospital chose to receive a routine telephone follow up (call from provider), and 23 women (2%) had a clinic visit with ultrasound arranged as routine follow-up.

3.1. Demographics

The demographics of women choosing self-assessment are shown in Table 1. The only difference between women assessed at hospital and SRH sites was that a statistically significantly higher percentage of women were at 6 weeks gestation or less at the SRH site (47% vs. 29% at SRH and hospital, respectively; $p<0.0001$(Table 1).

A total of 220 women (13%) made contact with the service after the TOP (Fig. 2). In 188 cases (11%), primary contact was by telephone, with only 32 women (2%) presenting to the hospital or SRH service with an unscheduled/emergency visit; mostly due to pain and/or heavy or persistent bleeding ($n=29$). Seven out of the 32 women who made an unscheduled visit required hospital admission for blood transfusion ($n=4$) and/or a surgical evacuation of the uterus ($n=3$) due to haemorrhage, and one woman required intravenous antibiotics for renal tract sepsis.

Of the 188 telephone calls, a clinic visit was subsequently scheduled for 120 women (7% of women having self-assessment). In 45 cases (2.6% of all women having self-assessment), the reason for the telephone call to the TOP service was a positive LSUP test ($n=17$) or invalid LSUP test result ($n=28$). In 43 cases, women called because they had less bleeding than expected (2% of women having self-assessment). A further 12 women (0.7% of total women having self-assessment) called due to concern about ongoing pregnancy symptoms ($n=7$) or because their next period after treatment had not arrived ($n=5$). In total therefore 100 women out of 1726 (6%), made a telephone call to the service on the basis of a self-assessment that indicated that they should contact the TOP service.

3.2. Detection of ongoing pregnancy

There were a total of 8 women in the self-assessment group (0.5%) with an ongoing pregnancy (95% CIs 0.2%–0.9%). Neither age, deprivation nor BMI affected the risk of ongoing pregnancy (results not shown). Of the ongoing pregnancies, the gestation at medical TOP had been 42 days or less ($n=2$), 43 to 49 days ($n=2$), 50 to 56 days ($n=1$) and 57 to 63 days ($n=3$). Two of the women telephoned the TOP service within 1 week of treatment to arrange a clinic review due to pain ($n=1$) and scant bleeding ($n=1$). An ultrasound confirmed the ongoing pregnancy, and both women proceeded to have a repeat medical TOP (both less than 9

Table 1
Demographics of women choosing self-assessment

	Hospital TOP clinic, *N*=1000	SRH TOP clinic, *N*=726	Total, *N*=1726
Age (years) range [a]	15–45	16–44	15–45
Mean (SD)	26.5 (6.5)	26.8 (6.5)	26.6 (6.5)
Deprivation score [b]			
Affluent 1–2	177 (18)	115 (16)	292 (17)
Moderate 3–5	705 (71)	524 (73)	1229 (71)
Deprived 6–7	111 (11)	78 (11)	189 (11)
Unknown	7 (0.7)	9 (1)	16 (0.9)
Reproductive history			
Previous birth	475 (48)	324 (45)	799 (46)
Previous abortion	316 (32)	220 (31)	536 (31)
Previous miscarriage	425 (43)	293 (41)	718 (42)
Previous ectopic	16 (2)	13 (2)	29 (2)
Gestation (days)			
≤42	290 (29)[c]	339 (47)[c]	597 (35)
43–49	238 (24)	141 (19)	356 (21)
50–56	254 (25)	157 (22)	406 (24)
57–63	209 (21)	88 (12)	295 (17)
64	9 (1)	1 (0)	10 (0.5)
BMI kg/m^2			
≤24.5	630 (63)	427 (61)	1057 (61)
25–29.5	235 (23)	165 (23)	400 (23)
30–34.5	80 (8)	74 (11)	154 (9)
35	33 (3)	35 (5)	68 (4)

Figures shown are number (%) except for age.
[a] Women should have been 16 years or older to be considered as an adult [12].
[b] Based upon Scottish post codes [15].
[c] p<0.0001 chi-squared.

weeks gestation). A further two women with ongoing pregnancies contacted the service between 2 and 4 weeks after treatment to arrange review due to scant bleeding/ongoing pregnancy symptoms (n=1) or a positive LSUP test (n=1). One woman chose to have a surgical TOP and the other a medical TOP (both less than 13 weeks gestation).

Two women contacted the service after missed menses, and the remaining two women presented only when they had missed two menses. In all four cases of delayed presentation, although bleeding post TOP lasted less than 4 days, this did not trigger contact with the TOP service. In two of the four cases presenting after 1 month, the LSUP test had been positive or invalid at 2 weeks but the other women reported that the LSUP test had been negative. All four women had a successful repeat TOP procedure performed either medically (n=2) or surgically (n=2) at between 12 and 22 weeks gestation.

Of the eight women with ongoing pregnancies, the method of contraception started post TOP was the combined oral contraceptive pill (n=3), injectable (n=1), progestogen-only pill (n=1) and no method (n=3). In one case, pregnancy symptoms and amenorrhoea were wrongly assumed to the due to progestogen-only injectable. In one case, the ongoing pregnancy was wrongly assumed to be a new intended pregnancy.

4. Discussion

This study showed that when given the option, most women who are planning to go home to expel a pregnancy following an early medical TOP choose not to receive a phone call from the TOP service. The proportion of women choosing this was considerably higher than the 50% or so that we had expected based upon our earlier survey [11], which may reflect changes in women's views about this over time, or provider's readiness to support women in this decision. Whatever the reasons, this does seem to suggest that most women feel comfortable with taking the responsibility for interpreting the result of LSUP test, in the knowledge that they can contact the TOP service directly should they have concern about the outcome of the test or about signs or symptoms. The study also showed that relatively few women (approximately 1 in 10) actually do make contact with the TOP service with a concern related to the procedure.

The study also confirmed the low rate of ongoing pregnancy with early medical TOP. Of course, compared to receiving a telephone call, self-assessment does place more responsibility on women to correctly interpret an LSUP test and to be sufficiently motivated to contact the TOP service should they have any suspicions that they might still be pregnant. Providers may therefore be concerned that ongoing pregnancies might be detected later. This may be particularly relevant in countries where midtrimester abortion is not legal or not available (in Great Britain the upper limit for abortion for nonmedical reasons is 24 weeks) [2]. However, our study provides some reassurance in this respect, since the delay between medical TOP and presentation at clinic with diagnosis of ongoing pregnancy did not appear to differ from previous reviews of ongoing pregnancy from our service when we scheduled a routine clinic visit with ultrasound [5] or had an active policy of telephone contact with women at 2 weeks [11,12]. Indeed, with a routine clinic visit for ultrasound to confirm success of TOP, we found that some women still presented late in the midtrimester for a repeat TOP or at childbirth [5,11,12]. Similar findings have been reported from a large retrospective review from the USA that showed that abandoning the clinic visit for routine follow up after surgical TOP does not affect the rate nor stage of detection of ongoing pregnancy [16]. A number of studies have also shown that even when women are concerned enough to call about a positive LSUP test and are scheduled for an urgent clinic review, many subsequently choose not to attend this [5,11,12]. Given that some ongoing pregnancies were in women who reported a negative LSUP test, this strengthens the need to remind women that no test is perfect and that scant bleeding, pregnancy symptoms or missed menses after treatment necessitate contact with the provider.

Although, it is important to start effective contraception immediately post TOP to prevent another unintended pregnancy, there is of course the potential that women with

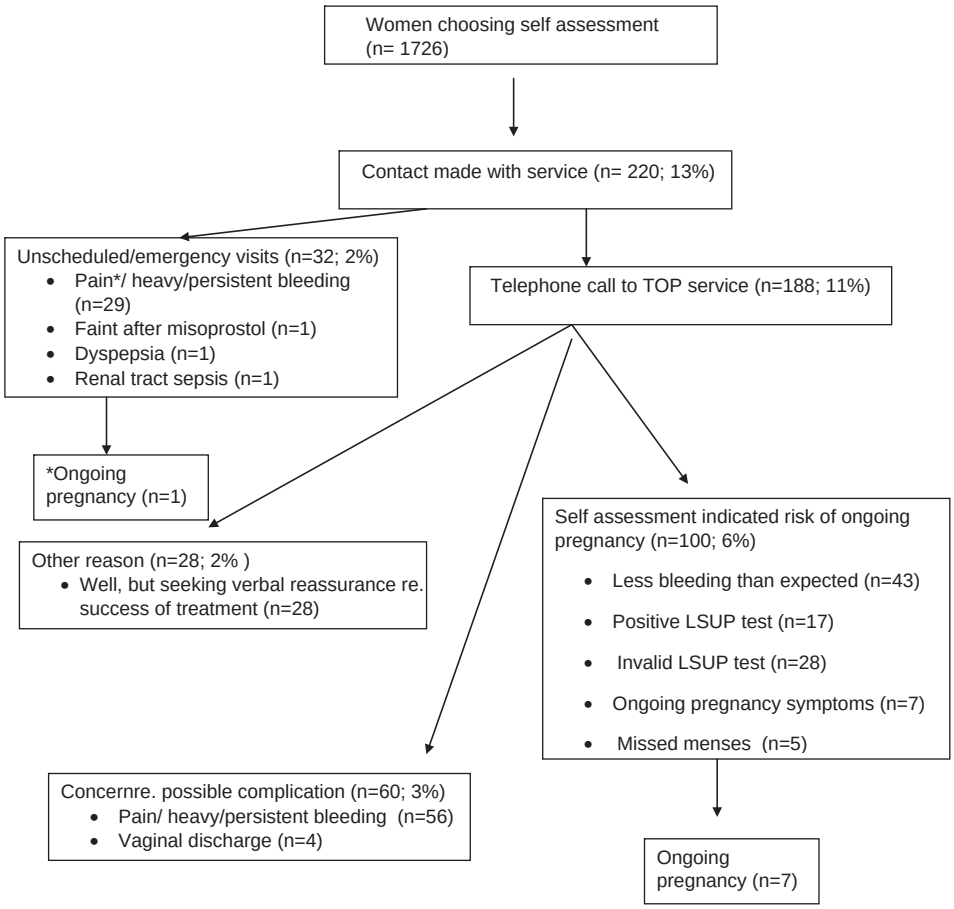

Fig. 2. Reasons for making contact with TOP service post abortion.

ongoing pregnancies might wrongly attribute paucity of bleeding or amenorhoea or pregnancy symptoms to the hormonal effect of the injectable or implant, and this was sadly a factor in one of our cases with ongoing pregnancy.

A strength of this study is that the data are from a large cohort of women having early medical TOP, the vast majority of whom have chosen self-assessment. We also went to considerable effort to search all available registers that could provide us with information of any unscheduled contact with the service related to the TOP. Furthermore, this is the only study to date to report a method of "follow up" that involves contact with a health care provider, only when initiated by the women themselves. Of course this study relates to a high income setting (Scotland), where all women have universal free access to health care. Furthermore, all women had to meet our criteria to be permitted to go home to pass the pregnancy, that is, adults with adult support at home and able to speak and understand English [12]. As such therefore, they represent a group of women who are already "selected" to be well-placed to be able to manage self-assessment and capable of contacting the TOP service with concerns. In addition, women attending our TOP service are provided with high-quality written [17] and pictorial information and can also access the same information in audiovisual format via the regional sexual health service Website.

A potential weakness of this study was that we were only able to verify ongoing pregnancies amongst women who presented in the same region. We believe it is unlikely that we will have missed other ongoing pregnancies, as we feel that women (or providers from other regions) would probably have contacted our service to complain or pursue litigation. However, we do accept that we cannot exclude the possibility that women may have been treated for an ongoing pregnancy in another region or another country.

There is good evidence that the pathway for women requesting an early medical TOP can be simplified. It has been shown that in uncomplicated cases, gestational age dating by ultrasound is not necessary [18]. Furthermore, both the assessment for medical TOP and the care can safely be delivered by midlevel providers [19,20]. It is also clear that most women can undergo the procedure just as safely at home as in a hospital setting [6]. We have previously shown that a clinic follow up is not routinely required and that in most cases this can be replaced with a self-performed pregnancy test with telephone support from a provider [11,12]. We now show that most women neither want nor need scheduled telephone contact from a provider.

This supports recent findings from a study in England that showed 84% of women randomized to clinic follow up with ultrasound after early medical TOP failed to attend [21]. Self assessment affords women greater control of their treatment and may minimize distress and costs to them, as a consequence of fewer visits to the service. In addition, it is possible that self-assessment could protect women from unnecessary intervention for ultrasonically visible but clinically unimportant retained products of conception that are commonly seen at a routine 2-week clinic visit [8,9]. For health care services, self-assessment is likely to result in reduced costs since the number of visits to the service is reduced. This will also free up clinical time for clinicians to see and treat more patients. Providers may worry that women may be more likely to make unscheduled visits to a TOP service if a clinic visit or telephone call is not scheduled; but our findings would negate this. Providers might also worry that women may not perform an LSUP test, perform it incorrectly or may try to seek litigation if a test is negative and they have an ongoing pregnancy. Whilst these are valid concerns, these risks can be minimized by careful counseling and documentation that the woman is taking responsibility for this assumed follow up and that any contact with the service is also documented. For women, it is important that they have easy access to specialist TOP advice and further assessment if required. In other areas of medicine there is a move away from routine follow-up visits after clinical procedures with emphasis being placed on advising patients how to reengage with a health care service if they require further care. This is generally viewed as a positive move in health service delivery and should encompass TOP care.

As clinicians, we should base treatment and care pathways on clinical evidence. The evidence now clearly shows that the pathway for women requesting an early medical TOP who are certain of their decision could consist of a single clinic visit. At this single visit all of the following could reasonably take place: counseling on TOP, administration of mifepristone with a supply of misoprostol for home use, instructions on when and how to conduct a pregnancy test, advice and contact numbers in case of emergency or if they require re-engagement with the TOP service, and provision of supplies of effective ongoing contraception.

Acknowledgments

We would like to thank the nursing staff of CHOICES, Chalmers sexual health service and Bruntsfield suite and reproductive health outpatients, Royal Infirmary of Edinburgh, for assistance with data collection.

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March 24, 2023

Evan Masingill
Chief Executive Officer
GenBioPro, Inc.
3651 Lindell Road
Suite D1041
Las Vegas, NV 89103

Mr. Masingill:

I write in acknowledgment of your March 1, 2023, letter addressed to the Commissioner of Food and Drugs, requesting "confirmation that any withdrawal of the approval of [GenBioPro, Inc.'s] abbreviated new drug application ('ANDA') for mifepristone—whether by court order or otherwise—will follow all applicable procedures afforded by law and regulation to GBP as the ANDA holder and that FDA will permit GBP to continue marketing and selling mifepristone until those procedures have been completed," including any applicable requirements of 21 U.S.C. § 355(e). Your letter has been referred to the Center for Drug Evaluation and Research for this response.

In their Complaint in *Alliance for Hippocratic Medicine v. FDA*, the Plaintiffs have asked the Court to issue "a preliminary and permanent injunction ordering Defendants to withdraw mifepristone . . . as [an] FDA-approved chemical abortion drug[]." According to the transcript of the March 15, 2023 hearing in this matter, the Plaintiffs have argued that "the Court, on its own accord, can order the FDA to withdraw or suspend the approval of the drug," rather than "order the FDA to begin a suspension or withdrawal" process under 21 U.S.C. § 355(e). Arg't Tr. at 145–46. The Court stated that it plans to "issue an order and opinion as soon as possible." *Id*. at 155. FDA will, of course, need to review the Court's opinion and order before determining what steps may be necessary to comply with it.

Sincerely,

Patrizia Cavazzoni

Patrizia Cavazzoni, MD
Director, Center for Drug Evaluation and Research
Food and Drug Administration



CC:

The Honorable Robert M. Califf, MD
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Hon. Xavier Becerra
Secretary
Department of Health and Human Services
200 Independence Avenue SW
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Brian D. Netter
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Washington, DC 20530

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Reproductive Health

REVIEW

Open Access

Telemedicine for the provision of medication abortion to pregnant people at up to twelve weeks of pregnancy: a systematic literature review and meta-analysis

Leonardo Cely-Andrade[1*], Karen Cárdenas-Garzón[1], Luis Carlos Enríquez-Santander[1], Biani Saavedra-Avendano[2] and Guillermo Antonio Ortiz Avendaño[3]

Abstract

Background Telemedicine represents an important strategy to facilitate access to medication abortion (MAB) procedures, reduces distance barriers and expands coverage to underserved communities. The aim is evaluating the self-managed MAB (provided through telemedicine as the sole intervention or in comparison to in-person care) in pregnant people at up to 12 weeks of pregnancy.

Methods A literature search was conducted using electronic databases: MEDLINE, Embase, Cochrane (Central Register of Controlled Trials and Database of Systematic Reviews), LILACS, SciELO, and Google Scholar. The search was based on the Population, Intervention, Comparison, Outcome, and Study Design (PICOS) framework, and was not restricted to any years of publication, and studies could be published in English or Spanish. Study screening and selection, risk of bias assessment, and data extraction were performed by peer reviewers. Risk of bias was evaluated with RoB 2.0 and ROBIS-I. A narrative and descriptive synthesis of the results was conducted. Meta-analyses with random-effects models were performed using Review Manager version 5.4 to calculate pooled risk differences, along with their individual 95% confidence intervals. The rate of evidence certainty was based on GRADE recommendations.

Results 21 articles published between 2011 and 2022 met the inclusion criteria. Among them, 20 were observational studies, and 1 was a randomized clinical trial. Regarding the risk of bias, 5 studies had a serious risk, 15 had a moderate risk, and 1 had an undetermined risk. In terms of the type of intervention, 7 compared telemedicine to standard care. The meta-analysis of effectiveness revealed no statistically significant differences between the two modalities of care (RD = 0.01; 95%CI 0.00, 0.02). Our meta-analyses show that there were no significant differences in the occurrence of adverse events or in patient satisfaction when comparing the two methods of healthcare delivery.

Conclusion Telemedicine is an effective and viable alternative for MAB, similar to standard care. The occurrence of complications was low in both forms of healthcare delivery. Telemedicine services are an opportunity to expand access to safe abortion services.

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Plain English summary

Globally, unsafe abortion causes 47,000 deaths and 5 million sexual and reproductive dysfunctions in young pregnant people due to complications of the procedure. This practice is related to barriers to accessing safe abortion services secondary to health system limitations and inequities in the distribution of resources.

Telemedicine has proven to be an efficient care alternative to reduce distancing gaps, decrease waiting time and rationalize the costs derived from the procedure. Consequently, several health systems in the world use this model with differences in treatment schemes, weeks of gestation, pregnancy confirmation methods and measurement of reported outcomes. For this reason, evaluating the effectiveness and safety of self-managed medication abortion (MAB) by telemedicine is a support for decision makers who consider implementing or expanding remote care services.

This systematic review integrated studies that evaluated MAB only by Telemedicine or in comparison with standard care on pregnant people with 12 weeks gestation or less. Available studies until January 2023 were chosen. Screening and selection of studies, data extraction, and risk of bias assessment were performed by expert reviewers. Aspects such as the effectiveness, safety, and satisfaction of the procedure, among other outcomes, were reviewed. A narrative and descriptive synthesis was carried out, as well as several meta-analyses of the differences in risks between Telemedicine and in-person care.

The meta-analysis of studies comparing telemedicine care with standard services reveals that the type of care provided does not affect the effectiveness and safety of MAB, nor does it affect user satisfaction, follow-up, or medication adherence.

Keywords Medication abortion, Telemedicine, Standard care, First trimester, Effectiveness, Adverse effects, Acceptability, Satisfaction, Systematic review, Meta-analysis

Introduction

Unsafe abortion poses significant challenges to pregnant people's health, public health, and the overall well-being of nations. Each year, approximately 47 000 pregnant people die and nearly 5 million experience sequelae or sexual and reproductive dysfunctions due to complications associated with this procedure [1, 2]. Unsafe abortion predominantly occurs among pregnant people aged 20 to 25 or those in vulnerable situations, such as migrants and those living in poverty, belonging to specific ethnic groups, or with low levels of education [3]. According to estimates, 90% of unsafe abortions occur in low- and middle-income countries, particularly in Africa, Southeast Asia, Latin America, and the Caribbean, where there is a higher burden of morbidity, mortality, and increased healthcare costs due to procedure-related complications [3, 4].

The political and legal landscape surrounding abortion plays a pivotal role in this regard, as, in countries with more favorable laws and well-funded healthcare systems, pregnant people have better access to safe abortion procedures. Conversely, in nations where abortion is either prohibited or restricted to specific circumstances, pregnant people seeking to terminate their pregnancies are compelled to undergo procedures performed by unqualified individuals or in unsanitary environments. This significantly heightens the risk of complications and fatal outcomes [1, 5].

To provide high-quality abortion services, it is crucial to establish a comprehensive political, legal, and healthcare framework that safeguards pregnant people's rights and considers their specific needs and social, economic, and cultural contexts [6, 7]. As a result, most countries have decriminalized abortion either entirely or under specific circumstances and have adapted their institutional guidelines to provide care to pregnant people seeking voluntary termination of pregnancy. However, universal access to sexual and reproductive health services remains a distant goal given the limitations within the healthcare system and social inequities, which turn a right into a privilege mostly accessible to pregnant people residing in urban areas with sufficient financial resources to afford such services [2, 4, 8, 9].

Safe abortion refers to the induced termination of pregnancy by healthcare professionals or qualified individuals using methods recommended by the World Health Organization (WHO), which are selected based on weeks' gestation [2]. For instance, a medication abortion (MAB) considered a safe option for pregnancies up to twelve weeks, involves orally administering a single 200-mg dose of mifepristone, followed by the use of misoprostol 24–48 h later. In some cases, additional doses of misoprostol are taken every 3–4 h. The concentrations and administration routes of misoprostol may vary depending on gestational weeks and user preference [1]. This treatment can be provided by healthcare

professionals or, if users have received sufficient information and counseling, it can be self-managed at home [10]. Consequently, the outpatient option somewhat liberates users from the structural limitations of healthcare services [11] and opens up possibilities for innovative care alternatives such as the use of Information and Communication Technologies (ICTs), including telemedicine services [11, 12].

As part of the broader concept of digital health or e-health, *telemedicine* is defined by the WHO as ""the practice of healthcare using interactive audio, visual, and data communications. This includes healthcare delivery, consultation, diagnosis, and treatment, as well as education and transfer of medical data"" [13]. This form of healthcare delivery has seen significant growth over the past 20 years, due to advancements in mobile technologies and the widespread availability of digital media, especially the internet [13–15]. Furthermore, the COVID-19 pandemic and the declaration of a public health emergency by the WHO in January 2020 led to a shift in healthcare delivery models due to mobility restrictions and lockdown measures. In response to these new and adverse public health conditions, remote care services were massively implemented worldwide, demonstrating their effectiveness in reducing geographical barriers, improving the quality and timeliness of care, optimizing costs for both patients and healthcare systems, and reducing healthcare disparities [11, 16–21].

One particular application of remote care is the provision of healthcare services during a MAB. Currently, several studies have shown that self-managed and telemedicine-guided MAB is a comparable alternative to in-person care in terms of effectiveness, safety, and patient satisfaction [10, 18, 20–34]. It also reduces the time required to access care and brings healthcare services to remote or underserved communities [35]. Yet, in order to promote the integration and appropriate use of these technologies, ongoing evaluation is necessary alongside the implementation and strengthening of these services [15, 16].

In most countries, the use of scientific evidence serves as the basis for prescribing interventions in healthcare services. Therefore, providing data on the effectiveness and safety of MAB provided through telemedicine is crucial for decision-makers to justify its implementation and widespread adoption. Moreover, given variations in treatment protocols, gestational weeks, methods of pregnancy confirmation, and outcome measurements reported in studies assessing MAB provided via telemedicine, it is important to consolidate the information through a Systematic Literature Review (SLR). Hence, the purpose of this study is to evaluate the effectiveness, safety, satisfaction, and acceptability of self-managed and telemedicine-guided MAB, either as the sole intervention or in comparison to standard or in-person care.

Materials and methods

For this SLR, we used Cochrane methods [36] and the PRISMA 2020 guidelines [37] as the reporting standard. The SLR protocol employed in this study can be accessed on PROSPERO (CRD42023416407).

Eligibility criteria

This SLR included studies that evaluated MAB provided through telemedicine as the sole intervention or in comparison with standard or in-person care. The research question was defined using the Population, Intervention, Comparison, Outcome, and Study Design (PICOS) framework [36].

Population

Pregnant people of childbearing age (aged 10–50 years) who used telemedicine services for MAB before or during the twelfth week of pregnancy, without restriction to any specific country or region.

Intervention

Telemedicine as a comprehensive model for self-managed MAB care. This involved the provision of healthcare services (in this case, MAB) through remote communication technologies.

Comparison

MAB through standard or in-person care.

Outcome

The primary outcomes assessed in this study were effectiveness of the procedure (successful completion of MAB without the need for additional medications and/or surgical intervention), safety (adverse effects/complications: death, surgical intervention, blood transfusion, hospitalization, antibiotic treatment, and emergency department visits), and user acceptability or satisfaction with the service. Other outcomes included follow-up (completion of all phases of MAB), user feelings regarding the procedure, emotional support provided to users, waiting time to treatment (in days), and adherence to prescribed regimens (compliance with correct dosage, administration route, and recommended intake times).

Study design

Experimental studies (Randomized Controlled Trials -RCTs-) and observational studies (cohort studies, case–control studies, and cross-sectional studies). To be eligible, studies had to be available as full publications, and pre-print publications were also considered. Publications

in English or Spanish were accepted, and there were no restrictions on the publication date. Excluded publications included abstracts, narrative reviews, expert consensus, study protocols, case studies or case series, comments, and letters to the editor.

Sources of information

A literature search was conducted in January 2023 using the following electronic databases: MEDLINE (via PubMed), Embase (via Elsevier), Cochrane Library (including the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials), LILACS (via the Virtual Health Library), and SciELO. Additionally, Google Scholar was consulted as a source of gray literature, with the first ten pages of results being examined. To identify additional relevant research, the snowball search method was employed, checking the references of the included studies.

The search strategy was designed by two of the authors (KCG and LCES) and subsequently reviewed by the main author (JLCA). For the searches, key terms were chosen from the list of Medical Subject Headings (MeSH) and Health Sciences Descriptors (DeCS), and free terms based on opinions from subject-matter experts were used as well. The search strategies were tailored to each specific database, incorporating field identifiers, truncation, proximity operators, and Boolean operators as appropriate. Detailed information on the search terms and search strategies used for each database can be found in Appendix A.

Study selection

The study selection process consisted of two stages. In the first stage, the titles and abstracts of the retrieved papers were downloaded, duplicates were removed using Rayyan [38], and the papers were screened based on title and abstract. This initial screening was performed by two reviewers (KCG and LCES) in a double-blind peer review format. Disagreements were resolved through consensus, and if consensus could not be reached, a third reviewer (JLCA) was consulted.

In the second stage, the full text of the pre-selected studies was reviewed by the same two authors in a double-blind peer review format. Disagreements were resolved using the same methodology employed in the initial screening.

Data extraction

Data were extracted independently by two of the authors (KCG and LCES) using Excel®, and disagreements were resolved either between them or with the involvement of the main author (JLCA). The following details were documented: study title, first author, year of publication, country, study design, timeframe, objective, characteristics of the population (age group and diagnoses), number of participants (total and per group), intervention and comparison details (dose, frequency, duration), outcomes (measurement method and follow-up time), specific results for each outcome, and conclusion.

Risk of bias assessment

The risk of bias of the selected studies was assessed independently by two evaluators (KCG and LCES), and any disagreements were resolved through consensus between them. If disagreements persisted, a third evaluator (JLCA) was involved in the discussion.

To assess the risk of bias of the RCTs, Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) [36] was used, and for the observational studies, the Risk of Bias In Non-randomized Studies—of Interventions (ROBINS-I) tool [39] was employed.

Data synthesis

A narrative and descriptive synthesis was conducted for each outcome. In studies that included a comparator, similar results were grouped together. For meta-analyses, Cochrane's Review Manager version 5.4 [40] was used to generate random-effects models and calculate pooled risk differences, along with their corresponding 95% Confidence Interval (CI) and p-values, which were then presented in a forest plot. Statistical heterogeneity was estimated using the I^2 statistic, where a value greater than 75% indicates significant heterogeneity. For the effectiveness outcome, two a-posteriori subgroup analyses were carried out: the first, according to gestational week (up to weeks 9, 10 and 12); and the second, according to the test used to determine the treatment results (self-assessment, blood test, ultrasound, or a combination of these methods). A Summary of Findings (SoF) table was elaborated to summarize the main results for each outcome (patients and studies, relative and absolute effects, certainty and observations), as well as an assessment of the quality of evidence rating based on GRADE recommendations [41] (rate evidence certainty as high, moderate, low or very low) using the GRADEpro tool [42].

Results

Data search

A total of 821 records were retrieved in the initial search, out of which 87 were duplicates. After reviewing the 734 remaining publications, only 21 met the eligibility criteria (Fig. 1).

Characteristics and risk of bias of the selected studies

Table 1 summarizes the characteristics of the 21 studies included in our review. Out of such studies published

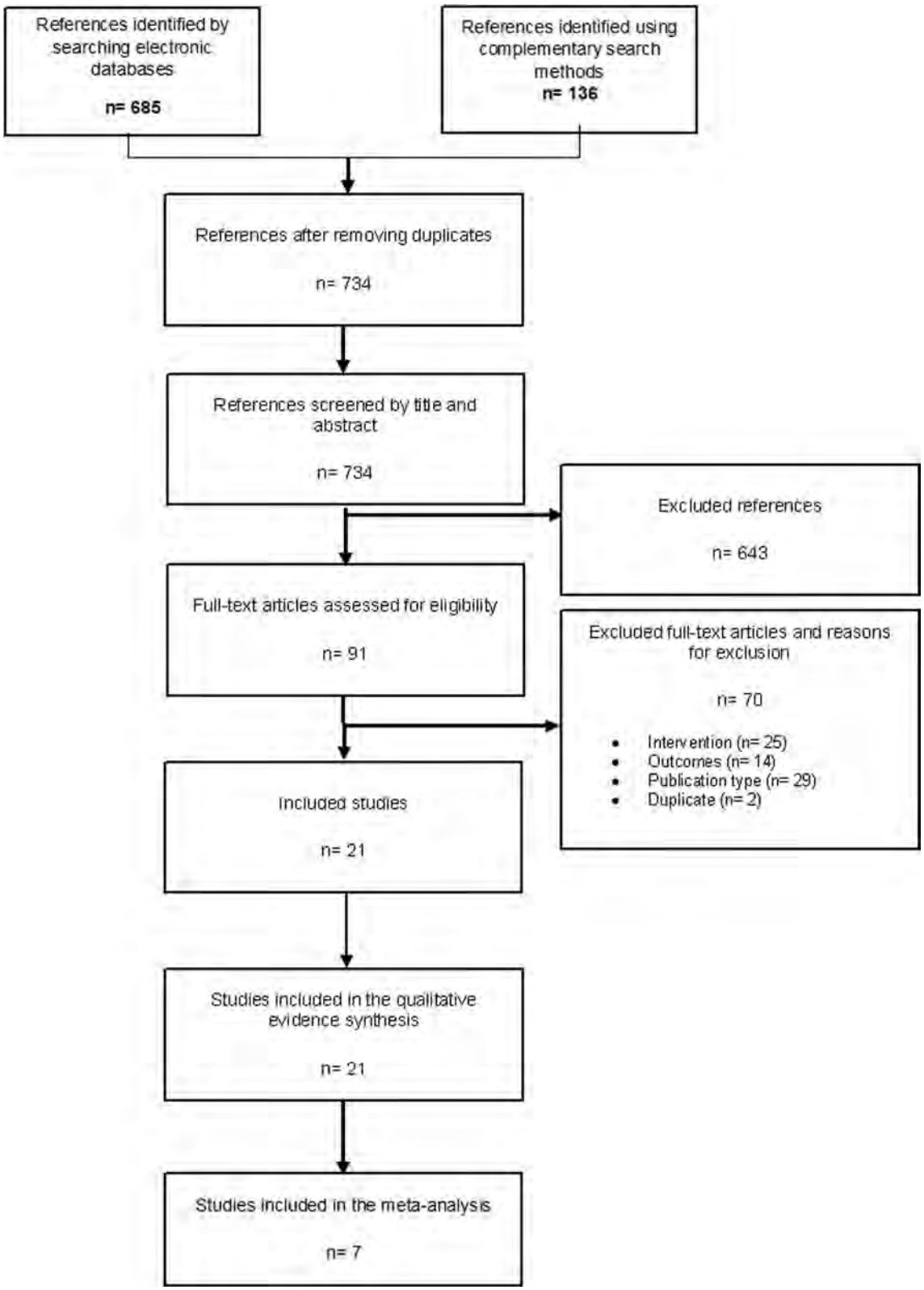

Fig. 1 PRISMA diagram: flow of search, screening, and selection of studies

Table 1 Characteristics of the studies included in the SLR

No	Author/ Year	Location	Study design	Population	Medical abortion	Intervention (I)	Comparison (C)	Outcome(s) and results	Risk of bias
1	Aiken/ 2021	England	Observational	Women up to 9 weeks pregnant	*200 mg mifepristone *800 µg mg misoprostol 24–28 h later *Up to an additional 400 µg 3–4 h after initial misoprostol	Telemedicine (n = 29 984)	Standard care (n = 22 158)	Effectiveness I: 98.8%; C: 98.2%; p = 0.999 Preference for telemedicine I: 80%; C: 13% Average waiting time for medications I: 6.5 days (SD 13.5); C: 10.7 days (SD 19.9); p < 0.001 Hemorrhage and transfusion I: 0.02%; C:0.04% Ectopic I: 0.2%; C: 0.2%	Moderate
2	Aiken/ 2016	Ireland and Northern Ireland	Observational	Women up to 9 weeks pregnant	*200 mg mifepristone *800 µg misoprostol 24–28 h later *Up to an additional 400 µg 3–4 h after initial misoprostol	Telemedicine (n = 5650)	-	Emotional support I: 76% Feelings of relief I: 70% Feelings of sadness I: 12% Feelings of guilt I: 17%	Moderate
3	Aiken/ 2022	USA	Observational	Women up to 10 weeks pregnant	*200 mg mifepristone *800 µg misoprostol 24–28 h later *Up to an additional 400 µg 3–4 h after initial misoprostol	Telemedicine (n = 3186)	-	Effectiveness I: 96.4% Blood transfusion I: 0.5% Intravenous antibiotics I: 0.5% Serious adverse events I: 0.9% Death I: 0.0%	Serious

Table 1 (continued)

No	Author/ Year	Location	Study design	Population	Medical abortion	Intervention (I)	Comparison (C)	Outcome(s) and results	Risk of bias
4	Aiken/ 2017	Ireland and Northern Ireland	Observational	Women up to 9 weeks pregnant	*200 mg mifepristone *800 µg misoprostol 24–28 h later *Up to an additional 400 µg 3–4 h after initial misoprostol	Telemedicine (n = 1000)	-	Effectiveness I: 99.2% Antibiotics I: 2.6% Blood transfusion I: 0.7% Adverse events I: 3.1% Death I: 0.0%	Moderate
5	Chong/ 2021	USA	Observational	Women up to 10 weeks pregnant	*200 mg mifepristone *800 µg misoprostol 24–28 h later *Up to an additional 800 µg 3–4 h after initial misoprostol	Telemedicine (n = 1356)	-	Effectiveness I: 95.3% Emergency care I: 6.0% Emergency/outpatient care I: 7.8% Serious adverse events I: 0.9% Hospitalization I: 0.7% Blood transfusion I: 0.4% Very satisfied/satisfied I: 99.1%	Moderate
6	Comedant/ 2022	Moldova	Observational	Women up to 9 weeks pregnant	*200 mg mifepristone *800 µg misoprostol 24–28 h later *Up to an additional 800 µg 3–4 h after initial misoprostol	Telemedicine (n = 531)	-	Effectiveness I: 91.1% Very satisfied/satisfied I: 99.0%	Moderate

Table 1 (continued)

No	Author/ Year	Location	Study design	Population	Medical abortion	Intervention (I)	Comparison (C)	Outcome(s) and results	Risk of bias
7	Gomperts/ 2014	Brazil	Observational	Women up to 12 weeks pregnant or more	*200 mg mifepristone *800 µg misoprostol 24–28 h later *Up to an additional 400 µg 3–4 h after initial misoprostol	Telemedicine (n = 307)	-	Effectiveness I: 76.9% Continuous pain I: 10.9% Heavy bleeding I: 12.5% Fever and vaginal discharge I: 3.1% Pain/bleeding greater than expected I: 21.9%	Serious
8	Gomperts/ 2012	Multi-country	Observational	Women up to 9 weeks pregnant	*200 mg mifepristone *800 µg misoprostol 24–28 h later *Up to an additional 400 µg 3–4 h after initial misoprostol	Telemedicine (n = 2323)	-	Effectiveness I: 4.7%-14.8% Acceptability I: 86%	Serious
9	Grossman/ 2017	USA	Observational	Women up to 9 weeks pregnant	*200 mg mifepristone *800 µg misoprostol 24–28 h later *Up to an additional 800 µg 3–4 h after initial misoprostol	Telemedicine (n = 8765)	Standard care (n = 10 405)	Serious adverse events I: 0.18% C: 0.32% Hospitalization I: 0.07% C: 0.12% Blood transfusion I: 0.07% C: 0.07% Emergency I: 0.15% C: 0.21%	Moderate

Table 1 (continued)

No	Author/ Year	Location	Study design	Population	Medical abortion	Intervention (I)	Comparison (C)	Outcome(s) and results	Risk of bias
10	Grossman/ 2011	USA	Observational	Women up to 9 weeks pregnant	*200 mg mifepristone *800 µg misoprostol 24–28 h later *Up to an additional 800 µg 3–4 h after initial misoprostol	Telemedicine (n = 281)	Standard care (n = 297)	Effectiveness I: 98.7% C: 96.9% Blood transfusion I: 0.3% C: 0.1% Satisfaction I: 94% C: 88% Service recommendation I: 90% C: 83%	Moderate
11	Hyland/ 2018	Australia	Observational	Women up to 10 weeks pregnant	*200 mg mifepristone *800 µg misoprostol 24–28 h later *Up to an additional 1200 µg 3–4 h after initial misoprostol	Telemedicine (n = 1010)	-	Follow-up I: 98% Effectiveness I: 96% Hospitalization I: 3%	Serious
12	Kohn/ 2019	USA	Observational	Women up to 12 weeks pregnant	*200 mg mifepristone *800 µg misoprostol 24–28 h later *Up to an additional 800 µg 3–4 h after initial misoprostol	Telemedicine (n = 738)	Standard care (= 5214)	Effectiveness I: 99.5% C: 98.2% Hospitalization I: 0.00% C: 0.08% Blood transfusion I: 0.14% C: 0.08% Emergency I: 0.00% C: 0.17% Follow-up I: 60.3% C: 76.9%	Moderate

Table 1 (continued)

No	Author/ Year	Location	Study design	Population	Medical abortion	Intervention (I)	Comparison (C)	Outcome(s) and results	Risk of bias
13	Larrea/ 2015	Latin America	Observational	Women up to 12 weeks pregnant or more	*200 mg mifepristone *800 µg misoprostol 24–28 h later *Up to an additional 400 µg 3–4 h after initial misoprostol	Telemedicine (n = 872)	-	Effectiveness I: 93.3% Hemorrhage I: 6.2% Antibiotics I: 9.3%	Moderate
14	Meurice/ 2021	United Kingdom	Observational	Women up to 10 weeks pregnant	*200 mg mifepristone *800 µg misoprostol 24–28 h later *Up to an additional 400 µg 3–4 h after initial misoprostol	Telemedicine (n = 1144)	-	Very satisfied/satisfied I: 96.9%	Moderate
15	Nortén/ 2022	Multi-country	Observational	Women up to 10 weeks pregnant	*200 mg mifepristone *800 µg misoprostol 24–28 h later *Up to an additional 400 µg 3–4 h after initial misoprostol	Telemedicine (n = 81 683)	-	Effectiveness I: 87.9% Acceptability I: 99.0% Service recommendation I: 96.1% Blood transfusion I: 0.6%	Moderate
16	Peña/ 2022	Mexico	Observational	Women up to 10 weeks pregnant	*200 mg mifepristone *800 µg misoprostol 24–28 h later *Up to an additional 800 µg 3–4 h after initial misoprostol	Telemedicine (n = 393)	-	Effectiveness I: 93.0% Service satisfaction I: 87.0% Hospitalization and transfusion I: 0.2% Follow-up I: 87.3%	Moderate

Table 1 (continued)

No	Author/ Year	Location	Study design	Population	Medical abortion	Intervention (I)	Comparison (C)	Outcome(s) and results	Risk of bias
17	Reynolds-Wright/ 2021	Great Britain	Observational	Women up to 12 weeks pregnant	*200 mg mifepristone *800 µg misoprostol 24–28 h later *Up to an additional 1600 µg 3–4 h after initial misoprostol	Telemedicine (n = 663)	-	Pain I: 94.0% Analgesic medication I: 93.0% Nausea, vomiting, diarrhea, or headache I: 77% Hemorrhage I: 77% Antibiotic prophylaxis I: 90% Antiemetics I: 92% Extra dose of misoprostol I: 13%	Moderate
18	Reynolds-Wright/ 2021 (2)	Great Britain	Observational	Women up to 12 weeks pregnant	*200 mg mifepristone *800 µg misoprostol 24–28 h later *Up to an additional 1600 µg 3–4 h after initial misoprostol	Telemedicine (n = 663)	-	Effectiveness I: 98% Very acceptable/ Acceptable I: 94.7%	Moderate
19	Seymour/ 2022	Australia	Observational	Women up to 9 weeks pregnant	*200 mg mifepristone *800 µg misoprostol 24–28 h later	Telemedicine (n = 2222)	Standard care (n = 17 333)	Effectiveness I: 97.2% C: 95.4% Adverse events I: 0.5% C: 0.3%	Without information

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Table 1 (continued)

No	Author/ Year	Location	Study design	Population	Medical abortion	Intervention (I)	Comparison (C)	Outcome(s) and results	Risk of bias
20	Wiebe/ 2020	USA	Observational	Women up to 10 weeks pregnant	*200 mg mifepristone *800 µg misoprostol 24–28 h later	Telemedicine (n = 182)	Standard care (n = 199)	Follow-up I: 94.5% C: 93.4% Effectiveness I: 90.1% C: 89.9% Intravenous antibiotic I: 0.5% C: 0.0% Extra dose of misoprostol I: 95.4% C: 96.6% Hemorrhage I: 0.5% C: 0.0% Emergency I: 3.3% C: 1.5%	Moderate
21	Endler/ 2022	South Africa	ECA	Women up to 9 weeks pregnant	*200 mg mifepristone *800 µg misoprostol 24–28 h later	Telemedicine (n = 450)	Standard care (n = 450)	Effectiveness I: 90.1% C: 89.9% Emergency I: 1.6% C: 1.4% Satisfaction I: 99.7% C: 98.7% Adherence I: 94.7% C: 96.1%	High

between 2011 and 2022, 20 were cross-sectional [18, 20, 24, 26, 28–31, 33, 34, 43–52] and 1 was an RCT [32]. Regarding their geographical distribution, 7 (33.3%) originated from.

European countries, 6 (28.6%) from the United States (US), 3 (14.3%) from Latin America, 2 (9.5%) from Australia, 2 (9.5%) were multi-country studies, and 1 (4.8%) was from South Africa. The overall risk of bias was from low to serious in the cross-sectional studies, while the RCT exhibited a high risk of bias (Fig. 2).

Furthermore, 14 (66.7%) evaluated MAB provided through telemedicine as the sole intervention, and 7 (33.3%) compared it with standard care. In terms of gestational weeks, 9 studies (42.8%) included pregnant people at up to 9 weeks of pregnancy, 7 (33.3%) at up to 10 weeks, 3 (14.3%) at up to 12 weeks, and 2 (9.5%) beyond 12 weeks. 16 studies (76.2%) reported on the effectiveness of MAB, 16 (76.2%) examined the safety of the procedure, and 9 (42.8%) addressed user acceptability or satisfaction with the service. Other outcomes assessed in the studies included follow-up (n = 4; 19%), feelings regarding the procedure (n = 3; 14.3%), and average waiting time to treatment (n = 1; 4.8%).

Effectiveness

Sixteen studies evaluated the effectiveness of MAB, with ten exclusively evaluating telemedicine patients [18, 30, 31, 33, 34, 43, 45–48], and the remaining six comparing this outcome among telemedicine patients and standard patients [20, 26, 29, 32, 50, 52]. Treatment success was primarily confirmed through blood tests, followed by ultrasound. Only one study [20] used self-assessment to confirm termination of pregnancy.

In the studies that focused on telemedicine patients, the average effectiveness was 91.9%. All studies reported a standard regimen of 200 mg of orally, vaginally, or sublingually administered mifepristone, followed by an 800 µg dose of misoprostol after 24–48 h. Moreover, additional doses of misoprostol were administered after 3–4 h: six studies [18, 30, 34, 43, 46, 47] reported doses of up to 400 µg, three studies [31, 45, 48] reported doses of up to 800 µg, and one study [33] reported doses of up to 1600 µg. According to the results, increasing additional doses resulted in higher effectiveness rates (90.2%, 93.1%, and 98% respectively).

Six studies [26, 29, 32, 50, 52, 53] were conducted to compare the effectiveness of MAB between patients receiving telemedicine compared with standard care. 77,682 pregnant individuals made up the total sample size, with 43% using the telemedicine modality and 57% using standard care. A meta-analysis of the comparative effectiveness of the studies revealed no statistically significant differences between the two modalities of care (98.6% for telemedicine vs. 97.1% for standard care; RD = 0.01; 95% CI 0.00, 0.02).

Three of them [26, 32, 52] included pregnant people at up to nine weeks of pregnancy, two [20, 29] at up to ten weeks, and one [50] at up to twelve weeks. Moreover, one study [20] reported an additional 400-µg dose of misoprostol after 3–4 h, and two studies [26, 50] reported additional doses of up to 800 µg of misoprostol after the same time interval.

A subgroup analysis according to gestational age (Fig. 3) revealed that, in pregnancies of less than 12 weeks of gestation, there were 10 more successful cases in the standard care group than in the telemedicine group for every 1,000 MAB performed (RD = 0.01; 95% CI 0.01, 0.02). No statistically significant differences were observed among the subgroups of pregnancies under 9 and 10 weeks of gestation (RD = 0.01; 95% CI -0.00, 0.03 and RD = 0.01; 95% CI 0.00, 0.01, respectively).

Assessing effectiveness based on the method used to confirm successful abortion (Fig. 4), the meta-analysis revealed a slight advantage for standard care when either a blood test alone (RD = 0.02; 95%CI 0.01, 0.02) or informed clinical opinion (RD = 0.01; 95%CI 0.01, 0.02) were used, where for 1000 abortions performed, 20 or 10 cases of successful abortion were found in favour of standard care than in telemedicine, respectively. The certainty of the evidence for this outcome was low and moderate (supplementary Table 1).

In their study, Kohn et al. [50] demonstrated a higher rate of ongoing pregnancy in standard patients compared to telemedicine patients (1.8% vs. 0.5%.; OR = 0.23; 95%CI 0.14, 0.39).

Adverse effects

Mortality

Two cross-sectional studies investigated the mortality associated with MAB provided via telemedicine [50, 52]. Both studies employed a standard dose of 200 mg of mifepristone and 800 µg of misoprostol, with variations in the additional doses of misoprostol. One of the studies did not employ any additional dose [52], whereas the other used up to an additional 800-µg dose [50]. No deaths were reported during the follow-up period.

Surgical intervention

Thirteen studies included surgical intervention as an adverse effect of MAB, with nine reporting the incidence of this event for telemedicine patients only [18, 30, 31, 34, 43, 45–48] and the other four comparing this outcome between telemedicine patients and standard patients [20, 26, 50, 52].

In the studies that focused on telemedicine patients, the average percentage of surgical interventions was

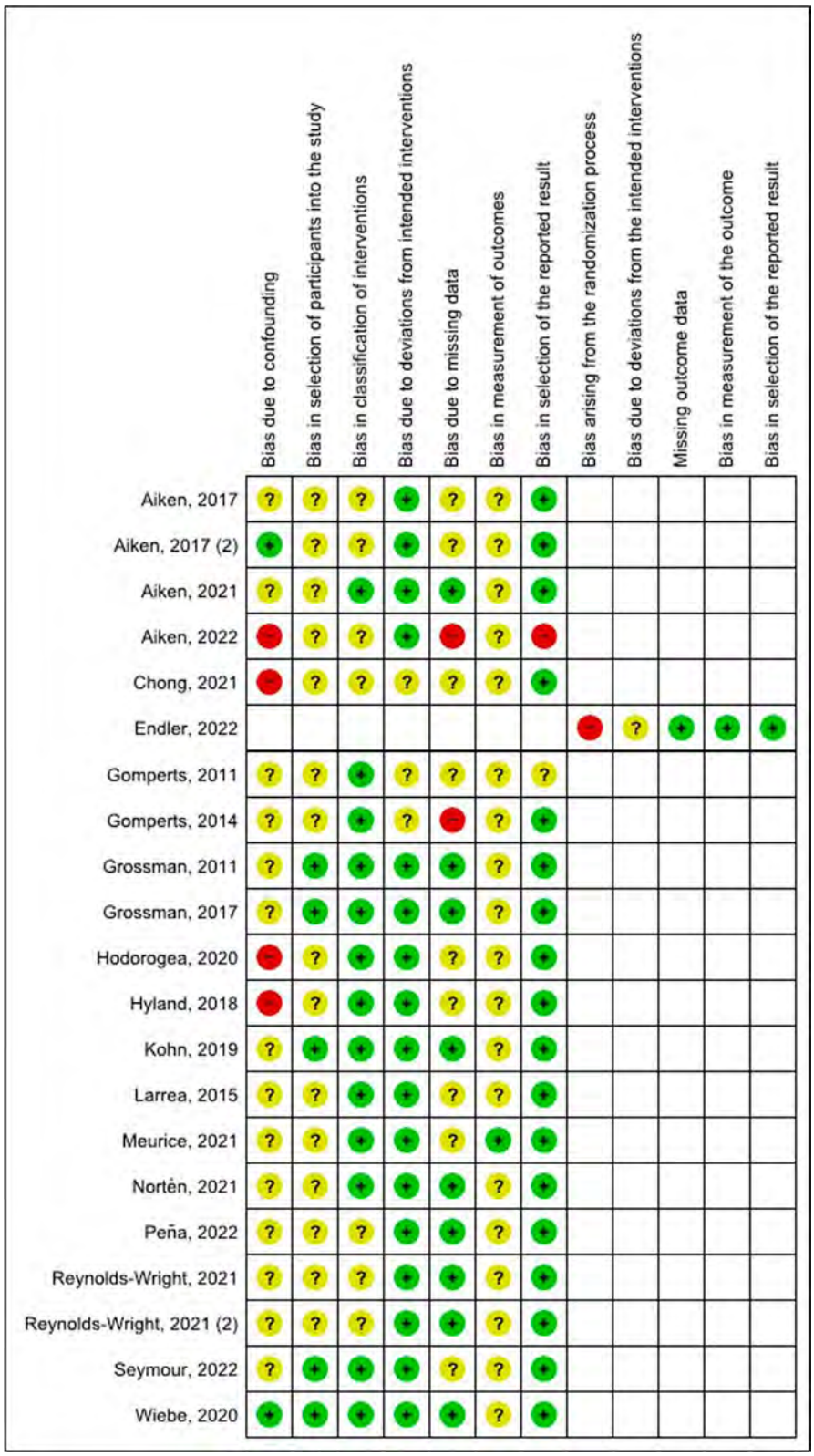

Fig. 2 Bias risk assessment of the included studies

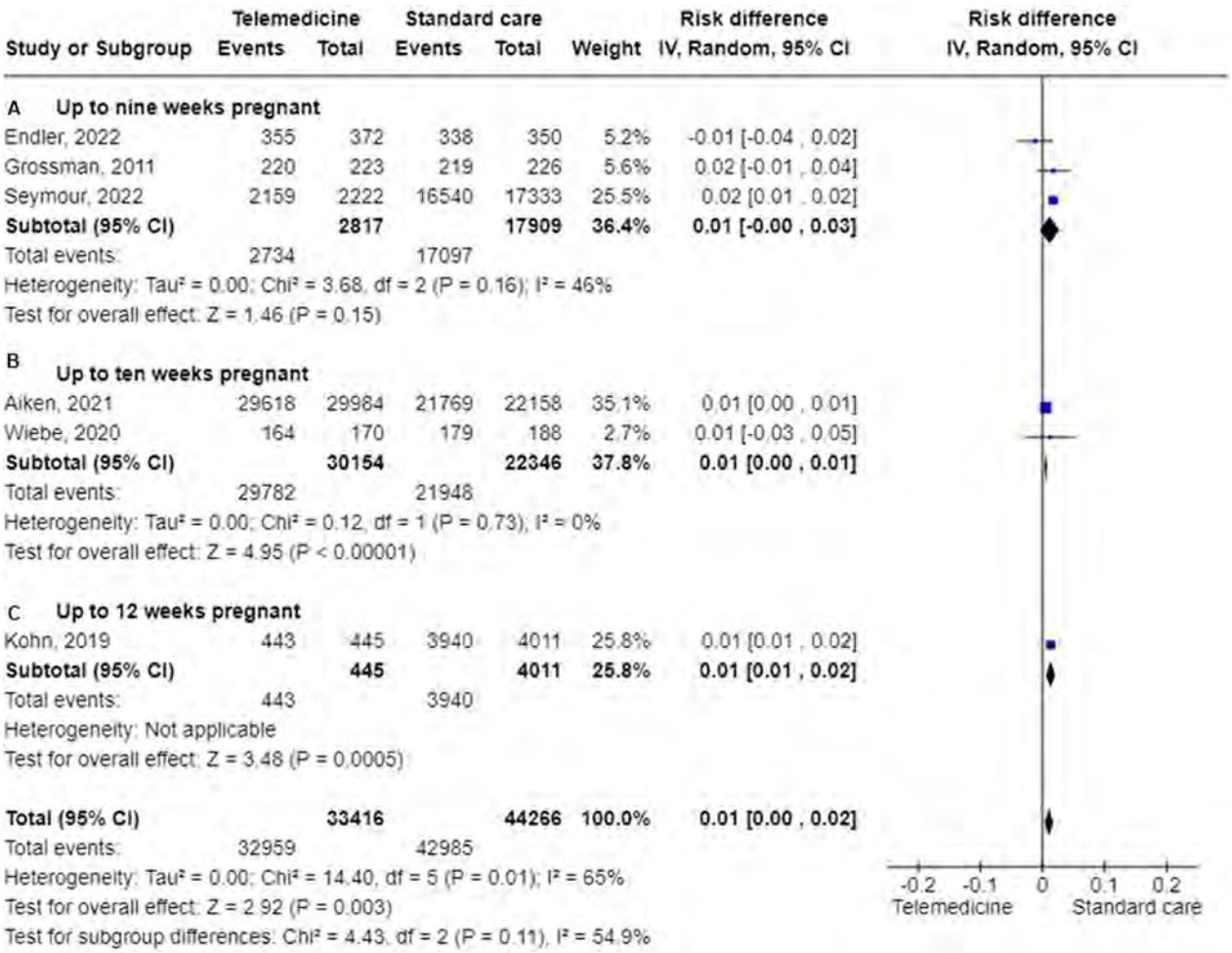

Fig. 3 Effectiveness of medication abortion via telemedicine compared to standard care by gestational week subgroups. **A**. Pregnant people up to 9 weeks pregnant, **B**. Pregnant people up to 10 weeks pregnant, **C** Pregnant people up to 12 weeks pregnant

8.1%. In all these studies, additional doses of misoprostol were administered. Six studies [18, 30, 34, 43, 46, 47] used additional doses of up to 400 µg [20], and the average percentage of surgical interventions was 10.4%. The other 3 studies [31, 45, 48] reported using additional doses of up to 800 µg, and the average percentage of surgical interventions was 3.6%.

In the four studies that compared the percentage of surgical interventions between telemedicine patients and standard patients, the treatment regimens varied in terms of the additional doses of misoprostol. One study did not employ any additional dose [52], another used a 400-µg dose [20], and two studies reported using 800 µg of misoprostol [26, 50]. Regarding gestational weeks, two studies included pregnant people up to nine weeks [20, 26], one up to ten weeks [52], and one up to twelve weeks [50]. The combined effect analysis did not reveal any differences between the two forms of healthcare delivery (RD = 0.00; 95%CI—0.00, 0.00; n = 78, 098; $I^2 = 94\%$) (Fig. 5). In the subgroup meta-analyses (based on gestational weeks), no differences were found in the occurrence of surgical interventions following MAB. The certainty of the evidence was very low (supplementary Table 1).

Blood transfusion

Eight studies examined the occurrence of blood transfusion events following MAB, with four exclusively focusing on telemedicine patients [18, 34, 43, 45] and the other four comparing this outcome among telemedicine patients and standard patients [26, 28, 32, 50]. Considering telemedicine patients alone, the incidence of this adverse effect was found to be approximately 0.5%.

Among the four studies that compared the occurrence of blood transfusion events between telemedicine patients and standard patients, one study used the standard dose of mifepristone and an initial dose of 800 µg of misoprostol without any additional doses

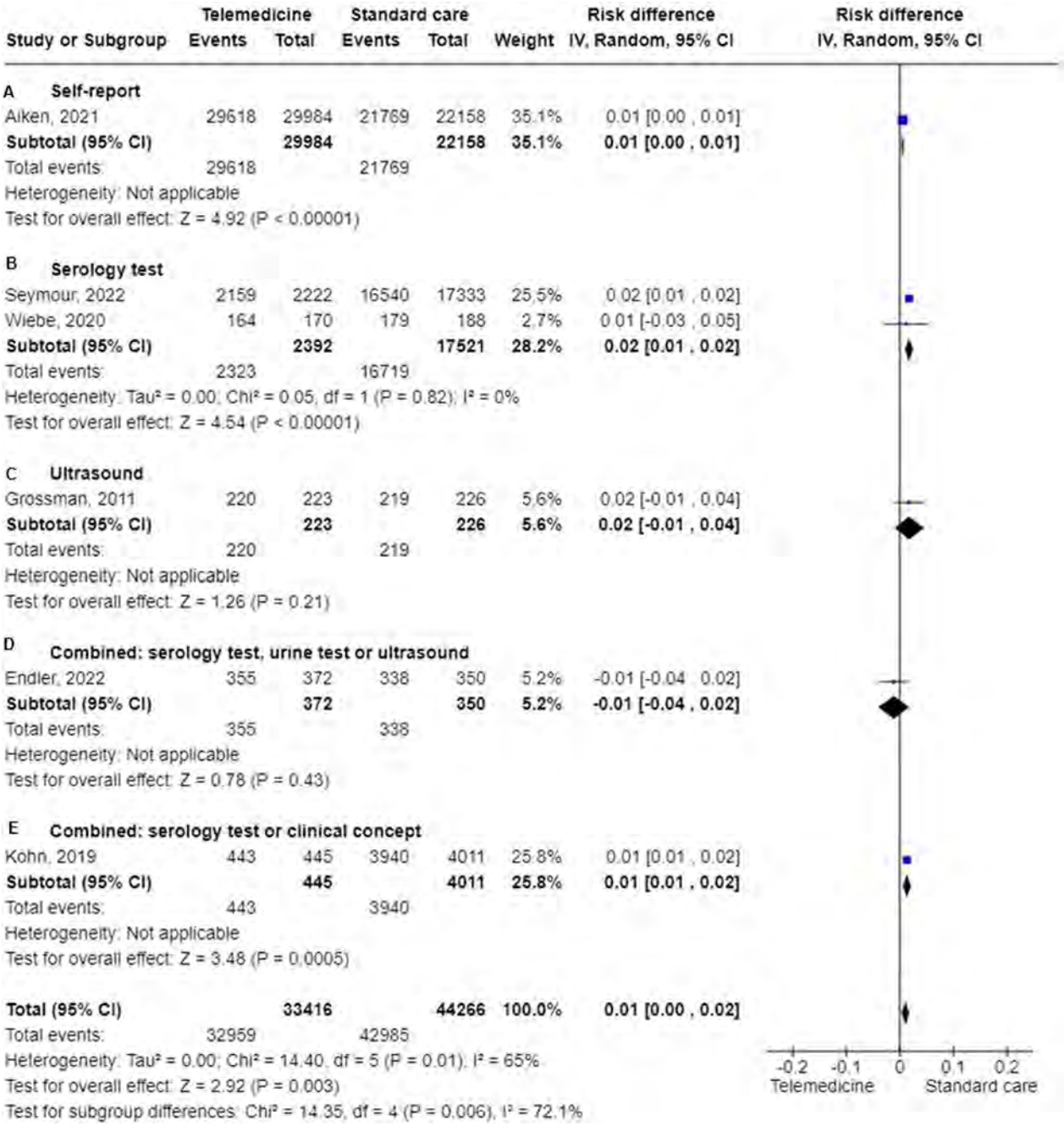

Fig. 4 Effectiveness of medication abortion via telemedicine compared to standard care by method of pregnancy confirmation. **A** Self-report, **B** Serology test, **C** Ultrasound, **D** Combined: serology test, urine test or ultrasound, **E** Combined: serology test or clinical concept

[32], while the other three studies employed an additional dose of 800 µg of misoprostol [26, 28, 50]. Three of the studies included pregnant people up to nine weeks [26, 28, 32], and one up to twelve weeks [50]. The combined effect analysis did not reveal any significant differences between the telemedicine and standard groups (RD = 0.00; 95%CI -0.00, 0.00; n = 26,307; $I^2 = 0\%$). In the subgroup meta-analyses (based on gestational weeks), no differences were found in the need for blood transfusions following MAB. The certainty of the evidence was low (supplementary Table 1).

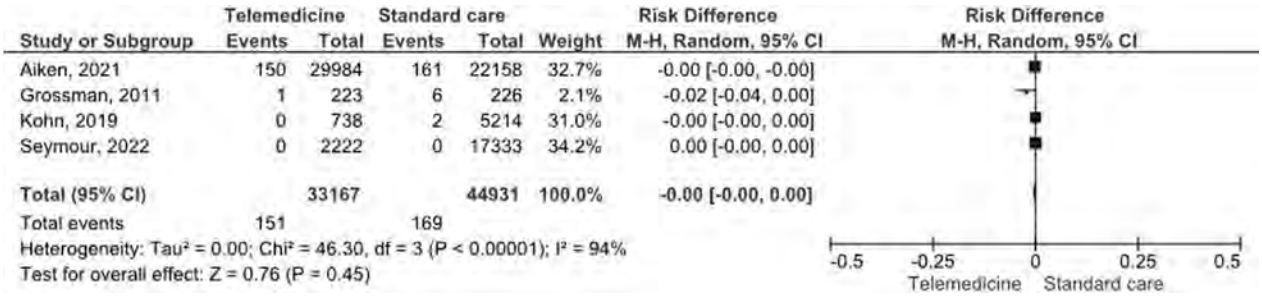

Fig. 5 Surgical intervention after medication abortion via telemedicine compared to standard care



Fig. 6 Hospitalization after medication abortion via telemedicine compared to standard care

Hospitalization

Six studies analyzed hospitalization cases following MAB, with three [31, 45, 49] exclusively focusing on telemedicine patients and the other three [28, 50, 52] comparing this outcome among telemedicine patients and standard patients.

In the three studies that solely considered telemedicine patients, the average occurrence of this event was 1.3%. In the other three comparative studies [28, 50, 52], no statistically significant differences were observed between the telemedicine group, which had an average hospitalization rate of 0.1%, and the standard care group, which had an average hospitalization rate of 0.2% (RD = 0.00, 95%CI -0.00, 0.00; n = 34,677; $I^2 = 58\%$) (Fig. 6). In the subgroup meta-analyses (based on gestational weeks), no differences were found in hospitalization rates following MAB. The certainty of the evidence was low (supplementary Table 1).

Antibiotic treatment

Five studies assessed the need for antibiotic treatment in patients with a clinical suspicion of infection following MAB. Three of such studies focused exclusively on telemedicine patients [30, 34, 43], revealing an average incidence of 4.1% for this outcome. In the other two studies [29, 52], the average incidence of antibiotic treatment in the telemedicine group was 0.4%, while it was 0.05% in the standard group (RD = 0.00; 95%CI -0.00, 0.01; n = 19,913; $I^2 = 0\%$). The certainty of the evidence was moderate (supplementary Table 1).

Emergency department visits

One cross-sectional study [45] examined the frequency of emergency department visits among pregnant people who used MAB services provided through telemedicine and reported a frequency of 7.8%. Another cross-sectional study [28] compared this outcome between telemedicine patients and standard patients. The frequency of emergency department visits in the telemedicine group was 0.1%, while it was 0.2% in the standard group. No significant risk difference was observed between the two groups of interest (n = 20,343; p = 0.3).

Acceptability/Satisfaction

Acceptability

Three observational studies [18, 24, 46] evaluated the acceptability of MAB provided via telemedicine, with an average acceptability rate of 93.2%.

Satisfaction

Three observational studies [45, 48, 51] analyzed user satisfaction with MAB provided via telemedicine, with an average satisfaction rate of 98.3%. One clinical trial [32] and one cross-sectional study [26] compared this outcome between two forms of healthcare delivery. According to their results, the average satisfaction rate among telemedicine users was 99.3%, while it was 98.2% among

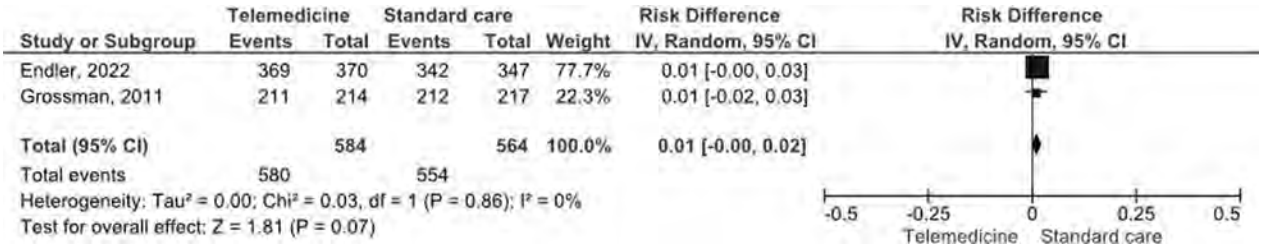

Fig. 7 Service satisfaction with medication abortion via telemedicine compared to standard care

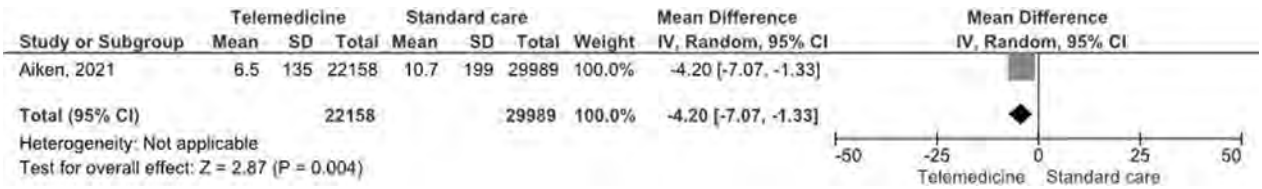

Fig. 8 Waiting time for delivery of medication abortion via telemedicine compared to standard care

standard users (RD = 0.01; 95%CI -0.02, 0.03; n = 1,134; $I^2 = 0\%$) (Fig. 7). The certainty of the evidence was low (supplementary Table 1).

Another noteworthy finding was the preference for telemedicine services. In a clinical trial [32], significant differences were observed in the proportion of pregnant people who preferred remote care, being higher in telemedicine care (97%) than in standard care (46%) (n = 717; $p < 0.001$).

Other outcomes

Successful follow-up

Two observational studies [31, 49] reported that, on average, 92% of patients who used telemedicine services for MAB had successful follow-up, typically occurring 45 days after taking the mifepristone dose.

Additionally, three cross-sectional studies [26, 29, 50] analyzed the follow-up rates after MAB, indicating that 77% and 70% of pregnant people using standard care group and telemedicine respectively, had successful follow-ups. The meta-analysis revealed no significant differences in lost to follow-up (RD = 0.05; 95%CI -0.18, 0.08; $I^2 = 95\%$), although it is evident that remote care exhibited higher rates of lost to follow-up. The certainty of the evidence was low (supplementary Table 1).

Waiting time to treatment

One prospective study [20] reported a reduction of 4.2 days in the waiting time to treatment for MAB via telemedicine when compared to standard care (Median Difference-MD = -4.2; 95%CI -7.07, -1.33; n = 52,147) (Fig. 8). The certainty of the evidence was low (supplementary Table 1).

Adherence to prescribed regimens

One clinical trial [32] evaluated adherence to abortion medication regimens. According to the results, the adherence rate was 94.7% in the telemedicine group and 96.1% in the standard care group, with no significant differences (n = 732; p = 0.89). The evaluation considered proper medication intake in terms of dosage, dose interval, route or manner of administration, and weeks' gestation limits.

Discussion

This SLR included twenty studies published between 2011 and 2022, half of them between 2021 and 2022. Nineteen studies have an observational design. Of these, seven present data collected during the COVID-19 global health crisis. One of the included studies is an RCT conducted between February 2020 and October 2021, which compares telemedicine abortion care with in-person services. Overall, the risk of bias for the cross-sectional studies ranged from low to severe, while the RCT had a high risk of bias. Taken together, this body of literature provides up-to-date evidence on indicators of success, safety, and acceptability in the use of telemedicine to expand the provision of abortion care in the first trimester of pregnancy.

Based on observational studies with no control group, a 91.1% effectiveness was identified. This is similar to what Ngo et al. [54] reported in an SLR published in

2011, which evaluated the same research question and reported an 86–97% effectiveness of home MAB.

The effectiveness found in this SLR increased when care protocols included additional doses of misoprostol to the basic drug regimen (200 mg of mifepristone and 800 µg of misoprostol).

The meta-analysis of studies comparing telemedicine with standard care services indicates that the effectiveness of MAB is not influenced by the type of care provided. The analysis of effectiveness by subgroups, including weeks' gestation and method of confirming treatment success, suggests that there are no significant interactions between the variables, as the estimated risk differences are minimal or negligible. Additionally, the results of the chi-square tests suggest that there is no statistically significant heterogeneity between the subgroups. It is important to note that, in forming the subgroups, the sample size was significantly reduced in some of them, which may affect the statistical power of the tests and, consequently, generate erroneous inferences.

Effectiveness decreases as the gestational limit increases; however, there were no statistically significant differences between telemedicine and in-person services for this variable. The effectiveness of MAB in pregnant people at 10-week gestation or less has been reported, with no differences between modalities of care [55]. In 2002, Ashok et al. [56] supported the effectiveness and safety of MAB between gestational weeks 10 and 13. However, in 2020, Schmidt-Hansen [55] proposed that more research is needed to support MAB in this period.

Effectiveness increased when doses of misoprostol were added to the basic drug regimen (200 mg of mifepristone plus 800 µg of misoprostol). A study on the use of abortion medications [57] identified that the use of 800 µg of misoprostol is more effective than 400 µg of misoprostol. Furthermore, it may increase the success of abortion if administered on the first day rather than on the third day, and there is no difference in its effectiveness if administered at home or in a clinic. In their study, Phupong et al. [58] concluded that the use of 600 µg and 1200 µg of misoprostol are equally effective, although the first dose reduces the occurrence of diarrhea as an adverse event. Another study that compared these two misoprostol regimens found a slightly greater effectiveness with the use of 1200 µg (66% with 600 µg and 70% with 1200 µg) and found no difference in the adverse effects produced [59]. The study recommended 800 µg of misoprostol for pregnant people under 10 weeks of gestation and 1000 to 1200 µg of misoprostol for pregnant people at 10–13 weeks of gestation. Another RCT [60] comparing these two doses of misoprostol found no difference in effectiveness between the two regimens given.

There are three methods that can be used for this: ultrasound, β-hCG levels in serum or urine. The most widely used for telemedicine services is the urine pregnancy test because it is easy to use at home. Studies support the use of this test [61, 62], although it should be considered that due to the detection threshold of β-hCG (< 50 mIU/mL), it may take a few weeks to become negative and thus interpret the result as a continuation of pregnancy, when it was actually a successful abortion. The other two tests (serum β-hCG and ultrasound) have been described as equally effective in measuring the outcome of abortion [63, 64].

Outcome on the need for surgery after MAB was measured both in observational studies without a comparison group and in those that compared the telemedicine care model with in-person services. As with the effectiveness indicator, surgical interventions interact with the additional doses of misoprostol added to the basic drug regimen. In this regard, the studies that added doses of misoprostol had a lower average prevalence of surgical interventions. In the meta-analysis of the comparative studies, no differences were found between the groups in the prevalence of postabortion surgery.

The safety of the telemedicine abortion procedure was documented in most of the included studies, with low rates of adverse events. No maternal deaths were reported. In observational studies without a comparison group, an average of 7.8%, 4.1%, 1.3%, and 0.5% of telemedicine patients attended the emergency department, required antibiotics, were hospitalized, or had a blood transfusion, respectively. However, there were no statistically significant differences in these indicators when comparing in-person services with telemedicine. The SLR by Ngo et al. [54] conducted in 2011 also found a low proportion of complications of MAB, finding that pain and vomiting were slightly longer lasting (0.3 days longer) among pregnant people who performed the procedure at home rather than in a medical facility.

In the meta-analysis, there were no differences in the proportion of pregnant people with follow-up after the abortion procedure, nor in adherence to treatment between the two modalities (telemedicine and in-person care). Nevertheless, the waiting time to receive abortion treatment was shorter among telemedicine patients.

The 2011 study by Grossman et al. went beyond establishing overall patient satisfaction, finding that initiating the abortion procedure as early as possible was a highly important factor [26]. This SLR found a significant difference in the waiting time for treatment initiation in favor of telemedicine. As in the satisfaction analysis, it is not possible to analyze this difference at all stages of the process. This result comes from an RCT conducted in a United States population [32], with a high risk of

bias, which may vary significantly in regions with fewer human, financial, and technological resources. The same study reports that telemedicine is the preferred modality. In fact, nearly half of the pregnant people who used in-person modality preferred telemedicine[32]. This result may be affected by situations of availability or timeliness of telemedicine care, thus showing that there is room for strengthening virtual care services to meet their demand.

In 2022, Endler et al. [32] reported that adherence to the recommended drug regimens in telemedicine and in-person care was 94.7% and 96.1%, respectively, with no statistically significant differences between the two groups. This result may indicate that the information provided by the counseling staff of both health care modalities is sufficient and understandable to the public at large.

The average acceptability of telemedicine from three non-comparative studies was greater than 90%. Systematic reviews [25, 65] as well as observational studies [66] report results in the same trend, but with ranges of 60–100% acceptability [25]. However, several of the studies were developed based on data from organizations that provide abortion care exclusively by remote consultation, such as Women on Web; therefore, it is not known whether users had access to other care alternatives to choose from in terms of convenience or cost. These results contrast with those obtained by Dagousset et al., who reported that 55% of the pregnant people accepted home treatment if the health institution gave them the option of choosing place for treatment [67].

Similar to the results reported by Ngo et al. in their 2011 SLR [54], satisfaction was 88.4% in the telemedicine care group and 85.4% in the in-person care group. Since satisfaction is an indicator of the quality perceived by patients, the values obtained may be explained by the effectiveness and safety of the procedure. It should be noted that both modalities of care include several stages that are not documented in all studies, such as the assessment of the means of communication, appointment scheduling, care provided by health professionals, delivery or acquisition of medication, instructions for the home abortion process, and other related issues, which may be the subject of evaluation in future research.

The results of this study and the contrast with the scientific evidence that supports interventions in sexual and reproductive health provide sufficient evidence to sustain the effectiveness and safety of MAB managed through the provision of in-person or remote health services.

However, there is no consensus on the conditions necessary for the implementation of telemedicine services that can be adapted to each context, including the description of technological, infrastructure, cultural, and social needs for the widespread use of this abortion modality. This method also requires proposing solutions when Internet connection difficulties arise, in addition to promoting training on information and communication technologies and the provision of equipment that adequately supports the service.

This SLR does not address the analysis of the potential impact of intermediate determinants such as educational level or social representations of abortion of those who access it and those who perform it and promote it as a sexual and reproductive health right, and how these elements may affect the outcomes assessed. This is illustrated in the study by Ennis et al. (2023), which concludes that existing stigma toward health workers who provide abortion services impacts service delivery in terms of quality and frequency [68]. Regarding the experience of individuals accessing abortion services, social support is a determining factor in the mental health of patients, as noted in the study by Hendrix et al. [69].

Patient safety is a major concern when providing telemedicine care. Health care providers must ensure that patients meet the established eligibility criteria for MAB and that they receive the necessary information to make informed decisions. In this regard, there is extensive literature showing the ability of pregnant people to establish their weeks' gestation from the date of last menstrual period [70–73]. Moreover, it is crucial to establish clear protocols for emergency care and appropriate referral in case of complications and adverse events.

Conclusions

Providing data of MAB provided through telemedicine is crucial for decision-makers to justify its implementation and widespread adoption. The published data support that MAB in the first-trimester abortion with telemedicine is an effective and safe alternative, similar to standard care. There were no differences between the care modalities in terms of other outcomes like user satisfaction, follow-up, and adherence; however, the telemedicine modality had a shorter waiting time for medication delivery.

Abbreviations

β-hCG	Beta-human chorionic gonadotropin
CI	Confidence interval
DeCS	Descriptores en Ciencias de la Salud (Health Sciences Descriptors)
ICT	Information and Communication Technology
MeSH	Medical Subject Headings
MAB	Medication abortion
MD	Median difference
PICOS	Population, Intervention, Comparison, Outcome, and Study Design
RCT	Randomized Controlled Trial
RD	Risk difference
SLR	Systematic Literature Review
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12978-024-01864-4.

Additional file 1: Appendix A. Search terms and search strategies used for each database.

Additional file 2: Table S1. Summary of findings and certainty of evidence: telemedicine compared with standard care for provision of medication abortion.

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Author contributions
LCA, KCG and LCES contributed with the conception and design of the SLR. Data curation and analysis was performed by LCA, KCG and LCES. Interpretation of data was done by LCA, KCG, LCES, BSA and GAOA. The manuscript was written by LCA, KCG, LCES and BSA. LCES produced the figures. KCG elaborated the table. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

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Not applicable.

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Competing interests
The authors declare no competing interests.

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Original research article

A randomized controlled trial of different buccal misoprostol doses in mifepristone medical abortion☆

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Abstract

Background: An 800-mcg dose of buccal misoprostol following mifepristone has been shown to be highly effective in terminating pregnancies through 63 days since the last menstrual period (LMP) (B. Winikoff, I.G. Dzuba, M.D. Creinin, et al., Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. *Obstet Gynecol* 2008; 112: 1303–1310). However, a two 200-mcg misoprostol pill option would simplify administration, and potentially reduce costs and increase women's satisfaction. This study compares a 400-mcg dose (Group I) to an 800-mcg dose (Group II) of buccal misoprostol.
Study Design: Eligible and consenting women requesting medical termination of early pregnancy (n=1122) were randomized and instructed to take misoprostol 36 to 48 h after taking 200 mg mifepristone. Follow-up visits occurred 12 to 15 days after mifepristone administration.
Results: Ninety-six percent of women in both groups had successful abortions. Women in Group I experienced significantly less vomiting and fever/chills than women in Group II. Ninety-six percent of women in both groups found the procedure very satisfactory or satisfactory.
Conclusions: Four hundred micrograms of buccal misoprostol is as effective as the standard 800-mcg dose in terminating pregnancies up to 63 days LMP and reduces side effects.
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Keywords: Medical abortion; Mifepristone; Misoprostol; Buccal

1. Introduction

Since the introduction of mifepristone+misoprostol medical abortion, much research has been conducted to improve the regimen to make it more accessible and acceptable to both women and providers. One area of research has focused on finding doses and routes of misoprostol administration that are effective through 63 days since the last menstrual period (LMP). An 800-mcg dose of vaginal misoprostol following mifepristone is highly effective through 63 days LMP and is recommended by the World Health Organization [1]; however, some women express discomfort with this route and prefer in-the-mouth routes of administration [2,3]. Misoprostol taken orally (swallowed) after mifepristone offers the easiest administration, but the efficacies of an oral regimen using a 400-mcg dose [4,5] or an 800-mcg dose [5–7] both decline with increasing gestational age to as low as 77% and 85%, respectively, in the ninth week after LMP.

Research has also looked at sublingual and buccal administration of misoprostol, in which the pills are held under the tongue or between the cheek and the gum until they dissolve. Initial studies with 800-mcg and 600-mcg doses of sublingual misoprostol after mifepristone found the regimens to be highly efficacious but also resulted in substantial levels of fever, chills, vomiting and diarrhea [8,9]. Subsequent studies suggest that the dose of misoprostol can be reduced to 400 mcg to minimize side effects, but still maintain a high success rate in the later gestational ages [10,11].

Clinical trials have shown an 800-mcg dose of buccal misoprostol after mifepristone to be highly effective through 56 and 63 days LMP [6,12]. A randomized controlled trial comparing 800 mcg oral to 800 mcg buccal misoprostol

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found that, in the ninth week LMP, the buccal regimen had a significantly higher success rate than the oral regimen (94.8% vs. 85.1%) and a significantly lower ongoing pregnancy rate (1.7% vs. 7.9%) [6]. Additionally, Planned Parenthood centers in the United States reported a 98% success rate with the buccal regimen in a 2006 audit in terminating pregnancies up to 59 days LMP [13].

Very little is known about the efficacy of a 400-mcg dose of buccal misoprostol after mifepristone; however, one study has been published that compared 400 mcg buccal misoprostol to 400 mcg sublingual misoprostol after mifepristone [14]. This study found comparable success rates between the two regimens (97.1% and 97.4%, respectively). Efficacy remained high at later gestational ages (100% and 94.6% among pregnancies 50–63 days LMP), although the sample size was small (38 and 37 women 50–63 days LMP). We were interested to see if, like misoprostol administered via the sublingual route, a reduced dose of buccal misoprostol after mifepristone would still be highly effective, yet reduce the side effects women experience. A two 200-mcg misoprostol pill option would simplify administration, substantially reduce the costs associated with the method in some settings and potentially increase women's satisfaction.

2. Materials and methods

The study was conducted from May 2007 to September 2009 at three clinics in Tbilisi, the Republic of Georgia [Zhordania Institute of Human Reproduction (ZIHR), Maternity House #2 and Maternity House #4), and at Hoc Mon Hospital, about 10 km outside Ho Chi Minh City, Vietnam. Two sites (ZIHR and Hoc Mon Hospital) had experience providing medical abortion prior to this study, while the other two sites were trained in medical abortion provision at the same time they were trained in the study procedures.

Women who presented for termination of pregnancy with gestations up to 63 days since LMP were recruited to participate in the study. Exclusion criteria included concurrent anticoagulant therapy, concurrent long-term corticosteroid therapy, adrenal insufficiency, inherited porphyria, suspicion of ectopic pregnancy, and known allergy to mifepristone or misoprostol. Gestational age was determined by ultrasound in 98% of cases; LMP and clinical examination were also used. Ethical committees at the ZIHR and Hoc Mon Hospital reviewed and approved the study protocol. All women gave their informed consent to participate in the study.

Women swallowed one 200-mg pill of mifepristone [in Georgia: Mirpharma or Pentcroft Pharma (Russia); in Vietnam: STADA (Vietnam)] at the clinic and were given the option of taking the misoprostol at the clinic or at home 36 to 48 h after taking mifepristone. After eligibility was confirmed, allocation to the 400-mcg or 800-mcg group was determined based on a random code generated in blocks of 10 by Gynuity Health Projects in New York, whose staff packed the pills and organized them in sequential, sealed envelopes. Randomization was stratified by study site. This study was double-blinded; women in the 400-mcg group received two 200-mcg misoprostol (U-miso; U-Liang Ltd, Taiwan) pills and two placebo pills, and women in the 800-mcg group received four 200-mcg misoprostol pills. The group

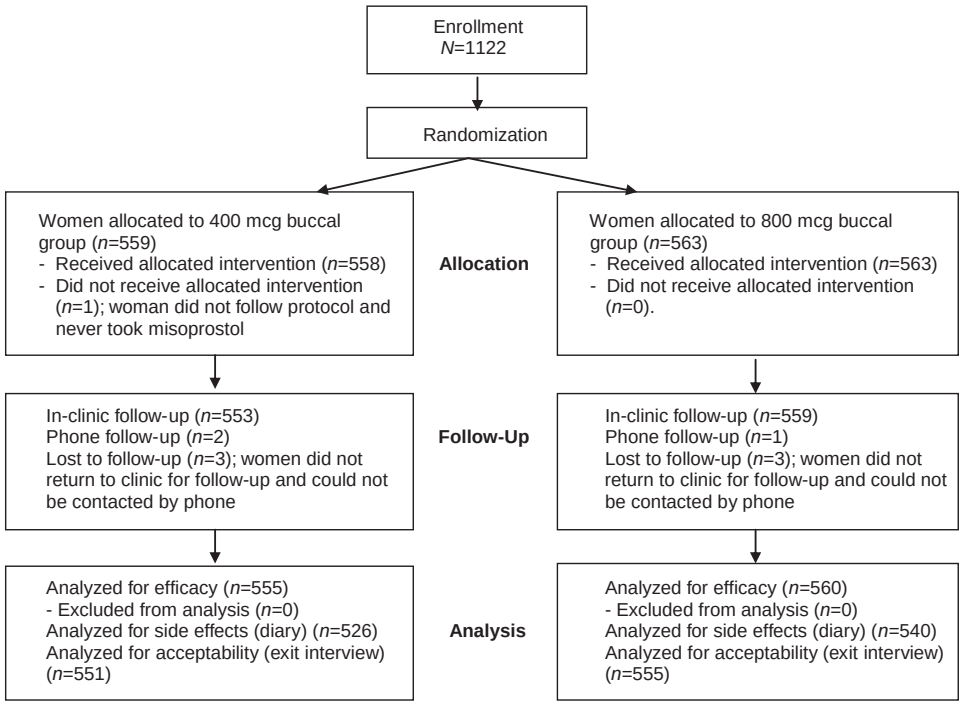

Fig. 1. Treatment flowchart.

Table 1
Participant characteristics

	400 mcg	800 mcg	Georgia	Vietnam
Age, years (mean, range)	27.4 (17–44)	27.9 (15–45)	27.9 (15–45)	26.4 (18–45)**
Highest educational level completed, %				
Primary	13.5	13.3	0.9	63.2**
High school	29.4	28.6	27.6	34.5
University	57.1	58.0	71.5	2.2
Currently married, %	81.2	81.7	78.6	92.9**
Gravidity, mean	3.9	4.2	4.5	2.5**
Parity, mean	1.2	1.2	1.2	1.1*
Previous abortion, %	58.3	61.8	65.9	36.6**
Gestational age, days (mean)	48.0	48.2	46.6	54.3**

All differences between 400-mcg and 800-mcg groups are not significant.
For Georgia vs. Vietnam:
* $p \leq .05$.
** $p \leq .001$.

assignments were maintained at the Gynuity office in New York and were not disclosed to the participants or the providers.

For those women who elected to take misoprostol at the clinic, providers stapled assigned envelopes to the women's study forms at the initial visit, and those pills were taken at the next (misoprostol) visit. Women were instructed to place the pills between the cheek and gums and to hold them there for 30 min, after which they should swallow any remaining fragments. In Georgia, women were given a prescription for paracetamol (500 mg) and advised to take it as needed; in Vietnam, all women were given four tablets of paracetamol (500 mg) and similarly advised. Women were asked to fill out patient diaries documenting the level of bleeding and any side effects that occurred in the 14 days following mifepristone administration. If women forgot to bring the diary with them to the follow-up visit, they were asked to complete at new diary at that time.

Follow-up visits were scheduled 12 to 15 days after the initial visit to determine abortion status. If the abortion was determined to be complete, women underwent an exit interview and were discharged from the study. Women with ongoing, viable pregnancies were offered a surgical completion. Women with incomplete abortions were offered the option of a surgical completion or waiting another week, with or without an additional dose of 800 mcg buccal misoprostol. If the abortion was still incomplete after the additional week, a surgical completion was recommended. Women could request a surgical completion at any time during the study.

Table 2
Treatment outcomes by study group and gestational age

	400 mcg	800 mcg	RR (95% CI)
Success (total)	96.4 (535/555)	96.4 (540/560)	1.00 (.98–1.02)
42 days or less	98.8 (164/166)	95.8 (159/166)	1.03 (.99–1.07)
43–49 days	97.2 (106/109)	96.2 (100/104)	1.01 (.96–1.06)
50–56 days	94.3* (182/193)	98.5* (201/204)	.96 (.92–.99)
57–63 days	95.4 (83/87)	93.0 (80/86)	1.03 (.95–1.10)

* $p<.05$, comparing 400-mcg and 800-mcg groups.

The study had two primary objectives: (1) to compare the efficacy of the two regimens, especially among women with gestations >49 days LMP, and (2) to compare the incidence of side effects of each regimen. We assumed that the 800-mcg buccal misoprostol regimen would be 95% effective, and therefore, 334 women per group were needed to detect a 5% lower efficacy with 400 mcg misoprostol (α=0.05, $1-\beta$=0.8, with a one-tailed test). An additional 10% was added to account for loss to follow-up, for a total sample size of 735. Initially, study enrollment occurred only at the three sites in the Republic of Georgia. An interim analysis of 383 women enrolled found too few women with gestational age >50 days LMP were being enrolled to permit comparison of efficacy at higher gestational ages once enrollment was complete.

Based on the interim analysis, we assumed that efficacy in the 800-mcg group would be 93% for gestational ages 50–63 days LMP, requiring a sample of 303 women in each study arm to detect a 6% lower efficacy with 400 mcg (α=0.05, $1-\beta$=0.8). Adding 5% to account for loss to follow-up, we sought a final sample of 640 women in this gestational age range. In Vietnam, enrollment was limited to women presenting at 50–63 days LMP. We stopped the study when 1115 women had been enrolled and followed up, including 570 women in the 50–63-day gestational age group, when efficacy in both groups substantially exceeded that hypothesized based on interim review.

Table 3
Reasons for failure by study group and gestational age

	400 mcg	800 mcg	RR (95% CI)
Failure (total)	3.6	3.6	
Ongoing pregnancy	1.4 (8/555)	0.9 (5/560)	1.61 (.53–4.9)
42 days or less	0.6 (1/166)	1.2 (2/166)	0.5 (.05–5.46)
43–49 days	0.0 (0/109)	0.0 (0/104)	–
50–56 days	2.6 (5/193)	0.5 (1/204)	5.28 (.62–44.8)
57–63 days	2.3 (2/87)	2.3 (2/86)	.99 (.14–6.86)
Incomplete abortion	0.9 (5/555)	1.1 (6/560)	.84 (.26–2.74)
Excessive/prolonged bleeding	0.4 (2/555)	1.1 (6/560)	.34 (.07–1.66)
Provider/patient request	0.9 (5/555)	0.5 (3/560)	1.68 (0.4–7.0)

All differences between 400-mcg and 800-mcg groups are not significant.

Table 4
Probability of failure, unadjusted and adjusted analyses

	Unadjusted		Adjusted, full model		Adjusted, backward stepwise Wald model[a]	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Treatment group	1.01 (.54–1.90)	.98	1.04 (.55–1.96)	.92	1.03 (.55–1.94)	.94
Country			.86 (.22–3.34)	.82		
Age			1.01 (.95–1.08)	.74		
Gestational age[b]						
43–49 days			1.30 (.47–3.55)	.62		
50–56 days			1.74 (.71–4.28)	.23		
57–63 days			2.91 (1.12–7.58)	.03		
Highest education completed[c]						
High school			1.97 (.41–9.55)	.40		
University			3.10 (.54–17.81)	.20		
Married			.91 (.36–2.28)	.84		
Parity			.99 (.65–1.51)	.96		
# of previous abortions			1.05 (.96–1.15)	.25	1.07 (.99–1.15)	.10

[a] Treatment group was force entered into the model as the initial term; all other variables were entered with PIN=0.05, POUT=0.10.
[b] Compared with ≤42 days.
[c] Compared with primary school.

Data were entered in Georgia and Vietnam, merged in New York and analyzed using SPSS 14.0 (SPSS Inc., Chicago, IL, USA) and EpiInfo™ Version 3.4.3 (Centers for Disease Control, Atlanta, GA, USA). The χ^2 with Fisher's Exact Test was used as appropriate for independent nominal data, and independent *t* tests were used for continuous variables. Statistical significance was defined as a p value of <.05. Hierarchical logistic regression analyses were conducted to adjust for possible confounders and the effects of including women solely with later gestation abortions in Vietnam, with forced entry of the term for treatment group and using both forced entry and, separately, the backwards stepwise Wald method with probability of score statistic for variable entry (PIN)=0.05 and probability of the Wald statistic to remove a variable (POUT)=0.10 for all covariates (age, gestational age, country, completion of high school, completion of university, marital status, parity, and number of previous abortions). Success was defined as a complete abortion using mifepristone and misoprostol without any surgical intervention. In the few cases where the woman did not return for follow-up, telephone follow-up was deemed acceptable to determine the abortion outcome. Per-protocol analysis was used since there was only one woman who did not follow the protocol (she took mifepristone but not misoprostol). The analyses excluded six women who were lost to follow-up and one woman who did not take misoprostol (Fig. 1). Data on adverse effects were stratified by country to illustrate cultural differences in experiencing and reporting of these symptoms.

3. Results

One thousand one hundred twenty-two women were enrolled in the study, of which 559 were randomized to the 400-mcg buccal group of misoprostol and 563 to the 800-mcg buccal group. Three women did not return to the clinic for follow-up but confirmed by phone that they received surgery elsewhere (Fig. 1). There were no statistically significant differences between the two study arms with respect to mean age, education, marital status, gravidity and parity, abortion history and gestational age (Table 1). In general, participants in this suburban area of Vietnam

Table 5
Adverse effects (% reporting ever experiencing)

Adverse effect	Total			Georgia			Vietnam		
	400 mcg	800 mcg	RR (95% CI)	400 mcg	800 mcg	RR (95% CI)	400 mcg	800 mcg	RR (95% CI)
Nausea	44	47	.93 (.81–1.06)	42	48	.88 (.75–1.02)	49	42	1.16 (.87–1.55)
Vomiting	16**	22**	.72 (.56–.92)	16*	22*	.72 (.54–.95)	15	21	.71 (.41–1.26)
Pain/cramps	77	81	.96 (.9–1.02)	81	83	.96 (.91–1.03)	64	70	.92 (.76–1.11)
Fever/chills	26**	33**	.78 (.65–.94)	31**	41**	.75 (.63–.91)	9	5	1.68 (.63–4.47)
Headache	32	33	.97 (.82–1.16)	32	33	.97 (.8–1.18)	32	32	.98 (.67–1.44)
Dizziness	26	24	1.08 (.88–1.33)	24	25	.98 (.78–1.25)	33*	22*	1.49 (.97–2.31)
Weakness	38	42	.88 (.76–1.02)	44	48	.92 (.8–1.07)	13	21	.59 (.32–1.08)

* p<.05, comparing 400-mcg and 800-mcg groups.
** p<.01, comparing 400-mcg and 800-mcg groups.

tended to be less educated, less likely to have had a previous abortion and more likely to be married than women in Georgia.

Ninety-five percent of Georgian participants decided to take the misoprostol at home, whereas only two women in Vietnam availed themselves of this option. Ultrasound use at the follow-up visit varied widely by site, ranging from 37% at Maternity House #4 to 90% at Hoc Mon Hospital. Eighty-four women had incomplete abortions at follow-up, and 83 decided to wait an additional week (47 taking an additional dose of misoprostol/oxytocin and 36 opting for expectant management). Ninety-two percent of women who took additional misoprostol and 78% of women using expectant management had complete abortions at the extended follow-up visit [relative risk (RR)=1.18, 95% confidence interval (CI) 0.97–1.43].

Overall, the efficacy of the two regimens was identical, with 96.4% of women having a successful abortion in each arm (Table 2). The two regimens maintained a high success rate at the later gestational ages as well, with 95.4% of the 400-mcg group and 93.0% of the 800-mcg group successfully aborting in the ninth week of gestation.

The ongoing pregnancy rate was slightly, but not significantly, higher in the 400-mcg study arm than the 800-mcg study arm (1.4% vs. 0.9%, RR 1.61, 95% CI .53–4.9) (Table 3). However, the ongoing pregnancy rate was the same in both arms in the ninth week of gestation (2.3%). No significant differences were seen in the rates of incomplete abortion, heavy or prolonged bleeding, or provider preference/patient request. Adjustment for covariates including country did not influence the difference in rates of success [fully adjusted model odds ratio (OR)=1.03, 95% CI 0.55–1.94; unadjusted model OR=1.01, 95% CI 0.54–1.90] (Table 4).

Since side effects are experienced and reported differently in different cultures, Georgia and Vietnam data are reported separately as well as in aggregate (Table 5). In general, Georgian women tended to report side effects at a higher rate than Vietnamese women. In Georgia, women in the 800-mcg group were significantly more likely than women in the 400-mcg group to report experiencing nausea (48% vs. 42%, RR=.88, 95% CI 0.75–1.02), vomiting (22% vs. 16%, RR=.72, 95% CI 0.54–0.95) and fever/chills (41% vs. 31%, RR=.75, 95% CI 0.63–0.91). In Vietnam, the only significant difference in the side effects reported actually occurred in the opposite direction, with 33% of women in the 400-mcg group and 22% of women in the 800-mcg group reporting dizziness (RR=1.49, 95% CI 0.97–2.31). No serious adverse events occurred.

Nearly all women reported feeling very satisfied or satisfied with their abortions, regardless of study group allocation (Table 6). Women in the 800-mcg group were slightly less likely than women in the 400-mcg group to say that buccal administration of misoprostol was very acceptable or acceptable (88% vs. 92%, RR=1.05, 95% CI 1.01–1.09). Ninety-six percent of women in both groups would choose to have a medical abortion in the future should the need arise, and 98% would recommend the method to a friend.

4. Discussion

This study demonstrates that both 400-mcg and 800-mcg doses of buccal misoprostol after 200 mg mifepristone are highly effective at terminating pregnancy through 63 days LMP. Our results on the performance of the 800-mcg buccal regimen are consistent with the only previous study in the literature that looked at buccal misoprostol through 63 days LMP with an interval of at least 24 h between mifepristone and misoprostol [6]. The high success rate of the 400-mcg buccal regimen, even at later gestational ages, corroborates a study conducted in Moldova by Raghavan et al. [14] that found a 97% success rate overall, with no decline in efficacy at gestations 50 to 63 days LMP.

Halving the dose of misoprostol resulted in significantly fewer reports of vomiting and fever or chills in the Georgia sites, but not in the Vietnam site. Women in Georgia reported fewer side effects with the 400-mcg misoprostol regimen and found buccal administration of misoprostol to

Table 6
Women's satisfaction with the procedure

	400 mcg (*n*=551)	800 mcg (*n*=555)	RR (95% CI)
Satisfied with procedure	95.6 (527)	96.2 (534)	.99 (.97–1.02)
Buccal administration acceptable*	92.0 (507)	87.9 (488)	1.05 (1.01–1.09)
Side effects acceptable	86.0 (474)	84.7 (470)	1.02 (.97–1.07)
Pain medication adequate			
Yes[a]	72.1 (397)	76.2 (423)	.99 (.95–1.03)
No	6.4 (35)	5.9 (33)	1.12 (.71–1.77)
Did not take pain medication	21.6 (119)	17.8 (99)	1.21 (.95–1.54)
If in need of another abortion, would choose:			
Surgical	1.5 (8)	1.4 (8)	1.01 (.38–2.66)
Medical	96.2 (530)	96.2 (534)	1.00 (.98–1.02)
No preference	2.4 (13)	2.3 (13)	1.01 (.47–2.15)
Would recommend method to friend	98.4 (542)	97.8 (543)	1.01 (.99–1.02)

[a] Excluded 'did not take medication' to compare treatments.

* p<.05, comparing 400-mcg and 800-mcg groups.

be slightly more acceptable than women in the 800-mcg arm, despite the fact that both groups were instructed to hold four pills in their cheeks.

This study has very few limitations. As the study was double-blinded, the effects of provider bias should be minimal. Abortion outcomes were confirmed for nearly all participants, as less than 1% of women were lost to follow-up. However, we are limited in the trend analyses we can conduct on success rates by gestational age due to the uneven distribution of patients in the two countries. Also, because the study was powered to detect differences in efficacy between the two arms at later gestational ages, it was perhaps overpowered to detect differences in other outcomes, such as side effects. Thus, a six-percentage point difference in reporting of nausea in Georgia is statistically significant, but perhaps less important in clinical terms.

The findings of our research indicate that a regimen of 400 mcg buccal misoprostol after mifepristone is as safe and effective as a regimen of 800 mcg buccal misoprostol and results in fewer side effects. While 800 mcg vaginal misoprostol and 800 mcg buccal misoprostol remain excellent options for abortion through 63 days LMP, 400 mcg buccal misoprostol is highly efficacious as well. Clinicians interested in a two-pill in-the-mouth misoprostol regimen for ease of administration, decreased cost and increased acceptability may consider this method.

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Original Research Article

Expansion of a direct-to-patient telemedicine abortion service in the United States and experience during the COVID-19 pandemic

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ABSTRACT

Objective: To present updated evidence on the safety, efficacy and acceptability of a direct-to-patient telemedicine abortion service and describe how the service functioned during the COVID-19 pandemic.
Study Design: We offered the study at 10 sites that provided the service in 13 states and Washington DC. Interested individuals obtained any needed preabortion tests locally and had a videoconference with a study clinician. Sites sent study packages containing mifepristone and misoprostol by mail and had remote follow-up consultations within one month by telephone (or by online survey, if the participant could not be reached) to evaluate abortion completeness. The analysis was descriptive.
Results: We mailed 1390 packages between May 2016 and September 2020. Of the 83% (1157/1390) of abortions for which we obtained outcome information, 95% (1103/1157) were completed without a procedure. Participants made 70 unplanned visits to emergency rooms or urgent care centers for reasons related to the abortion (6%), and 10 serious adverse events occurred, including 5 transfusions (0.4%). Enrollment increased substantially with the onset of COVID-19. Although a screening ultrasound was required, sites determined in 52% (346/669) of abortions that occurred during COVID that those participants should not get the test to protect their health. Use of urine pregnancy test to confirm abortion completion increased from 67% (144/214) in the 6 months prior to COVID to 90% (602/669) in the 6 months during COVID. Nearly all satisfaction questionnaires (99%, 1013/1022) recorded that participants were satisfied with the service.
Conclusions: This direct-to-patient telemedicine service was safe, effective, and acceptable, and supports the claim that there is no medical reason for mifepristone to be dispensed in clinics as required by the Food and Drug Administration. In some cases, participants did not need to visit any facilities to obtain the service, which was critical to protecting patient safety during the COVID-19 pandemic.
Implications: Medical abortion using telemedicine and mail is effective and can be safely provided without a pretreatment ultrasound. This method of service delivery has the potential to greatly improve access to abortion care in the United States.

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Introduction

Telemedicine abortion is a broad term that describes the use of telecommunications (phone, videoconference, texting, email) to provide one or more aspects of abortion care such as counseling, eligibility assessment, medication provision, guidance through the process, and follow-up assessment. These services may be provided as part of or independent from the formal healthcare system and may involve some degree of in-person contact for parts of the process.

A substantial body of literature from around the globe provides evidence that telemedicine models of abortion provision are highly acceptable to clients and providers, and success rates and safety outcomes are similar to those reported for in-person care [1–6]. Furthermore, a growing amount of data from the United States suggests that telemedicine allows people to obtain abortions at an earlier gestational age, improves access to care for rural patients, and may be associated with decreases in time to schedule an appointment and distance traveled [7,8].

Having the option to receive abortion care via telemedicine is critical, as accessing in-person care has become increasingly challenging in certain regions of the country. In 2017, 95% and 94% of counties in the Midwest and the South, respectively, did not have a facility that provided abortion care [9]. Individuals who can get to a clinic find an increasingly hostile environment outside; the National Abortion Federation's 2019 annual report on violence and disruption statistics documented 3387 incidents of obstructing facilities (up from 3038 in 2018), and 123,228 incidents of picketing (up from 99,409 in 2018) [10].

The COVID-19 pandemic has exacerbated barriers to accessing abortion care by hindering people's ability to pay for the service (due to loss of income) and limiting mobility because of childcare needs, stay-at-home orders, and the imperative to limit in-person interactions [11,12]. To mitigate some of these effects, many abortion providers have modified their clinical protocols and incorporated telemedicine to varying degrees [13]. Experts have advocated for adoption of "no-test medication abortion," which, by not mandating screening ultrasound, blood tests, or follow-up tests unless clinically warranted, would allow the treatment to be provided without an in-person encounter [14].

The TelAbortion Project is a direct-to-patient service model whereby participating clinics counsel and screen patients remotely, and then send mifepristone and misoprostol by mail to those who are eligible. Because of restrictions on mifepristone imposed by the Food and Drug Administration (FDA) under the drug's Risk Evaluation and Mitigation Strategy (REMS), we implemented TelAbortion as a research study conducted under an Investigational New Drug (IND) application. Specifically, the REMS for mifepristone states that the drug must be dispensed to patients only in clinics, medical offices, and hospitals, which is commonly interpreted as prohibiting the mailing of the medication. Results from the first 32 months of the project (May 2016–December 2018) in which 248 packages were sent found that the service was safe, effective, efficient and satisfactory [6]. The objective of this analysis is to present data on safety, efficacy and acceptability collected from May 2016 through September 2020 (inclusive of the previously published data), during which time the study expanded dramatically both geographically and in sample size, and describe how the service functioned amidst the numerous challenges imposed by the COVID-19 pandemic.

Methods

In the reporting period, the study was implemented at 10 institutions (4 independent clinics, 4 Planned Parenthood affiliates, and 2 academic medical centers) that provided the TelAbortion service in 13 states (CO, GA, HI, IA, IL, MD, ME, MN, MT, NM, NY, OR, WA) and Washington, DC. Five sites provided the service in states where they were not physically located because their clinicians were licensed there. One site stopped recruitment in 2017 due to slow enrollment. Sites were added on a rolling basis, with the newest site beginning enrollment in May 2020. Before adding each state to our study, we confirmed that it had no laws that prohibited the service, although some state laws constrained or complicated the way the service was offered.

Patients interested in receiving a TelAbortion underwent a prescreening process by phone that reviewed basic eligibility requirements and explained the study procedures. Those who wished to proceed obtained any necessary tests at laboratories or radiology offices and had evaluations with a study clinician via videoconference during which the clinician confirmed eligibility, obtained consent electronically, and agreed on a plan for evaluating abortion outcome using ultrasound, serum hCG tests, or urine pregnancy test (UPT). Individuals were required to obtain a pre-abortion ultrasound or pelvic exam, and were deemed eligible for TelAbortion if the study clinician determined that the patient would be able to receive and take the mifepristone at $\leq$70 days of gestation and had no suspicion that the pregnancy was ectopic or nonviable (See the prior paper for a full description of procedures and eligibility requirements [6].).

Sites sent participants packages containing one tablet of mifepristone 200 mg and eight tablets of misoprostol 200 mcg (one site prescribed the misoprostol instead), an instruction sheet, and a UPT if indicated. Sites advised participants to take mifepristone followed by misoprostol 800 mcg within 48 hours either vaginally or buccally, as per standard clinic practice, and to take the other 800 mcg of misoprostol if no bleeding occurred within 24 hours after the first dose. In the event of any problems, sites instructed participants to call, recommended they seek in-person care if indicated, and followed up with them until the resolution of the problem. Following standard practice at the site, study clinicians evaluated abortion outcome using patient history, ultrasound, serum HCG tests before and after mifepristone ingestion, pelvic examination, and/or urine pregnancy testing. At sites that offered more than one method, the participant and clinician agreed on which method to use. Within a month after mailing each study package, sites conducted follow-up contacts to review any test results, assess abortion outcome, and inquire about any adverse events or unplanned visits. Once the abortion was complete, sites conducted a short, structured satisfaction questionnaire by telephone.

The study team made some modifications to study procedures over time. For the first 127 participants, the study paid for care and medications provided directly by sites. We offered participant compensation of $50 until late 2018, when we stopped to better mirror standard provision of abortion care and obtain more accurate data on acceptability and satisfaction (245 participants in our sample were offered compensation). Other changes included a switch from paper data forms to a secure browser-based electronic data capture application in early 2019. If a participant was

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Table 1
Characteristics of TelAbortion study participants who were sent a medical abortion package: n (%) or median (range)[a]

	N = 1356
Age	
15–24 years	346 (25.5)
25–34 years	735 (54.2)
35–47 years	275 (20.3)
Highest level of education completed	
Less than HS	65/1305 (5.0)
HS/GED	357/1305 (27.4)
More than HS	883/1305 (67.7)
Number of previous pregnancies	
0	344 (25.4)
1	291 (21.5)
≥ 2	721 (53.2)
Number of previous medical abortions	
0	1086/1348 (80.6)
1	210/1348 (15.6)
≥2	52/1348 (3.9)
Gestational age at prescreen[b]	
18–35 days	280 (20.6)
36–63 days	1053 (77.7)
64–68 days	23 (1.7)
Median (range)	42 (18-68)
Distance of residence from provider (Continental US)[c]	
1–9.9 mi	80/1075 (7.4)
10–49.9 mi	347/1075 (32.3)
50–99.9 mi	169/1075 (15.7)
100–149.9 mi	92/1075 (8.6)
≥ 150 mi	387/1075 (36.0)
Hawaiian island of residence	
Oahu	55/281 (19.6)
Other island	226/281 (80.4)
Race/ethnicity (more than 1 category allowed)[c]	
White	750/1073 (69.9)
Black	163/1073 (15.2)
Hispanic	87/1073 (8.1)
Asian/Pacific Islander	93/1073 (8.7)
Native American	42/1073 (3.9)
Multi-racial, not specified	8/1073 (0.7)
Classification of participant's current address[c]	
Urban	826/1031 (80.1)
Rural	205/1031 (19.9)
Payment method for care provided by site (more than 1 method allowed)[d]	
Private/public insurance	470/1228 (38.3)
Self-pay	899/1228 (73.2)
Abortion fund	175/1228 (14.3)
Actual/planned payment method for pre-abortion tests obtained elsewhere (more than 1 method allowed)[d]	
Private/public insurance	606/919 (65.9)
Self-pay	332/919 (36.1)
Abortion fund	26/919 (2.8)
None; did not have any preabortion tests	327

[a] Does not include 32 second abortions and 2 third abortions during the study period. For participants with multiple abortions, we included only the first.
[b] Using clinician's estimate of gestational age at time package sent and then backdated.
[c] Question not asked in first version of study forms.
[d] Does not include 127 participants who had study site services paid for by study.

Table 2
Abortion outcomes[a] and unplanned encounters, n (%)

	N = 1390
Neither medication taken, or medications taken after miscarriage diagnosis	47 (3.4)
Lost to follow-up	186 (13.4)
Known abortion outcome	1157 (83.2)
Abortion outcome at last contact	n = 1157
Complete abortion without surgical intervention	1103 (95.3)
Surgical intervention	47 (4.1)
Reason: ongoing pregnancy	14 (1.2)
Ongoing pregnancy; carrying to term or unknown[b]	7 (0.6)
Method used in outcome assessment among complete abortions with no surgical intervention	n = 1103
Facility-based test (ultrasound, serum HCG, and/or pelvic exam)[c]	396 (35.9)
No facility-based test	707 (64.1)
Urine pregnancy test (UPT)[d]	647 (58.7)
Patient history only	60 (5.4)
Abortion-related unplanned encounters[e]	n=1173
Emergency room (ER)/urgent care	70 (6.0)
Other outpatient visit	92 (7.8)
Serious Adverse Events	10 (0.9)
Hospitalization	8 (0.7)
Transfusion[f]	5 (0.4)

[a] Includes multiple abortions by same individual.
[b] Includes one abortion where participant threw up mifepristone after 10 minutes and then decided to continue pregnancy.
[c] Outcomes assessed with facility-based tests may also have utilized UPTs and/or patient history.
[d] In 3 cases, the UPT result(s) were positive and the diagnosis of complete abortion was made by patient history only.
[e] Denominator includes abortions with known outcome or any unplanned encounters that occurred after study consent was signed. Does not include encounters for lab tests, anti-D immunoglobulin, or contraception alone. Includes 1 hospitalization, 4 ER visits, and 12 other outpatient encounters that occurred prior to taking (or deciding not to take) mifepristone. Abortions may be included in more than one category.
[f] Two of the transfusions occurred in an ER and are not included in Hospitalization.

Table 3
Acceptability of TelAbortion to study participants at exit interview, among those with known abortion outcome: n (%)[a]

Satisfaction with the service	n = 1022
Very satisfactory	869 (85.0)
Satisfactory	144 (14.1)
Unsatisfactory/Very unsatisfactory	9 (0.9)
Satisfaction with speaking to provider remotely	n = 891
Very satisfactory	763 (85.6)
Satisfactory	123 (13.8)
Unsatisfactory/Very unsatisfactory	5 (0.6)
Experience getting pre-abortion tests[b]	n = 693
Easy or very easy	594 (85.7)
Difficult or very difficult	99 (14.3)
Future preference	n = 886
TelAbortion	754 (85.1)
In-person abortion	56 (6.3)
No preference	76 (8.6)
Would recommend TelAbortion to a friend	n = 892
Yes	863 (96.7)
No	9 (1.0)
Maybe	20 (2.2)

[a] Includes multiple abortions by same individual.
[b] Does not include abortions where no pre-abortion tests were planned.

lost to follow-up and outcome and/or satisfaction data had not been collected, the sites sent via email a link to an online survey for the participant to complete. As new practice guidelines became available, sites could make corresponding changes in care for their TelAbortion patients (as permitted within the constraints of the study protocol); these included forgoing Rh typing or prophylaxis with anti-D immunoglobulin for participants under a certain gestational age and advising participants to take a second dose of misoprostol routinely in the 9th and/or 10th week of gestation [15].

Here we present descriptive analyses of our service delivery data. For data on participant characteristics (Table 1) our unit of analysis was the individual so that participants who had multiple abortions were not counted more than once. For abortion outcome, unplanned encounters, and satisfaction data (Tables 2 and 3), we utilized the abortion as the unit of analysis as we did not want to undercount any of these outcomes. We defined an adverse event as serious if it was fatal, life-threatening or resulted in hospitalization, transfusion, or significant disability. An unplanned clinical encounter was any visit to a clinician after the study package was mailed, except visits to obtain anti-D immunoglobulin, con-

traception, or routine ultrasound or lab tests to evaluate abortion outcome in the absence of concerning symptoms. The study team evaluated the reason for each unplanned encounter to determine whether or not it was abortion-related. We used 3/13/20 as the start date of the COVID crisis as that was the date the federal government declared COVID-19 to be a "national emergency" [16].

Advarra Institutional Review Board, the University of Hawaii's Office of Research Compliance Human Studies Program, and Oregon Health and Science University's Institutional Review Board approved the protocol. We registered the study on clinicaltrials.gov (NCT02513043).

Results

Partnering sites sent 1390 packages to 1356 participants who were prescreened between May 11, 2016 and September 11, 2020. Thirty participants received 2 abortions and 2 received 3 abortions during the reporting period. Of the 1356 individuals who received a package, 26% were under 25 years of age, and 14 were minors (Table 1). Participants tended to contact the clinics early in the first trimester; 47% were less than 42 days gestation at the time of the prescreening. In the continental U.S., 60% of participants lived 50 miles or more from their study site, and 36% lived 150 miles or farther. Thirty participants had their packages mailed to a state that was not their state of residence. While only 38% used insurance to pay for care provided by the study site (e.g., counseling, abortion medications), 66% used insurance to pay for preabortion tests.

In 47 instances (3%), neither abortion medication was taken, or the medications were taken after a diagnosis of miscarriage (Table 2). The median gestational age on the day of mifepristone ingestion was 53 days gestation (range 29–76). In eleven abortions (1% of those with outcome information), the participant took mifepristone past 70 days of gestation. Of the 76 times (7%) a participant reported taking more than 800mcg of misoprostol from the study package, 20 did so due to gestational age, as advised by the site during counseling. In 42 instances, participants took another 800 mcg of misoprostol because of little or no bleeding, or due to concerns that they did not pass the pregnancy.

We obtained abortion outcome information on 83% of abortions (1157/1390) and satisfaction data after 74% of abortions (1022/1390). Fourteen percent of the satisfaction questionnaires (141/1022) were completed via the online survey. Of the 1157 abortions with outcome information, 95% were complete abortions without a procedure (Table 2). Twenty-one abortions (1.8%) resulted in ongoing pregnancy. The majority of complete abortions were confirmed using a method that did not require a visit to a facility; 59% relied on UPTs, and 5% depended on patient history alone.

There were seventy unplanned visits (6%) to emergency rooms or urgent care centers for reasons related to the abortion (Table 2). Ten serious adverse events (SAEs) occurred, including five transfusions (0.4%). We determined that none of the SAEs was attributable to the telemedicine delivery of the service (e.g., they would not have been avoided if the participants had had in-person screening or picked their pills up in person).

When the COVID-19 national emergency was declared, we worked with our study sites to adapt to new challenges. The FDA required that our protocol retain the screening ultrasound requirement, but on a case-by-case basis, and following broader FDA guidance on conduct of clinical trials during the pandemic [17], sites evaluated whether forgoing the ultrasound was necessary to protect patient and provider health and safety (e.g., if the patient's locale was under stay-at-home orders, or a patient was quarantining because of COVID exposure or infection). Overall, 52% (346/669) of abortions during COVID occurred without a screening ultrasound, though this proportion varied widely by site (0%–83%). No ectopic pregnancies were reported among those who received a package during the entire analysis period (pre- and during COVID).

Prior to COVID, we had already started encouraging sites to preferentially offer UPT follow-up to confirm abortion outcome because participants were reporting that getting testing at facilities was burdensome. Comparing the 6 months prior to COVID to the period during COVID, selection of UPT as a follow-up method increased from 67% (144/214) to 90% (602/669). While some sites were already doing UPT follow-up for nearly all participants in the pre-COVID period, four study sites that had rarely used UPT for follow-up before COVID reported substantial increases during the COVID period (Fig. 1).

Enrollment increased dramatically in the months after March 2020; compared to January and February 2020, monthly enrollment more than tripled in April, May, and June of the same year (Fig. 2), Months with high enrollment were also months in which large percentages of abortions occurred without screening ultrasounds, and also in which new states were added to the project.

Over the entire reporting period, participants were overwhelmingly satisfied with the service, and with speaking to their providers remotely (Table 3). Despite some difficulty obtaining preabortion tests reported by 14% of the sample, 85% would choose TelAbortion again, and nearly all would recommend the service to a friend.

Discussion

With a larger, more geographically diverse sample, these data confirm our earlier findings that the TelAbortion service is safe, feasible, effective, and acceptable. Mifepristone can safely be dispensed by mail, and the REMS requirement that mifepristone must be dispensed in person, instead of enhancing patient safety as it purports to do, could have the exact opposite effect, particularly during a pandemic. Our abortion success rate of 95% is comparable to rates in the literature for in-person care [18]. A substantial proportion of our participants lived significant distances from their providers (and in Hawaii, most lived on different islands), underscoring the potential of direct-to-patient services to improve access to care. Preabortion ultrasounds are usually unnecessary for safe and effective medication abortion [1,14,19,20], and we found during COVID that sites sometimes actually felt it necessary to omit the ultrasound to protect a participant's health. The finding that a higher proportion of participants used insurance to pay for preabortion tests than the abortion medications and counseling (66% vs 38%) suggests that the TelAbortion service model could lower costs for some patients. This may be true especially in states where insurance will not cover the cost of abortion but may cover the cost of tests (as there is nothing to link the tests to subsequent abortion care).

We were interested to see that only 7% of participants took a second dose of misoprostol. In light of the recent misoprostol shortage that began in September 2020 [21] (J. Price, personal communication, 2/26/21), and adhering to the general principle of conservation of resources, rather than send out a second dose to all patients as standard practice, services might consider only sending it to patients above a certain gestational age (e.g., above 64 days or 71 days depending on clinic protocols), and calling in additional doses to pharmacies as needed.

A small but noteworthy number of patients (n = 30) obtained a TelAbortion in a state other than their state of residence. As the practice of medicine occurs where the patient is physically, crossing a state border can allow a patient to access care in an environment with fewer restrictions. In these instances, participants crossed the border for their video conference and then sites mailed packages to courier or post office locations, or to friends or family

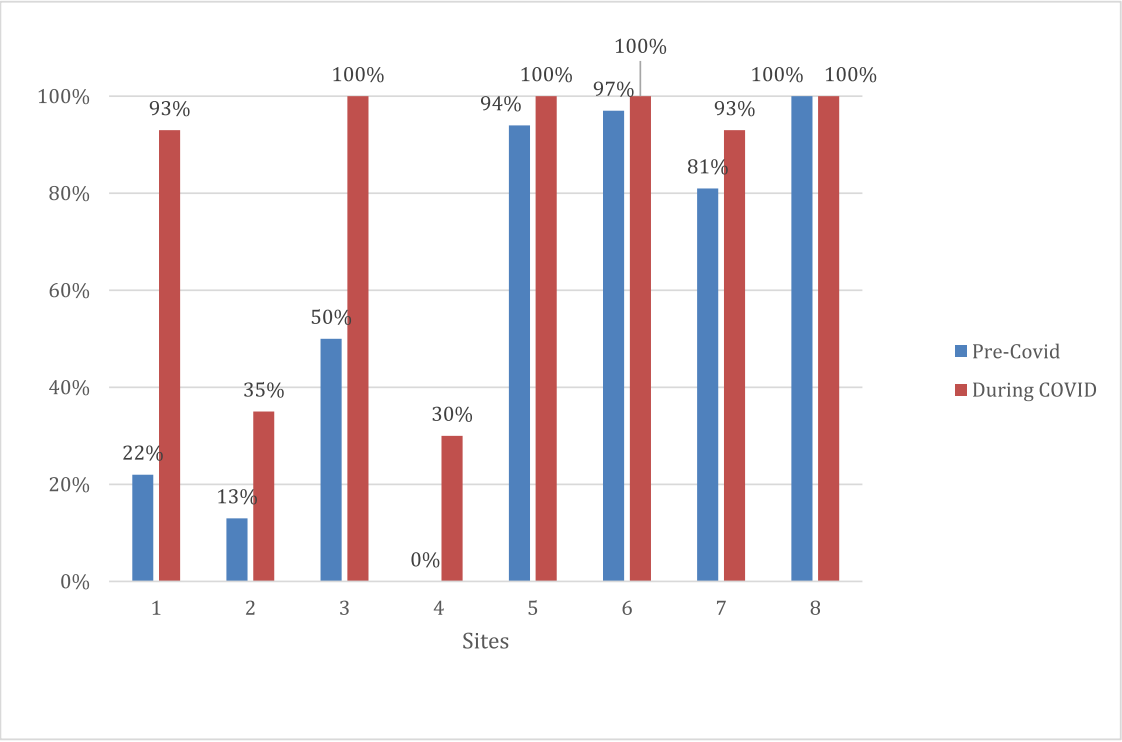

Fig. 1. Percentage of abortions with urine pregnancy test selected as follow-up method before COVID and during COVID, by site.[a,b]
[a]'Pre-COVID' period defined as 9/13/19–3/12/20; 'During COVID' period defined as 3/13/20–9/11/20.
[b]Does not include 1 site that did not enroll patients in the defined periods, and 1 site that did not enroll patients in the pre-COVID period (and enrolled 14 participants in the during COVID period).

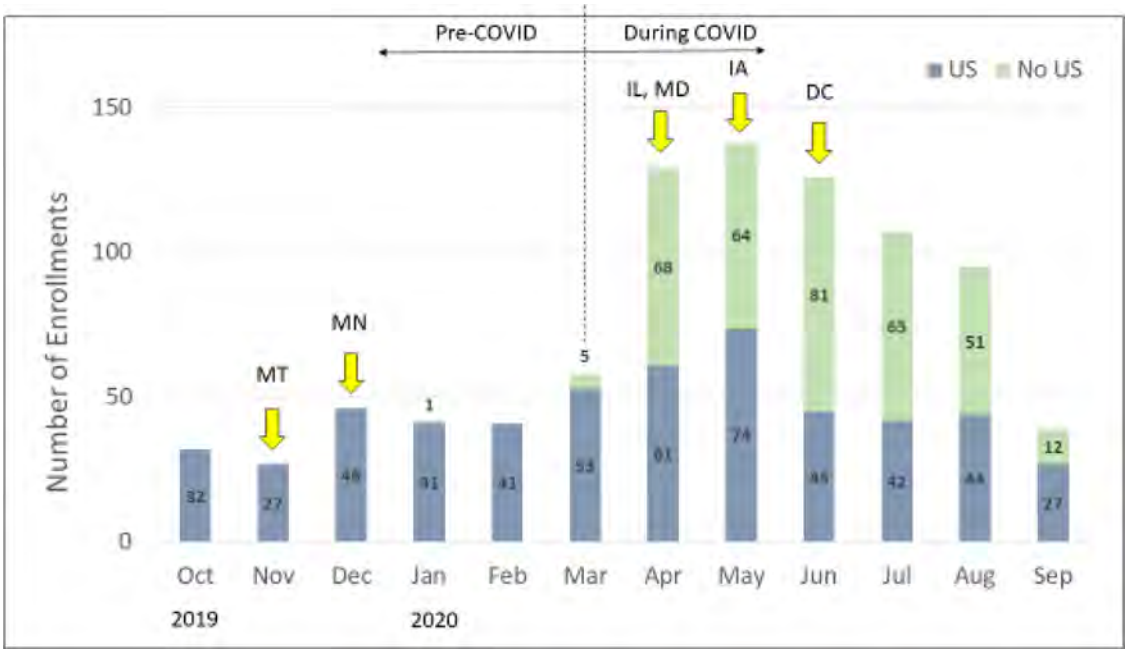

Fig. 2. Enrollment and pre-abortion ultrasound (U/S) over time.[a]
[a]Enrollment included from 10/1/19 through 9/11/20.
*Arrows denote when new states added to the project.

members, who held the package until the participant picked it up. While this still required participants to travel, this approach may have enabled them to travel shorter distances than they would have had to in order to get to the nearest in-person appointment, and it allowed some to bypass home-state restrictions on abortions such as in-person counseling or waiting period laws. Some sites actively conducted outreach to metropolitan areas with restricted access to abortion care that were located near a border with a project state. Since 19 states prohibit the use of telemedicine for medication abortion within their borders, this may be a strategy to explore further to increase access in more restrictive states [22].

When the first surge of COVID-19 occurred in the spring, enrollment in the service soared, likely due to greater challenges in accessing in-person care, the ability for some participants to obtain the service without having to get an ultrasound (which meant they could do the entire process from home), and the addition of new states to the project. This spike in enrollment at a time when barriers to abortion care were limiting access elsewhere emphasizes the critical value of our service delivery method. Changes in practice during COVID varied widely by site, and reflected a number of factors including provider preference, institutional policies, and the provider's perception of the degree to which obtaining tests increased a patient's risk of infection or the patient's risk of infecting others.

Our data have some limitations. While we were able to improve on the follow-up rate of 77% from our first analysis (possibly due to the adoption of the online exit survey), we did not have outcome data on 13% of participants. As such, our estimates of medical abortion failure or complications may be underestimated or overestimated. As this analysis was descriptive, we are limited in the associations we can make between various aspects of the service and outcomes.

Compared to people obtaining abortions in the United States, our study population had a higher proportion of people who were older, more educated, and more likely to identify as white [23]. Telemedicine innovations need to prioritize the most disadvantaged populations so that they are not left behind. Future innovations in our project should focus on addressing this issue.

When we started the TelAbortion Project in 2016, it was the first service in the United States in which people could obtain an abortion legally without an in-person visit to an abortion provider. After a federal district court issued an injunction in July 2020 blocking the FDA from enforcing the rule that patients must pick up the abortion medication in person from their provider, several new online services launched. These promising efforts were recently threatened by a Supreme Court decision in January 2021 that reinstated the prior harmful policy. We believe our data disprove the notion that medication abortion pills must be dispensed in-person, and that direct-to-patient services that mail the pills to patients are safe, effective and feasible, even without a screening ultrasound.

Declaration of Competing Interest

None.

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Commentary

Aligning mifepristone regulation with evidence: driving policy change using 15 years of excellent safety data

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Mifepristone was approved for sale in the United States 15 years ago this month. Use of mifepristone has steadily increased since its introduction; medical abortions now account for approximately 36% of the 1.1 million induced abortions that occur in the United States each year [1,2]. As clinical experience and research with mifepristone have expanded, the gold standard for medical abortion care has evolved beyond the protocol indicated in the FDA-approved label. Currently, the most common evidence-based protocols involve 200 mg mifepristone and 800 mcg misoprostol, and allow for use up to at least 63 days of gestation; these regimens are recommended by the World Health Organization [3], the American College of Obstetricians and Gynecologists and the Society of Family Planning [4] and the Planned Parenthood Federation of America [5]. The experiences of the hundreds of thousands of women who have had medical abortions using these protocols provide strong reassurance that mifepristone is extraordinarily safe; recent studies that include more than 423,000 women undergoing medical abortion with evidence-based regimens demonstrate that serious adverse outcomes are exceedingly rare [5–13].

Most complications associated with medical abortion are minor and include (but are not limited to) bleeding, cramping, fever and chills [9,13]. The outcomes of greatest clinical concern are heavy bleeding requiring transfusion, serious infection resulting in hospital admission, ongoing pregnancy, undiagnosed ectopic pregnancy and death attributable to the medical abortion regimen. In one large study [5], 0.10% (238/233,805) of patients presented to the emergency department for treatment following medical abortion; another recent study found that that, in the majority of cases, when women sought care in emergency departments following medical abortion, the complications were typically minor and expected [13]. Rates of hospital admission due to any medical-abortion-related complications are extremely low, with reports ranging from 0.04% (6/13,373) to 0.3% (119/45,528) [5,11,12]. Bleeding is an expected consequence of medical abortion, and it is only in the most extreme of circumstances that women require transfusion to replace excessive blood loss. Recent studies report that blood transfusion was required in 0.03% (4/13,373) to 0.14% (16/11,319) of medical abortion patients [5,7,8,11,12]. Serious infection requiring hospitalization following medical abortion is also rare; recent estimates range from 0.01% (2/13,373) to 0.23% (26/11,319) [5,7,12,13]. Infection is more prevalent when misoprostol is administered through a vaginal, rather than an oral or buccal, route [14]. Five deaths have been attributed to septic shock associated with serious bacterial infections after using misoprostol vaginally [15,16], prompting the Planned Parenthood Federation of America to adopt new guidelines in 2006 that include buccal administration of misoprostol.

Ongoing pregnancy does not pose health risks to the woman per se but is important to monitor because surgical intervention may be required to complete the abortion and because misoprostol can be teratogenic [17,18]. However, medical abortion using mifepristone and misoprostol is highly effective, with recent studies reporting very low rates of ongoing pregnancy ranging from 0.13% (70/13,373) to 1.1% (499/45,528) [5,11–13].

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Ectopic pregnancy is a serious, but rare, event; ectopic pregnancies make up 1.3% to 2.0% of pregnancies in the United States [19,20]. Half of the pregnancies in the United States are unintended [21], and therefore, many women may not even be aware that they are pregnant, which could delay diagnosis of an ectopic pregnancy. However, women seeking abortion services, by definition, know that they are pregnant and may therefore be more likely to receive an early diagnosis of ectopic pregnancy. Furthermore, some studies show that rates of ectopic pregnancy are substantially lower among women seeking abortion services compared with overall rates in the general population [4,22,23].

Updated evidence-based regimens for medical abortion have increased options and lowered costs for women seeking abortion, all while maintaining an excellent safety profile. Research and practice in medical abortion continue to evolve, creating the potential to expand the medical option to even more women seeking abortion services. New studies demonstrate safe and effective use of mifepristone for medical abortion up to 70 days of gestation [24–26]. In addition, a growing body of research supports the safety of moving medical abortion away from clinic-centered models of care, allowing women to use mifepristone and misoprostol in the privacy and comfort of their home and to use technologies such as semiquantitative pregnancy tests to assess whether clinic follow-up is needed [27–29].

The current FDA-approved label for mifepristone limits its use to 49 days of gestation and indicates a 600-mg dose of mifepristone. In addition, mifepristone is not available in pharmacies; unlike other medications for which a doctor writes a prescription that the patient fills at a pharmacy, the prescriber's agreement specifies that mifepristone can be dispensed only in medical offices, clinics and hospitals. Furthermore, the FDA-approved label for mifepristone requires that patients make three office visits to receive the medications and complete extensive follow-up [30,31]. Although the safety and efficacy of updated evidence-based regimens for medical abortion are clear, some states require that providers follow the original FDA-approved protocol for medical abortion [32]. Requiring adherence to the FDA label does not serve the best interests of women; rather, it restricts the population of eligible women because of gestational age limits, directs women to take three times more mifepristone than evidence has shown to be necessary and requires that they make repeat visits to the clinic, demanding that increasing numbers of women travel great distances to receive services [33]. An extensive and rigorous literature supports the safety of both the current evidence-based regimens as well as innovative expanded protocols, providing a strong foundation for improving access to medical abortion by aligning the mifepristone label with the evidence.

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Significant Adverse Events and Outcomes After Medical Abortion

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Abstract

Objective—To analyze rates of significant adverse events and outcomes in women having a medical abortion at Planned Parenthood health centers in 2009 and 2010, and to identify changes in the rates of adverse events and outcomes between the 2 years.

Methods—In this database review we analyzed data from Planned Parenthood affiliates that provided medical abortion in 2009 and 2010, almost exclusively using an evidence-based buccal misoprostol regimen. We evaluated the incidence of six clinically significant adverse events (hospital admission, blood transfusion, emergency room treatment, intravenous antibiotics administration, infection, and death) and two significant outcomes (ongoing pregnancy and ectopic pregnancy diagnosed after medical abortion treatment was initiated). We calculated an overall rate as well as rates for each event and identified changes between the 2 years.

Results—Amongst 233,805 medical abortions provided in 2009 and 2010, significant adverse events or outcomes were reported in 1,530 cases (0.65%). There was no statistically significant difference in overall rates between years. The most common significant outcome was ongoing intrauterine pregnancy (0.50%); significant adverse events occurred in 0.16% of cases. One patient death occurred due to an undiagnosed ectopic pregnancy. Only rates for emergency room treatment and blood transfusion differed by year, and were slightly higher in 2010.

Conclusion—Review of this large dataset reinforces the safety of the evidence-based medical abortion regimen.

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INTRODUCTION

First-trimester abortion with medications rather than surgery is widely used throughout the world, primarily utilizing a combination of mifepristone and misoprostol. Extensive experience with medical abortion has proven it to be highly effective and safe (1–6). As with surgical abortion, complications with medical abortion are relatively infrequent. The low probability of clinically significant adverse events and outcomes and varying protocols make it difficult to estimate these rates without a very large patient population.

Planned Parenthood is a large, multi-site provider of women's healthcare whose health centers have offered medical abortion as an option since 2001(6). Most Planned Parenthood affiliates (accredited by the Planned Parenthood Federation of America (PPFA)) operate several health centers; some health centers within one affiliate may offer medical abortion services while others may not. At Planned Parenthood health centers that offer medical abortion, this option is available up to and including 63 days of gestation (assuming that state regulations do not restrict providers to the FDA-approved regimen).

All Planned Parenthood affiliates are required to follow the PPFA Manual of Medical Standards and Guidelines as a condition of accreditation. The 2009 and 2010 guidelines outlined three acceptable medical abortion regimens using mifepristone and misoprostol (Table 1) including the FDA-approved regimen and two evidence-based regimens. All three regimens required that patients start a course of antibiotics the day they took mifepristone and that a follow-up appointment be scheduled within two weeks of mifepristone (PPFA Manual of Medical Standards and Guidelines, 2009 and 2010). PPFA internal data from affiliate surveys indicate that at least 99% of the medical abortions performed during 2009 and 2010 followed the evidence-based buccal regimen.

PPFA has a centralized reporting mechanism for significant adverse events and outcomes after medical abortion, which allows a large number of patient outcomes to be assessed through routine reporting. The primary objective of this study was to analyze rates of significant adverse events and outcomes in women having a medical abortion at Planned Parenthood health centers in 2009 and 2010. We also sought to identify changes in the rates of adverse events and outcomes between the 2 years, overall and separately for each event or outcome.

METHODS

Data Collection

This analysis includes data obtained from Planned Parenthood affiliates that provided medical abortion from January 1, 2009 through December 31, 2010. The total number of medical and surgical abortions provided by Planned Parenthood affiliates is collected by the PPFA national office via quarterly and annual summary reports. Abortion in the first trimester is defined as occurring through the 12th week of pregnancy. This study was approved by Allendale Investigational Review Board.

Planned Parenthood health center staff are trained in accurate and complete reporting of significant adverse events and outcomes after medical abortion, and such reporting is centralized through the PPFA national office. Since 2005, the PPFA accreditation process has included auditing to verify that significant adverse events and outcomes related to the use of mifepristone for medical abortion are reported as required. In accordance with the Mifeprex® (mifepristone) prescribing information, PPFA reports all significant adverse events and outcomes to Danco Laboratories, the U.S. distributor of mifepristone, which in turn reports them to the U.S. Food and Drug Administration (FDA).

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Planned Parenthood health center staff collect information about significant adverse events and outcomes after medical abortion from different sources including routine follow-up visits, reports from clinicians providing care at hospital inpatient units or emergency rooms, or voluntary reports by patients. The 2009 and 2010 PPFA Manual of Medical Standards and Guidelines included requirements to emphasize the importance of the follow-up visit to all patients, and staff members were required to make three attempts (two in writing) to reach patients who did not return for follow-up. Despite substantial effort to follow up with patients, complete information on the proportion of women who did not return for follow-up as well as any complications they may have experienced is not available.

Study procedures

During the study period, protocols for providing medical abortion and reporting significant adverse events and outcomes remained consistent, with the exception that beginning in July 2010, affiliates had the ability to submit reports via a secure web-based system in addition to submitting reports via fax. We analyzed reports of significant adverse events and outcomes after medical abortion, and rates were evaluated for both years together, as well as individually for 2009 and 2010. We excluded 2010 data from one affiliate (that had reported only two cases of adverse events or outcomes) which as of September 2010 was no longer a member of PPFA. Because delays in reporting adverse events and outcomes are common, we could not be certain that all adverse events and outcomes that may have occurred at this affiliate during the first nine months of 2010 had been adequately reported.

Per the Danco Laboratories Mifepristone Prescriber's Agreement "adverse events, such as hospitalization, blood transfusion, ongoing pregnancy, or other major complications after the use of Mifeprex® and misoprostol must be reported to Danco Laboratories"(7). In this report, we evaluate six clinically significant adverse events (hospital admission, blood transfusion, emergency room [ER] treatment, intravenous antibiotics administration, infection requiring treatment with IV antibiotics or admission to the hospital, and death) and two significant outcomes (ongoing intrauterine pregnancy and ectopic pregnancy diagnosed after medical abortion treatment was initiated) after medical abortion. In this analysis, blood transfusion is binary (whether or not blood products were administered) because not all reports included the specific components or amount.

The PPFA Manual of Medical Standards and Guidelines defined ongoing pregnancy as "a living, viable pregnancy that is growing. For example, the ultrasound shows a fetal pole with cardiac activity or a gestational sac that has grown appropriately since mifepristone was given" (PPFA Manual of Medical Standards and Guidelines, 2009 and 2010). The PPFA Manual of Medical Standards and Guidelines permitted use of a repeat dose of misoprostol when the initial follow-up evaluation demonstrated an ongoing pregnancy up to and including 63 days gestation. In this analysis, if a repeat dose of misoprostol was successful, the case was not included as an ongoing pregnancy.

Categories of significant adverse events and outcomes are not mutually exclusive; in some cases, one problem could be counted as more than one event or outcome. For example, if a patient with a serious infection was admitted to the hospital and treated with intravenous antibiotics, this case would be counted in each of the three outcome categories.

Statistical analysis

We calculated 95% exact binomial confidence intervals for rates, and used Fisher's Exact Test to test the statistical significance of differences in proportions. Two-sided p-values of less than 0.05 were considered to be indication of statistical significance. All calculations were performed using StataSE 11 (College Station, TX).

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RESULTS

As of December 31, 2010, PPFA included 85 independent affiliates operating 810 health centers in 49 states and the District of Columbia; 39% (324) of health centers provided abortion care, and nearly all of these (97.8%, 317) offered medical abortion. In 2009, 314,772 first-trimester abortions were provided by PPFA affiliates, 35% of which were medical abortions. In 2010, medical abortion comprised 38% of the 320,991 first-trimester abortions. Overall, in 2009 and 2010, medical abortion comprised 37% of all first-trimester abortions provided by Planned Parenthood health centers.

Amongst the 233,805 medical abortions provided at Planned Parenthood health centers in 2009 and 2010, significant adverse events or outcomes were reported in 1,530 (0.65%) cases. There was no statistically significant difference in overall rates between years (p=0.29). Rates for each significant adverse event and outcome are shown in Table 2. A clinically significant adverse event occurred in 0.16% of cases; this rate did not differ by year. A clinically significant outcome occurred in 0.5% of cases (with no difference by year). Of importance is the rarity of an undiagnosed ectopic pregnancy, which occurred at a rate of 0.7 per 10,000 medical abortions. The most common significant adverse event or outcome after medical abortion during the study period, ongoing intrauterine pregnancy, was reported in 0.50% of cases for both years combined. Among 1,158 ongoing intrauterine pregnancies, 1,095 (94.6%) were known to be terminated surgically, and 63 (5.4%) were either lost to follow-up or patients indicated that they would continue or were considering continuing the pregnancy.

The only adverse event rates that differed in statistical significance in bivariate models between 2009 and 2010 were ER treatment (0.07%, n=87 *versus* 0.12%, n=151, respectively, p=0.001) and blood transfusion (0.04%, n=42 *versus* 0.06%, n=72, respectively, p=0.024). There was one death, due to an undiagnosed ectopic pregnancy, for a mortality rate of 0.4/100,000 over the two year study period.

DISCUSSION

As the largest provider of abortion care in the United States, PPFA is in a unique position to provide reliable, large-scale data on the efficacy and safety of abortion procedures. The data presented here reinforce the infrequency of clinically significant adverse events and outcomes after medical abortion. The vast majority (99.34%) of medical abortions provided at Planned Parenthood health centers in 2009 and 2010 were completed with no known complications. Clinically significant adverse outcomes were rare, occurring at a rate of 16 per 10,000 medical abortions. The most common significant adverse event or outcome reported was ongoing intrauterine pregnancy, occurring in 0.5% of all medical abortion procedures.

Ongoing pregnancy is reportable to Danco Laboratories per the Mifepristone Prescriber's Agreement. Since it is the efficacy metric for medical abortion, data on ongoing intrauterine pregnancy should be reported and reviewed. However, ongoing intrauterine pregnancy is not a complication that is related to the safety of medical abortion the same way serious infection or blood transfusion are. The risk associated with ongoing pregnancy is tied to the potential teratogenicity of misoprostol (8,9). Continuing pregnancy is of clinical significance only if it is unrecognized through follow-up and the patient does not have a surgical abortion.

Although we present data for ongoing pregnancy rates, we are unable to assess an overall "failure rate" for the two year reporting period. Treatment failure encompasses all reasons for a D&C, including incomplete abortion. While incomplete abortion managed outside the

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Planned Parenthood health center is reportable when it is tied to an adverse event (i.e. treatment in the ER or hospital), incomplete abortion managed at the health center is not. Therefore, we have data only on rates of surgical evacuation for ongoing pregnancy.

Ectopic pregnancy diagnosed after medical abortion treatment was initiated was extremely rare with a rate even lower than the likelihood of maternal death during delivery (10) Our study includes only ectopic pregnancies that were diagnosed after the medical abortion regimen had begun, not those diagnosed during the initial screening process. One death occurred during the study period due to an undiagnosed ectopic pregnancy.

The overall rate for all clinically significant adverse events and outcomes combined did not differ between 2009 and 2010; nor did the rate for most of these events differ by year. Exceptions were ER treatment and blood transfusion, both of which were higher in 2010 than in 2009. Because each health center has different local resources available, and patients may travel from more rural areas to some health centers, ER treatment may be related to where the original service was provided. Patients who drove for several hours to a health center to obtain care might be more likely to need ER treatment for a complication because of less access to a health center for any urgent issue. We do not have any data regarding locale of patients to compare whether ER treatment or blood transfusion is related to distance from home to the health center.

The findings in this paper are of timely significance as some states in the United States have passed or are considering legislation to restrict mifepristone and misoprostol use to the FDA-approved regimen. The largest U.S. trial of mifepristone and misoprostol using the FDA-approved regimen through 49 days gestation showed an ongoing pregnancy rate of 1% amongst 827 women (11). The 92% efficacy rate of the FDA-approved regimen (11,12) is lower than the 96% efficacy rate for the evidence-based regimen using buccal misoprostol through 63 days gestation (13). This current large database analysis reinforces the low ongoing pregnancy rate when using one 200 mg mifepristone tablet and buccal misoprostol.

Potential limitations to this analysis should be considered. The data analyzed in this paper are those reported to or received by PPFA; we cannot exclude the possibility that some clinically significant adverse events or outcomes were not included. Some patients may have experienced a significant adverse event or outcome but did not follow-up after their medical abortion. Additionally, despite intensive efforts at training affiliate and national office staff in procedures for reporting significant adverse events and outcomes, there remains the potential for human error and omission in the reporting process. Additionally, because experiencing, treating, and reporting an adverse event is subjective, an event may not always reflect the severity of the condition, but rather the concern of the patient. Similarly, treatments with blood products and intravenous antibiotics for the same condition may vary substantially among physicians or institutions.

The last potential limitation to consider is the lack of information available about women who did not experience a significant adverse event or outcome. Detailed information about patient age and gestational age (but no other demographic information) is collected through the PPFA reporting system only for those women with significant adverse events or outcomes after medical abortion. Therefore, we are unable to analyze rates of significant adverse events and outcomes based on patient age, gestational age or other demographic variables, or to identify the exact regimens used in the 232,275 medical abortions with no reported complications. Despite these potential limitations, the findings in this study confirm that evidence-based medical abortion is highly effective and extremely safe.

The FDA allows and encourages off-label use of registered products when existing medical evidence supports such use (14). The data presented in this paper contribute to existing

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information in the medical literature; all of this evidence, taken together, does not support legislation restricting providers to use of the FDA-approved regimen. Every woman deserves factual medical information whenever she is faced with a decision of whether or not to terminate her pregnancy (15). Mandating the FDA-approved regimen, without a scientific basis, does not protect patients from unsafe abortion; it only limits access to safe and effective medical abortion for women desiring a pregnancy termination. This review of PPFA's medical abortion data confirms the safety and efficacy of medical abortion, and should be taken into consideration both by clinicians and legislators when considering policy and protocols related to abortion.

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Table 1

Medical Abortion Regimens Provided at Planned Parenthood Health Centers in 2009 and 2010*

Regimen†	Gestational Limit (up to and including)	Mifepristone	Misoprostol	
			Days after Mifepristone	Dosage
FDA-approved	49 days	3 200-mg tablets, orally, in office	Two days (only if needed)	2 200 mcg tablets, orally, in office
Evidence-based, oral misoprostol	49 days	1 200-mg tablet, orally, in office	One day	4 200 mcg tablets (split into two doses over two hours), orally, at home
Evidence-based, buccal misoprostol	63 days	1 200-mg tablet, orally, in office	One or two days	4 200 mcg tablets, bucally, at home

*Follow-up appointment scheduled within 2 weeks of mifepristone ingestion for all regimens.

†All medical abortion regimens required that patients start a course of antibiotics on the day mifepristone was administered. Patients received doxycycline 100 mg orally twice a day for 7 days; if a patient was allergic to doxycycline, acceptable alternatives included azithromycin 1 gram orally, erythromycin base 500 mg orally four times a day for 7 days; erythromycin ethylsuccinate 800 mg PO four times a day for 7 days; ofloxacin 300 mg twice a day for 7 days or levofloxacin 500 mg PO once a day for 7 days).

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Table 2

Rates of Significant Adverse Events and Outcomes after Medical Abortion, 2009 and 2010*

Event	Number of Cases	Rate†	95% Confidence Interval	P‡
All Significant Adverse Events and Outcomes				
Any significant AE or outcome	1,530	0.65%	0.62–0.69%	0.293
2009	706	0.63%	0.59–0.68%	
2010	824	0.67%	0.62–0.72%	
Significant adverse events				
Any significant adverse event	385	0.16%	0.15–0.18%	0.092
2009	166	0.15%	0.13–0.17%	
2010	219	0.18%	0.16–0.20%	
Emergency room treatment	238	0.10%	0.09–0.11%	0.001
2009	87	0.07%	0.06–0.10%	
2010	151	0.12%	0.10–0.14%	
Hospital admission	135	0.06%	0.05–0.07%	0.343
2009	70	0.06%	0.05–0.08%	
2010	65	0.05%	0.04–0.07%	
Transfusion§	114	0.05%	0.04–0.06%	0.024
2009	42	0.04%	0.03–0.05%	
2010	72	0.06%	0.05–0.07%	
Intravenous antibiotics	57	0.02%	0.02–0.03%	0.292
2009	23	0.02%	0.01–0.03%	
2010	34	0.03%	0.02–0.04%	
Infection	37	0.016%	0.011–0.021%	0.254
2009	14	0.013%	0.001–0.021%	
2010	23	0.019%	0.001–0.028%	
Significant outcomes				
Any significant outcome	1,174	0.50%	0.47–0.53%	0.953
2009	556	0.50%	0.46–0.54%	
2010	618	0.50%	0.46–0.54%	
Ongoing intrauterine pregnancy	1,158	0.50%	0.47–0.52%	0.929
2009	548	0.49%	0.45–0.54%	
2010	610	0.50%	0.46–0.54%	
Ectopic pregnancy	16	0.007%	0.004–0.011%	1.00
2009	8	0.007%	0.003–0.014%	
2010	8	0.007%	0.003–0.013%	

*Events are not mutually exclusive.

†Denominator is all medical abortions; N=111,022 in 2009, N=122,783 in 2010, and N=233,805 for 2009 and 2010 combined.

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[‡] Difference between 2009 and 2010 rates.

[§] Transfusion is any blood product transfusion, regardless of the number of units.

Mifepristone and Misoprostol Administered Simultaneously Versus 24 Hours Apart for Abortion

A Randomized Controlled Trial

*Mitchell D. Creinin, MD, Courtney A. Schreiber, MD, MPH, Paula Bednarek, MD, MPH, Hanna Lintu, MD, MPH, Marie-Soleil Wagner, MD, MS, and Leslie A. Meyn, MS, for the Medical Abortion at the Same Time (MAST) Study Trial Group**

OBJECTIVE: Mifepristone and oral misoprostol are typically used for medical abortion in women up to 49 days of gestation, with a 36- to 48-hour interval between the medications. Alternative routes of misoprostol administration allow for use beyond 49 days of gestation. We designed this randomized, noninferiority trial to compare the efficacy, adverse effects, and acceptability of misoprostol 800 mcg vaginally administered simultaneously with, or 24 hours after, mifepristone 200 mg orally for abortion in women up to 63 days of gestation.

METHODS: The 1,128 participants swallowed mifepristone 200 mg and were then randomized to self-administer misoprostol intravaginally immediately in the office (group 1) or 24 hours later at home (group 2). Subjects returned for an evaluation, including transvaginal ultrasonography, 7±1 days after initiating treatment. Women who had not aborted were offered a second dose of misoprostol and returned for another evaluation in approximately 1 week. A phone contact was also attempted approximately 5 weeks after treatment. Treatment was considered a failure if a suction aspiration was performed for any indication.

RESULTS: The complete abortion rate for group 1 (95.1%, 95% confidence interval [CI] 93.0–96.8%) was statistically noninferior to that for group 2 (96.9%, 95% CI 95.1–98.2%) (P=.003). The abortion rates between groups did not significantly differ by gestational age. Adverse effects were mostly similar, although nausea, diarrhea, and warmth or chills were significantly more common in group 1.

CONCLUSION: Mifepristone 200 mg and misoprostol 800 mcg vaginally used simultaneously is as effective for abortion as compared with regimens using a 24-hour dosing interval.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00269568

(Obstet Gynecol 2007;109:885–94)

LEVEL OF EVIDENCE: I

See related article on 895.

** For members of the MAST Study Trial Group, see the Appendix.*

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Medical abortion techniques have evolved over the past 2 decades based on scientific advances. The original mifepristone and misoprostol regimens included 600 mg of oral mifepristone, followed 36–48 hours later by 400 mcg of oral misoprostol in women up to 49 days of gestation. Large, prospective, randomized trials support equal efficacy with regimens using a lower dose of mifepristone (200 mg).[1–3] Addi-

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tionally, alternative methods of administration of misoprostol, including vaginal,[4–6] buccal,[7] and sublingual,[8,9] allow for use of the medications for gestations beyond 49 days of gestation.

Over the past 5 years, multiple studies have focused on the time interval between medications. Regimens with oral misoprostol are not very effective when the time interval decreases below the recommended 36–48 hours.[10] Buccal regimens appear effective with dosing intervals as little as 24 hours in women up to 56 days of gestation.[7] The largest trials include vaginal misoprostol, with which efficacy is maintained in women up to 63 days of gestation when the time interval is as little as 6–8 hours.[11] Decreasing the time interval allows most women to complete a medical abortion in less than 1 day. Additionally, because approximately 50% of women have vaginal bleeding during the 48-hour interval between mifepristone and misoprostol administration with the standard regimen,[10,12,13] administering the drugs on the same day would decrease undesirable adverse effects like bleeding.

The natural progression in the evaluation of the effect of time between mifepristone and vaginal misoprostol administration is simultaneous administration of the agents. Such studies appear scientifically rational based on available pharmacokinetic and clinical data. Vaginal administration appears to act as a depot of misoprostol acid.[14] Typically, cramping begins approximately 2 hours and bleeding about 3 to 3½ hours after misoprostol placement.[11,15,16] Significant serum levels of misoprostol acid are still present 4 hours after administration based on the pharmacokinetic profile,[14] thereby rationalizing simultaneous application.

Pilot trials were performed with the primary objective of evaluating 24-hour expulsion rates after simultaneous administration of mifepristone 200 mg and vaginal misoprostol 800 mcg.[17,18] These trials included 120 women, with 40 women in each of the gestational age ranges of 49 days or less, 50–56, and 57–63 days of gestation. The expulsion rates of 90%, 88%, and 85%, respectively, were similar to those seen in regimens with intervals of 6–8 hours,[15,16] demonstrating the potential efficacy of these drugs for medical abortion when administered simultaneously. We performed this prospective, randomized, multicenter trial to compare the efficacy, adverse effects, and acceptability of misoprostol 800 mcg vaginally administered simultaneously with, or 24 hours after, mifepristone 200 mg orally in women up to 63 days of gestation. This study is designed as a noninferiority trial, with efficacy as the primary outcome variable.

MATERIALS AND METHODS

The study was conducted at four centers: the University of Pittsburgh, Oregon Health and Science University, Northwestern University, and the University of Southern California. The study was reviewed and approved by the institutional review boards of the respective institutions and by the U.S. Food and Drug Administration (FDA). The University of Pittsburgh served as the sponsoring institution; all protocol changes were submitted and approved by the University of Pittsburgh Institutional Review Board before submission to other institutions. All participants provided written consent before participation in the study.

We enrolled 1,128 healthy women who were requesting an elective abortion, had an intrauterine pregnancy at 63 days of gestation or less on the day of mifepristone administration as confirmed by vaginal ultrasonography, were willing to comply with the visit schedule, were willing to have a surgical abortion if indicated, and had access to a telephone. Potential subjects were excluded if they had any contraindication to mifepristone, including chronic systemic corticosteroid administration or adrenal disease; had any contraindications to misoprostol, including glaucoma, mitral stenosis, sickle cell anemia, poorly controlled seizure disorder, or known allergy to prostaglandin; had a hemoglobin level less than 10 g/dL; had cardiovascular disease, including angina, valvular disease, arrhythmia, or cardiac failure; had a known coagulopathy or were receiving treatment with anticoagulants; had a pregnancy with an intrauterine device in utero; had an ultrasound examination that demonstrated any evidence of an early pregnancy failure; had active cervicitis on examination; were breastfeeding; or had previously participated in the trial.

After obtaining informed consent, a medical history was reviewed, hemoglobin and blood type were obtained, and pelvic and transvaginal ultrasound examinations performed. Only women with a visible intrauterine gestational sac were eligible. Mean sac diameter ([length+width+depth]/3) was used to determine estimated gestational age (EGA) when an embryonic pole was absent using the formula: mean sac diameter (EGA [days]=mean sac diameter [mm]+30).[19] For gestations with an embryonic pole, the formula embryonic pole (EGA [days]=embryonic pole [mm]+42) was used.[20] Last menstrual period (LMP) was used to determine EGA if the LMP was within 3 days of the ultrasound EGA, but the ultra-

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sound estimate was used if it differed by 4 days or more from the EGA by LMP.

At the University of Pittsburgh, subjects returned for enrollment at least 24 hours after signing informed consent as required by the Pennsylvania Abortion Control Act. At all other sites, screening and enrollment occurred at the same visit. Once entry criteria were confirmed, each woman was counseled further about the correct method of inserting the misoprostol. She then swallowed mifepristone 200 mg, after which the randomization envelope was opened by the research staff. Women randomized to immediate insertion (group 1) went into an examination room in the office and inserted 4 tablets of misoprostol 200 mcg as high up as possible into the vagina within 15 minutes of swallowing the mifepristone. Those women randomized to routine insertion (group 2) were given the misoprostol tablets to take home with instructions to insert the misoprostol tablets 23–25 hours after taking the mifepristone. Group assignment was performed in a randomized fashion using sequentially numbered opaque envelopes containing a card with computer-generated assignment information and prepared for each center by the Data Coordinating Center. Randomization was stratified by center with equal frequency to the two treatment arms. Random allocations were performed in a permuted block design with varying block sizes as described by Pocock.[21]

Rh-immune globulin 50 mcg intramuscularly was administered to all subjects who were Rh-negative. Subjects were given written instructions regarding pain medication use and bleeding parameters. Women were advised to contact the research office if vaginal bleeding exceeded two soaked sanitary pads per hour for 2 consecutive hours. Participants were given a prescription for or supply of 20 tablets of codeine phosphate (30 mg), oxycodone (5 mg), acetaminophen with codeine (300 mg/30 mg) (with instructions not to take more than 13 tablets in a 24-hour period), or acetaminophen with hydrocodone (500 mg/5 mg) (with instructions not to take more than 8 tablets in a 24-hour period). Subjects were instructed to use ibuprofen or acetaminophen initially and to use the prescribed narcotic only if necessary. Subjects were asked to maintain a daily diary of medication use and adverse effects throughout the study. At each follow-up visit, the diary was reviewed and data collected regarding bleeding, cramping, other adverse effects, and medication use since the prior visit. An investigator was available 24 hours a day in the case of emergency and to answer subjects' questions.

Participants were scheduled to return for a follow-up examination 7 (±1) days after taking mifepristone, during which transvaginal ultrasonography was performed. Women who had not expelled the gestational sac were offered a repeat dose of misoprostol and scheduled to return. Subjects who missed the first follow-up visit and were not seen again until 12 or more days after receiving the mifepristone could not receive a second dose of misoprostol.

All women had a follow-up contact scheduled at 14 (±2) days after mifepristone administration. Those women who had expelled the pregnancy received a phone call from the researchers, and those who had not expelled the gestational sac returned for a visit that included transvaginal ultrasonography. Subjects who had not aborted by the second follow-up and had a viable gestation were offered a surgical abortion. Women with a nonviable persistent gestation at the second follow-up were offered a surgical abortion or scheduled to return again in another 3 weeks. If the abortion had not been completed by this final follow-up visit, subjects were offered a surgical abortion or weekly follow-up. Suction aspiration was also performed at any time if it was clinically necessary because of uterine hemorrhage or incomplete abortion, or at the subject's request.

Five weeks after initiating the study, we attempted to contact by telephone all women who had expelled the gestational sac by the first or second follow-up visit to review if there have been any problems since the abortion. The procedure was considered successful if the abortion occurred without requiring a suction aspiration. Neither the study staff, investigators, or participants were blinded to treatment group, as is common in medical abortion trials.[11]

Immediately before enrollment, women completed a questionnaire regarding their prior experience with abortion and a visual analog scale (VAS)[22,23] measuring the amount of pain and bleeding they anticipated. At each participant's final follow-up visit, she was questioned about her satisfaction with this medical abortion regimen and completed a VAS measuring the amount of perceived bleeding and pain experienced during the abortion process and her preference for medical or surgical abortion if she needed an abortion again in the future. On a 100-mm line, with 0 equaling no bleeding and 100 equaling heavy bleeding, subjects were asked to mark the amount of bleeding they experienced. In a similar fashion, level of pain was recorded, with 0 equaling no pain and 100 representing severe pain. Likewise, preference for abortion method was recorded, with 0

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equaling medical abortion and 100 representing surgical abortion.

On-site monitoring was performed by staff from the Data Coordinating Center at a minimum of every 4 weeks or upon request of the Principal Investigator. The monitor reviewed the center's documents to ensure appropriate institutional review board approval and communication as well as accurate and appropriate reporting of source data.

Sample size was estimated to demonstrate noninferiority of the study treatment (simultaneous administration) to standard treatment (24-hour interval). The complete abortion rate in the standard care group (group 2) was set at 97%.[11] Using a one-sided, two-group test of equivalence, 552 subjects per group were required to demonstrate equivalence within a 3% observed difference (upper 95% confidence interval of 5%).[24] This sample size was statistically able to establish noninferiority with the same 3% observed difference, with an efficacy in the standard group as high as 100% and as low as 95%. To allow for 2% of subjects to not have documentation of a final outcome, the total sample size was increased to 1,128 women. Because individual adverse effects in medical abortion regimens using these agents typically occur at a rate exceeding 10%,[11,13,15,16,25] this sample size had 80% power to detect at least a 60% difference in the rates of adverse effects between the two treatment groups. For adverse effects occurring at rates of 20%, this study had 80% power to detect at least a 45% difference between the two groups.

Baseline demographic data were compared according to treatment group using Student *t* test, Fisher exact test, χ^2 test, or χ^2 test for linear trend, where appropriate, to assess for clinically significant differences. An intent-to-treat analysis was performed to include all women with adequate follow-up defined as having at least one follow-up visit, more than one phone contact beyond 7 days after using the medications with a history by phone consistent with expulsion, or by review of outside records that confirmed expulsion.

The primary objective of this study was to compare complete abortion rates in women who received mifepristone followed by vaginal misoprostol within 15 minutes (experimental group) and 24 hours later (standard care group) using a one-sided equivalence test of proportions, with an equivalence limit of 5%. The null hypothesis for the test of equivalence is that two treatments are not equivalent. Rejecting the null hypothesis, indicated in this study by $P \leq .05$, implies that the two treatments are equivalent.[24] Interim analyses based on the complete abortion rate (both overall and stratified by gestational age) were conducted when 360 women and 720 women (approximately 33% and 66% of the study population, respectively) completed their follow-up visits. This interim analysis reduced the alpha for the final analysis to 0.0472 according to the O'Brien and Fleming method.[26]

Secondary outcomes included evaluation of the efficacy of mifepristone and one dose of misoprostol, adverse effects, bleeding, and acceptability data. Gestational age efficacy (overall, within group, and after mifepristone and a single dose of misoprostol) and the rate of adverse effects by gestational age were evaluated using the χ^2 for linear trend. Efficacy within groups by study site was evaluated using the χ^2 test. The rate of adverse effects (nausea, vomiting, and pain medication use), bleeding, and acceptability, as measured by positive or negative answers, between the two abortion regimens was compared using Fisher exact test. The length of bleeding after treatment, and the pre- and posttreatment VAS assessments were compared between treatment groups using the Mann-Whitney *U* test because these data did not appear to be normally distributed when their frequency distributions were graphically displayed. For analyses of adverse effects, bleeding, and acceptability data, two-tailed *P* values less than .05 were considered statistically significant.

RESULTS

Between April 2004 and May 2006, 1,128 subjects were enrolled (Fig. 1). Both groups were similar in demographic characteristics (Table 1). The gestational age was set by LMP and confirmed by ultrasonography in 49% and 45% of women in groups 1 and 2, respectively. The remaining women had their gestational ages adjusted by the ultrasound examination.

A final outcome was established for 1,100 women, with 26 (2.3%) women lost to follow-up (Fig. 1). A small number of women (19, 1.7%) had follow-up consisting only of multiple phone contacts or by review of medical records subsequent to the occurrence of the medical abortion; all of these women had histories consistent with expulsion and no signs of a continuing pregnancy. The median times of misoprostol administration in groups 1 and 2 were 5 minutes and 24 hours after mifepristone, respectively. All subjects in group 1 (0.2%) except for one used the misoprostol within 15 minutes of the mifepristone; the one outlier used her dose at 24 minutes. In group 2, four (0.7%) women did not use the misoprostol at the correct time, defined as more than 15 minutes outside of the assigned time interval. These four women used

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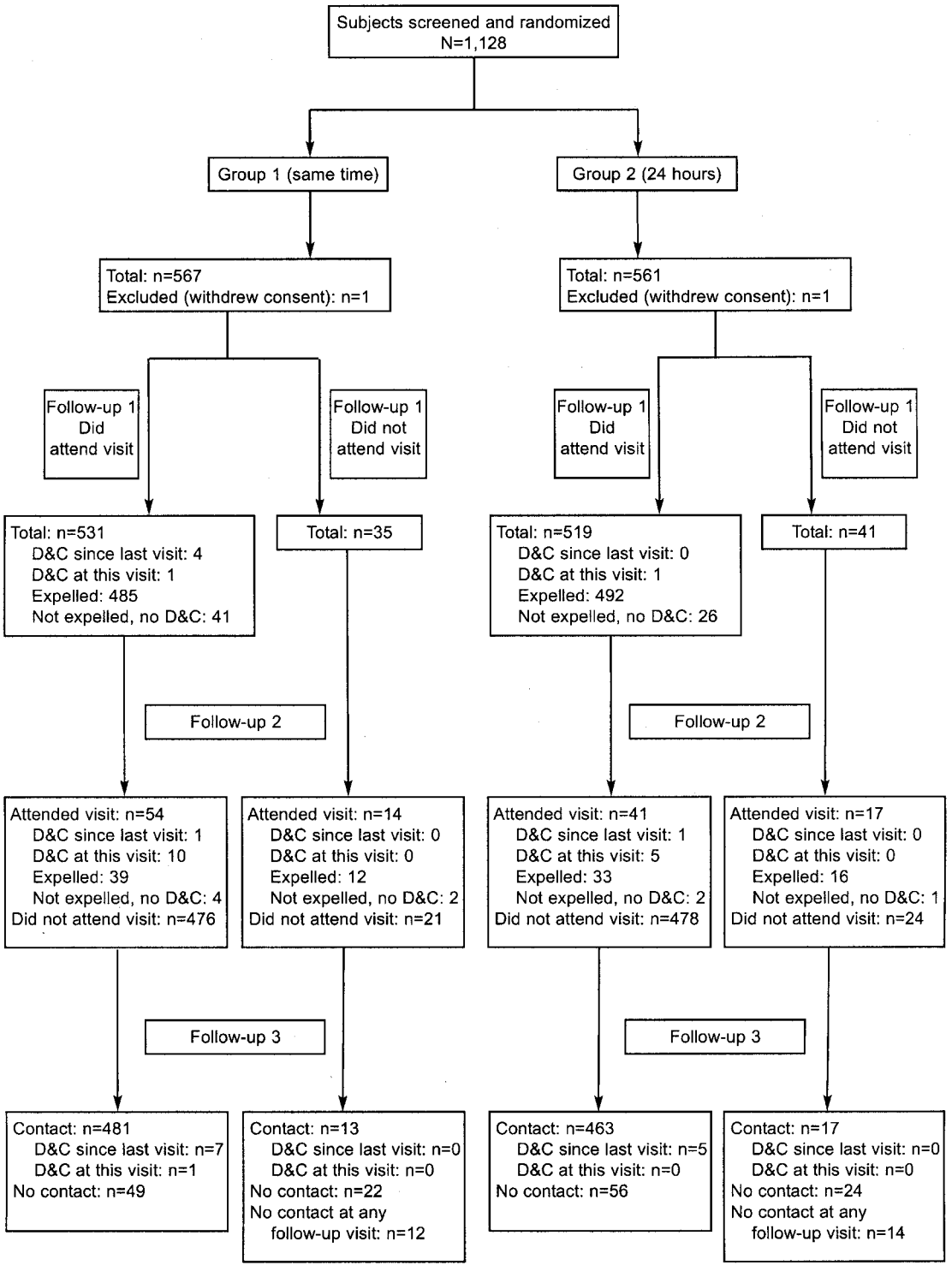

Fig. 1. Flow of study participants. Group 1: mifepristone 200 mg orally followed within 15 minutes by misoprostol 800 mcg vaginally. Group 2: mifepristone 200 mg orally followed by misoprostol 800 mcg vaginally 23–25 hours later. Follow-up 1: scheduled visit 7 (±1) days after mifepristone. Follow-up 2: scheduled visit 14 (±2) days after mifepristone. Follow-up 3: scheduled visit (if patient had not expelled pregnancy by follow-up 2 and pregnancy was nonviable) or scheduled phone call 5 weeks after mifepristone. Two subjects in group 1 and five subjects in groups 2 had dilation and curettage (D&C) after the final scheduled follow-up contact. One subject in group 1 received additional misoprostol at the day 35 visit and was considered a treatment failure.

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Table 1. Baseline Demographics of Study Population

	Study Treatment (Interval 0–15 min) (n=554)	Standard Treatment (Interval 23–25 h) (n=554)
Gestational age (d)	50±8	51±8
49 or less	266 (48)	229 (42)
50–56	159 (29)	172 (32)
57–63	129 (23)	145 (27)
Age (y)	26±6	26±6
Gravidity		
1	161 (29)	143 (26)
2	111 (20)	108 (20)
3	100 (18)	105 (19)
4	67 (12)	83 (15)
5 or more	115 (21)	107 (20)
Parity		
0	246 (44)	216 (40)
1	147 (27)	140 (26)
2	88 (16)	127 (23)
3 or more	73 (13)	63 (12)
Race		
White	371 (67)	331 (61)
Black	152 (27)	175 (32)
Other/none of these	31 (5)	40 (7)
Hispanic ethnicity	60 (11)	69 (13)
Marital status		
Single	426 (77)	430 (79)
Married	80 (14)	66 (12)
Divorced/separated	48 (8)	50 (9)
Living with partner*	218 (39)	182 (33)
Prior elective abortion(s)	234 (42)	231 (42)
Prior medical abortion(s)	56 (10)	68 (12)

Data are expressed as n (%) or mean±standard deviation.
* P=.04. All other variables P>.05 by Fisher exact test, χ^2 test, χ^2 test for linear trend, or Student t test, where appropriate.

the misoprostol at 21.45 hours, 22.75 hours, 25.33 hours, and 44.75 hours. Additionally, one subject in group 2 swallowed her misoprostol; she was at 57 days of gestation and failed treatment but was included in the analysis.

The efficacy of treatment in women with simultaneous administration was noninferior to that in women who administered the medications 24 hours apart (Table 2) (P=.003). If the women who were lost to follow-up were included as treatment failures, the outcomes were still equivalent (data not shown). However, the success rates with mifepristone followed by a single dose of misoprostol were different (Table 2) (91% versus 94%, respectively, P=.1 for noninferiority). There was no trend for decreasing success overall or with mifepristone and a single dose

Table 2. Complete Abortion Rate With Mifepristone 200 mg Followed by Misoprostol 800 mcg Vaginally*

	Study Treatment (Interval 0–15 min)	Standard Treatment (Interval 23–25 h)	P†
Overall (d)	95.1 (93.0–96.8) (n=554)	96.9 (95.1–98.2) (n=546)	.003
49 or less	95.5 (92.3–97.6) (n=266)	98.3 (95.6–99.5) (n=229)	.08
50–56	94.3 (89.5–97.4) (n=159)	95.3 (91.0–98.0) (n=172)	.051
57–63	95.3 (90.2–98.3) (n=129)	96.6 (92.1–98.9) (n=145)	.06
With single dose misoprostol (d)	91.0 (88.3–93.2) (n=554)	94.0 (91.6–95.8) (n=546)	.1
49 or less	90.6 (86.4–93.8) (n=266)	94.3 (90.4–96.9) (n=229)	.3
50–56	89.9 (84.2–94.1) (n=159)	93.0 (88.1–96.3) (n=172)	.3
57–63	93.0 (87.2–96.8) (n=129)	94.5 (89.4–97.6) (n=145)	.1

Data are expressed as % (95% confidence interval).
* Women who were lost to follow-up are excluded.
† Values are from Fisher exact test; P<.05 implies noninferiority.

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of misoprostol with increasing gestational age within study groups ($P>.3$ for all comparisons). There was also no difference for overall efficacy within study groups by study site (data not shown).

Treatment failures in groups 1 and 2 included viable pregnancy at the second follow-up visit (four women and one woman, respectively), persistent nonviable pregnancy at the second follow-up visit (seven and four women, respectively), persistent nonviable pregnancy at the third follow-up visit (two women and 1 woman, respectively), incomplete abortion (12 and 11 women, respectively), and subject request (two and no women, respectively).

Cramping began after a median of 2.5 hours (range 0 to 143 hours) and 1.7 hours (range –24 to 115 hours) after misoprostol administration in groups 1 and 2, respectively ($P<.001$). Bleeding began after a median of 3.7 hours (range 0 to 74 hours) and 2.0 hours (range –23 to 24 hours), respectively ($P<.001$). Pad count data were available for 549 (99.1%) and 544 (99.6%) women in groups 1 and 2, respectively. For these women, 31.5% and 36.8% reported that the heaviest amount of bleeding they experienced was soaking at least two pads in 1 hour ($P=.07$). There was also no difference in the number of women who reported that the heaviest amount of bleeding exceeded two pads in 1 hour (9.7% versus 10.1%, $P=.8$). Bleeding and spotting duration was not different between groups, lasting a median of 10 and 15 days, respectively, for women in group 1, and 10 and 14 days, respectively, for women in group 2 (Table 3).

Adverse effects are presented in Table 4. Women in group 1 had statistically significantly higher rates of nausea, diarrhea, and warmth or chills after misoprostol administration. Bleeding, cramping, and acceptability information are presented in Table 3. Complete pre- and posttreatment VAS assessments were available for 533 (96%) and 527 (97%) women in groups 1 and 2, respectively. The median level of pain reported on the post-questionnaire was 64 mm and 62 mm, respectively. The indicated level of pain was 3 mm higher in group 1 and 2 mm lower in group 2 than that anticipated on pretreatment VAS assessment in both groups. The findings were similar for bleeding, with a median posttreatment severity of bleeding of 63 mm and 64 mm for groups 1 and 2, respectively, and the differences as compared with pretreatment estimation of bleeding, 8 mm and 7 mm lower, respectively.

Serious adverse events occurred in 17 (1.5%) women. Four women (0.4%) received a transfusion, all in group 2, with gestational ages at initiation of treatment of 50, 51, 57, and 63 days. One subject in group 1 had a heterotopic pregnancy and had surgery for the tubal gestation after a successful medical abortion. Two other women had hospitalizations for events unrelated to the medical abortion. In addition to these serious events, 10 women (0.9%), five in each group, were diagnosed with acute pelvic infection after the medical abortion but were treated as outpatients. One of these infections (in group 2) occurred after a suction aspiration for an incomplete abortion.

Table 3. Cramping, Bleeding, and Acceptability Information With Mifepristone 200 mg Followed by Misoprostol 800 mcg Vaginally

	Study Treatment (Interval 0–15 min) (n=554)	Standard Treatment (Interval 23–25 h) (n=546)	*P*
Cramping			
Onset (h, median)	2.5	1.7	<.001*
Range (h)	0–143	24–115	
Bleeding			
Onset (h, median)	3.7	2.0	<.001*
Range (h)	0–74	−23–24	
Bleeding duration			
Spotting (d, median)	10	10	.98*
Bleeding (d, median)	15	14	.4*
Heaviest bleeding (%)†			
Soaked 2 pads/h or more	31.5	36.8	.07‡
Soaked 3 pads/h or more	9.7	10.1	.8‡
Acceptability (%)§			
Would recommend to a friend	94	94	1.0‡
Would choose method again	88	89	.5‡

* *P* value from Mann Whitney *U* test.
† Greatest number of pads soaked in 1 hour; data available for 549 (99.1%) and 544 (99.6%) women in groups 1 and 2, respectively.
‡ *P* value from Fisher exact test.
§ Data available from 545 (98%) and 536 (98%) women in groups 1 and 2, respectively.

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Table 4. Adverse Effects After Treatment With Mifepristone and Misoprostol

	Standard Treatment (Between Mifepristone and Misoprostol) (n=544)	Standard Treatment (After Misoprostol) (n=544)	Study Treatment (n=550)	P*
Nausea	29	51	58	.04
Vomiting	9	31	31	1.0
Diarrhea	5	26	35	.002
Warmth/chills	15	56	69	<.001
Headache	18	36	40	.2
Dizziness	9	37	39	.5
Cramping	21	96	97	.3
Spotting	9	–	–	–
Bleeding	6	100	100	.2

Data are expressed as percentages.
All subjects received mifepristone 200 mg and misoprostol 800 mcg vaginally. Women receiving standard treatment inserted the misoprostol 23–25 hours after mifepristone; those receiving study treatment inserted the misoprostol within 15 minutes of mifepristone administration.
* Comparing adverse effects after misoprostol treatment.

DISCUSSION

We have demonstrated that simultaneous administration of mifepristone and vaginal misoprostol is at least as effective as administration of the medications 24 hours apart. The sample size was calculated to evaluate noninferiority for the overall study sample and was not large enough to determine noninferiority at each gestational age range. However, even with smaller samples within each gestational age range, the abortion rates within each gestational age range were almost noninferior, with *P* values of .051 to .08 (Table 2), suggesting that larger trials would likely demonstrate equivalence. The point difference between the two treatment groups was 3%, the value declared a priori for noninferiority of the overall complete abortion rates. Given that the standard treatment group had a single-dose efficacy below 95%, the sample was not large enough to demonstrate this 3% difference to be noninferior.

The complete abortion rates[4,11,27] and adverse effect rates[11] in the standard treatment groups were similar to those previously published for this regimen, inferring external validity. In a prior trial comparing dosing intervals of 6–8 hours and 23–25 hours, women in the shorter interval group experienced fewer adverse effects and were less likely to experience significant bleeding.[11] Further shortening the interval to simultaneous dosing does not appear to create these same benefits in relation to adverse effects or bleeding. It is possible that the lack of a decrease is, in reality, the result of women experiencing adverse effects from both the mifepristone and misoprostol when administered simultaneously. Importantly, the differences, albeit statistically significant, are relatively small and are not likely to have clinical relevance as evidenced by the high and equal satisfaction in both treatment groups.

When this study was initiated, the "evidence-based" use of vaginal misoprostol was very common in the United States. In December 2005, Fischer et al[28] reported four deaths in the United States from *Clostridium sordellii* infection in women who had received mifepristone and vaginal misoprostol. A fifth infectious death, related to *C perfringens*, was reported at a Centers for Disease Control and Prevention meeting in May 2006.[29] One theory about infection and medical abortion is that mifepristone causes immunosuppression[30]; however, more widespread and serious infections would be occurring with more common organisms. In our current study, mild infection was diagnosed in less than 1% of subjects, a rate that is too low to support the idea of significant immunosuppression. Another theory is that use of the misoprostol vaginally increases the likelihood of infection with rare organisms. Such a finding would obviate the importance of this study. Additional recent reports have linked *C sordellii* infection to the deaths of eight women who recently had delivered infants either vaginally or by caesarean, two women who had miscarriages, and one woman who was infected during her menstrual period.[29] Obviously, neither mifepristone nor vaginal misoprostol was routinely used in these cases. For now, the evidence does not allow any inference as to whether the use of vaginal misoprostol as opposed to other routes impacts this risk. It is unclear if these rare infectious deaths with medical abortion are a direct effect of the medications used or a result of the process of medical abortion caused by the medications.

We, as providers and policy makers, may not be able to globally categorize how women assess risks and benefits of pregnancy options, and it is likely that such decisions are complex and personal. If there really is an increased risk of death with medical as compared with early surgical abortion, that difference

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is likely 1 per 100,000 with medical abortion[31] and 1 per million with early surgical abortion.[32] For perspective, the mortality risk with a term delivery is 1 per 10,000.[33] The risk of death is small regardless of pregnancy outcome, but the experience of each process for the woman is vastly different. The current study shows that women can use regimens with vaginal misoprostol without any time delay between medications with efficacy that is similar to those with a delay. Studies with a 6–8 hour interval demonstrate fewer adverse effects than those with a 24-hour interval. For women, what is the relative value of all of these differences? Would women prefer a vaginal route with fewer adverse effects or the ability to have their abortion completed sooner? Are changes in mortality from very, very rare to very, very, very rare more relevant to a woman than significant decreases in adverse effects or timing issues? These are questions we need to understand better to provide the best options for women.

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APPENDIX

The following institutions and persons participated in the MAST Study Trial. The principal investigators at each center are indicated by asterisks.

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Fertility control

Safety and acceptability of medical abortion through telemedicine after 9 weeks of gestation: a population-based cohort study

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Objective To assess the safety and acceptability of abortion through telemedicine at $>9^{+0}$ weeks of gestation.

Design Cohort study.

Setting Poland.

Population Six hundred and fifteen women who requested and underwent a abortion through telemedicine from 1 June to 31 December 2016.

Methods Risks of adverse outcomes were calculated as adjusted odds ratios (aORs) with 95% confidence intervals (95% CIs) by unconditional logistic regression according to gestational age at abortion: ≤9 or >9 weeks of gestation.

Main outcome measures Self-reported clinical visits for complaints related to the abortion within 0–1 days of the treatment, heavy bleeding, pain or bleeding more than expected, and low satisfaction.

Results Among women undergoing a abortion at ≤9 or >9 weeks of gestation, 3.3 versus 11.7% went to hospital with concerns within 0–1 days of the termination (aOR 3.82, 95% CI 1.90–7.69). Among women undergoing a abortion from 11^{+1} to 14^{+2} weeks of gestation, the rate was 22.5% (aOR 9.20, 95% CI 3.58–23.60). Among women undergoing a abortion at ≤9 or >9 weeks of gestation, the rate of heavy bleeding was 6.8 versus 10.1% (aOR 1.65, 95% CI 0.90–3.04), the rate of low satisfaction was 2.4 versus 1.6% (aOR 0.69, 95% CI 0.14–3.36), the rate of bleeding more than expected was 45.6 versus 57.8% (aOR 1.26, 95% CI 0.78–2.02), and the rate of pain more than expected was 35.6 versus 38.8% (aOR 1.11, 95% CI 0.71–1.71).

Conclusions Medical abortion through telemedicine at >9 weeks of gestation is associated with a higher risk of same-day or day-after clinical visits for concerns related to the procedure, and this risk increases with gestational age. Self-reported rates of heavy bleeding, low satisfaction, or unmet expectations with medical abortion do not increase with gestational age.

Keywords Medical abortion, post-abortion care, safe and unsafe abortion, telemedicine.

Tweetable abstract A cohort study shows that abortion through telemedicine at >9 weeks of gestation is associated with more hospital visits but not with increased bleeding.

Linked article: This article is commented on by A Lavelanet, p. 618 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.15597.

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Introduction

Twenty-five million unsafe abortion and 43 000 termination-related maternal deaths are estimated to occur each year, predominantly in countries with restrictive abortion laws.[1,2] To investigate alternative options for providing abortion care is a stated research priority by the World Health Organization (WHO), in an effort to expand global access to safe abortion.[3]

Today, telemedicine abortion services bridge the lack of access to safe abortion in many countries. The abortion law in Poland is estimated to prohibit the termination of unwanted pregnancies in 97% of cases, allowing the procedure only in case of severe danger to the life of the woman or fetus, or if the pregnancy results from a criminal act, such as rape or incest.[4,5] Conscientious objection is constitutionally sanctioned, and the Polish parliament is now considering further restrictions to the legal access of abortion.[6] Many

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women in Poland wanting an abortion use the telemedicine service Women on Web (WoW), which provides online consultation and guidance and abortion medication by post.[7]

The gestational age limit for outpatient (at-home) self-administration of Misoprostol recommended by the WHO is 9 weeks of gestation, and this limit is adhered to in many countries.[8] The Food and Drug Administration (FDA) in the USA increased this limit to 10 weeks of gestation in 2016.[9] Home medical abortion and post-abortion evaluation up to 9 weeks of gestation, through regular (non-telemedicine) abortion clinics, have been shown to be non-inferior to in-hospital abortion, and are well tolerated.[10–12] Several studies have also indicated that medical abortion through telemedicine, up to 9 weeks of gestation, is safe and well tolerated in settings with an established healthcare infrastructure.[13–15] Outcomes after abortion through telemedicine after 9 weeks of gestation are, however, much less documented in published research.

The aim of this study was thus to assess whether medical abortion through telemedicine performed after 9 weeks of gestation is comparable, in terms of safety and acceptability for women, with abortion performed at or before 9 weeks of gestation.

Methods

We performed a retrospective cohort study investigating self-reported adverse outcomes among all women having requested a abortion through the telemedicine service WoW in Poland from 1 June to 31 December 2016. We included all women who were approved for home abortion with Mifepristone and Misoprostol, who received the medication by post, who confirmed taking the medication, and who provided follow-up through the online questionnaire or by email communication.

Women access the WoW telemedicine service and make a request for a abortion through the website www.womenonweb.org. They fill in an online questionnaire, where they self-report their obstetric history and gestational age, which is assessed by a physician at WoW. Routinely the gestational age limit to be eligible for a abortion through the service is 70 days of gestation at consultation. If no contraindications to home abortion exist, medical abortion treatment according to WHO recommendations (200 mg of mifepristone orally followed by 800 + 400 + 400 micrograms of the prostaglandin misoprostol to be administered sublingually, 1–2 days later) are sent by post to the woman's requested address.[8] If a woman is approaching 9 weeks of gestation, an additional four misoprostol tablets (200 μg each) are sent. The service and medication are donated for free if women are unable to make a donation. Online 24-hour support is available to women during and after the abortion by helpdesk staff trained in guidance for abortion. Five weeks after the medication is sent, the service sends a follow-up evaluation form by email including questions about symptoms during and after the abortion, complications of the abortion, in-hospital interventions, and experience of the abortion. Answers in the follow-up form are categorical. Women specify whether they took their medication 'less than 1 week after the package arrived' or 'more than 1 week after the package arrived'. If they went to hospital they specify 'yes, because I wanted to have an ultrasound like I was advised' or 'yes, because I had complaints and was worried I might have a complication'. If they had complaints they may specify: 'I was bleeding more than 2 maxi pads each hour for more than 2 hours' or 'I had pain that continued several days after the abortion and did not go away'. WoW send two follow-up evaluation form reminders in the case of non-response. Many women who do not fill in the questionnaire still confirm taking the medication and provide follow-up information through direct email communication.

Comparison groups

We compared women with a gestational age at abortion intake of abortion medication above 63 days of gestation, corresponding to 9 weeks of gestation (exposed group), with women at a gestational age at or below 63 days of gestation ($\leq$9 weeks of gestation, non-exposed group). We calculated the gestational age at intake of abortion medication by summing the gestational days according to the last menstrual period (LMP) reported in the online consultation, days until delivery of the medication, and the number of days until the woman took the medication. If a woman reported taking the medication within 1 week of delivery, we registered the gestational age at intake as that corresponding to the day of delivery. If a woman reported taking the medication later than 1 week after delivery, we registered the gestational age at intake as that corresponding to 7 days after delivery. If the woman specified her intake date through email, we registered the gestational days at intake corresponding to that date, otherwise we registered the gestational day corresponding to the day of delivery. In a subanalysis of the association between gestational age and emergency hospital visits, we stratified gestational age in the higher gestational age group into the span from 9^{+1} to 11^{+0} weeks of gestation and from 11^{+1} to 14^{+2} weeks of gestation.

Outcomes

The primary outcomes related to safety were heavy bleeding and a hospital or clinic visit for a concern related to the abortion within 0–1 days of the termination. Both these outcomes aimed to identify acute complaints related to the abortion. The outcome of heavy bleeding was registered if a woman reported in the follow-up evaluation form that 'I was bleeding more than 2 maxi pads each hour for more than 2 hours' during the abortion, or if she reported in her

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email communication heavy bleeding requiring a clinical assessment at any moment during the process of abortion.

The outcome 'clinical visit for a complaint within 0–1 days of the abortion' was registered if a woman reported, either in the follow-up evaluation form or in email communication, a hospital or clinic visit on the same day or on the day after taking the misoprostol, and also reported one of the following outcomes in the evaluation form: that she visited a hospital 'because I had concerns that I might have a complication', that she had heavy bleeding as defined above, or that she had pain 'that continued several days after the abortion and did not go away'. We stipulated that most clinical visits occurring in the immediate days following the termination would take place because of acute complaints related to the abortion (i.e. that most women would not seek medical attention immediately, unless they had symptoms that they believed required clinical attention). We added the presence of a suspected complication, heavy bleeding, and/or pain to this outcome in order to exclude the few anticipated cases where women went to a clinic within this time frame without symptoms.

The primary outcomes related to acceptability were unmet expectations for the experience of abortion and low satisfaction with the procedure. Unmet expectations in relation to pain were defined as an answer of 'more than expected' or 'much more than expected' to the question 'How much pain did you have?' Unmet expectations in relation to bleeding were defined as an answer of 'no, it was more than expected' or 'no, it was much more than expected' to the question 'Was the bleeding after taking the medication as expected?' Dissatisfaction with the abortion procedure was defined as an answer of 'no, I was dissatisfied' or 'no, I was very dissatisfied' to the question 'Was medical abortion an appropriate method for you?'

Secondary outcomes were surgical evacuation after abortion (dilatation and curettage or vacuum aspiration), and any medical intervention after the abortion in the form of surgical evacuation, blood or fluid transfusion, additional misoprostol treatment, or antibiotic treatment.

Confounding factors

Confounding factors adjusted for in the regression analysis were the woman's age at consultation and payment of a donation for the clinical service, which was used as proxy for financial status. Age and financial status may influence both the gestational age at which a woman requests a abortion and her self-reported symptoms and experience of the termination process.[16]

Data relating to exposures, outcomes, and confounding variables were recorded from the WoW pre-abortion consultation form, post-abortion follow-up evaluation form, and in email communication recorded in the patient records. If no answer was provided or an unintelligible answer was provided in relation to the outcomes, the variable was registered as missing. In the case of contradictory responses relating to the outcomes of whether, when, and why a women visited hospital after the abortion, an assessment was made of the written communication to the clinic or extra comments were made in the free-text portion of the questionnaire, to see if the correct answer could be ascertained.

Core outcomes sets, patient involvement, and study funding

Core outcome sets for medical abortion are yet to be formulated, so our study outcomes adhere to the overall aim of assessing the safety, effectiveness, and acceptability of medical abortion.[17] The study question was formulated based on the clinical demands of the telemedicine service, but the study did not have any direct public or patient involvement. It was funded by grants from the Swedish Research Council and the Karolinska Institutet.

Statistical analysis

Medians and ranges for non-normally distributed data and rates and associated risks were calculated group-wise for each gestational age group. Comparisons of medians between groups were performed using an independent-samples median test for non-normally distributed data. Odds ratios were calculated using unconditional regression analysis. The null hypothesis was rejected where $P < 0.05$. Statistical analysis was carried out using IBM SPSS Statistics for Windows, Version 23.0. (IBM Corp., Armonk, New York, NY, USA). The sample size was established in order to be able to show, with 80% power and a 95% confidence level, a doubling in the rate of our primary safety outcomes after abortion at ≤9 or >9 weeks of gestation, and with an expected baseline incidence of heavy bleeding and clinical visits for complaints related to the procedure within 0–1 days of 5% for abortion performed ≤9 weeks of gestation, and with a presumed loss to follow-up of 30%.

In order to address the uncertainty in the data regarding gestational age at intake of medication, we performed a sensitivity analysis where gestational age was increased by 7 days for all participants. This analysis allowed for the fact that women who reported taking the medicine 'within 1 week' of delivery of the medication could have taken the tablets after 7 days (and not at the day of delivery, as assumed in our main analysis), and that women who reported their intake 'after 1 week' could have taken the tablets 2 weeks after delivery (i.e. 7 days later than what is assumed in our main analysis).

Results

During the study period, 1220 women in Poland requested a medical abortion through WoW. All were approved for

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medical abortion and sent medication. The medication was not used by 166 women (13.6%). Intake was unconfirmed for 427 (35%) women who provided no follow-up information and were defined as lost to follow-up (LTFU). Twelve women confirmed intake through communication with the service but provided no follow-up with regards to the primary outcomes of interest. The main analysis consisted of 615 women who confirmed their intake and provided information for one or more of our primary outcomes, either in the follow-up evaluation (n = 419) or through email communication (n = 196). A study flowchart specifying the reasons for non-intake is shown in Figure 1.

The median age at first consultation for women who performed a abortion was 28 years (range 16–56 years) and 26 years (range 16–45 years) among women at ≤9 or >9 weeks of gestation, respectively (P = 0.13). The median gestational age at first consultation was 37 days of gestation (range 13–53 days of gestation) and 49 days of gestation (range 23–79 days of gestation) for women at ≤9 or >9 weeks of gestation, respectively (P < 0.001). At the time of intake of medication, 25.7% were at ≤7 weeks of gestation, 43.7% were between 7^{+1} and 9^{+0} weeks of gestation, 24.1% were between 9^{+1} and 11^{+0} weeks of gestation, and 6.5% were between 11^{+1} and 14^{+2} weeks of gestation. Among women at ≤9 or >9 weeks of gestation, 2.1 and 4.8%, respectively, did not make a donation to the clinic (OR 2.34, 95% CI 0.91–5.98). Background variables are summarised in Table 1.

Three women at ≤9 weeks of gestation (0.7%) and two women at >9 weeks of gestation (1.1%) had a viable or suspected viable pregnancy after the intake of medication (OR 1.57, 95% CI 0.26–9.52). Rates and associated risks of continuing pregnancy, symptoms during the abortion, medical interventions, and reason and timing of clinical visits during or after the abortion are presented in Table S1.

Fourteen out of 427 women at ≤9 weeks of gestation (3.3%) and 22 out of 188 women at >9 weeks of gestation (11.7%) went to hospital or clinic on the first or second day of the abortion for concerns related to the termination (aOR 3.82, 95% CI 1.90–7.69). In a stratified analysis this correlated to 8.8% of women between 9^{+1} and 11^{+0} weeks of gestation (aOR 2.76, 95% CI 3.94–23.57) and 22.5% of women between 11^{+1} and 14^{+2} weeks of gestation (aOR 9.20, 95% CI 3.58–23.60). The incidence of self-reported heavy bleeding at any point during the termination process was 6.8% among women at ≤9 weeks of gestation and 10.1% among women at >9 weeks of gestation (aOR 1.65, 95% CI 0.90–3.04). Among these women, none at ≤9 weeks of gestation and one at >9 weeks of gestation received a blood transfusion. One woman at >9 weeks of gestation received a blood transfusion but reported no heavy bleeding.

Extra medical treatment in the form of either surgical evacuation, antibiotic or misoprostol treatment, fluid or blood transfusion at any moment after the abortion was reported by 18.3 and 29.0% of women at ≤9 and >9 weeks of gestation respectively (aOR 1.84, 95% CI 1.13–3.00). The incidence of surgical evacuation alone was 12.5% among women at ≤9 weeks of gestation and 22.6% among women at >9 weeks of gestation (aOR 2.04, 95% CI 1.18–3.32). Forty-eight out of the 65 women (73.8%) who underwent surgical evacuation reported no heavy bleeding after the abortion, and 39 (60%) reported neither heavy nor prolonged bleeding.

Incidence rates and associated risks for primary and secondary outcomes related to safety and acceptability are presented in Tables 2 and 3.

Low or very low satisfaction with the procedure was reported by 2.4% of women at ≤9 weeks of gestation and by 1.6% of women at >9 weeks of gestation (aOR 0.69, 95% CI 0.14–3.36). Among women at ≤9 weeks of gestation and >9 weeks of gestation, 45.6 and 57.8%, respectively, reported that the blood loss was more than expected (aOR 1.26, 95% CI 0.78–2.02), and 35.6 and 38.8%, respectively, reported the pain to be more than expected (aOR 1.11, 95% CI 0.71–1.71). Incidence rates and associated risks for outcomes related to patient acceptability are presented in Table 2.

Women LTFU were of similar median age at first consultation (29 versus 27 years, P = 0.08), median gestational age at first consultation (40 versus 39 years, P = 0.61), and median gestational age at delivery of medication (57 versus 56 days, P = 0.37), compared with women who confirmed their intake of medication. They were, however, more likely to have been at >9 weeks of gestation at first consultation (OR 1.34, 95% CI 1.02–1.74), and were more likely not to have paid the service fee (OR 2.54, 95% CI 1.44–4.49). The sensitivity analysis of women LTFU is available in Table S2.

In the sensitivity analysis where we assumed the intake of abortion medication 1 week later than the assumed intake in the main analysis, 135 women were re-categorized from ≤9 to >9 weeks of gestation. Among women at ≤9 or >9 weeks of gestation in this analysis, 5.8 and 9.6%, respectively, reported heavy bleeding (aOR 1.80, 95% CI 0.95–3.43), and 1.4 and 9.9%, respectively, reported clinical visits for complaints within 0–1 days (aOR 3.91, 95% CI 1.65–9.25). Sensitivity analysis addressing the uncertainty of gestational age is available in Table S3.

Discussion

Main findings

In this study, medical abortion through telemedicine at >9 weeks of gestation compared with ≤9 weeks of gestation

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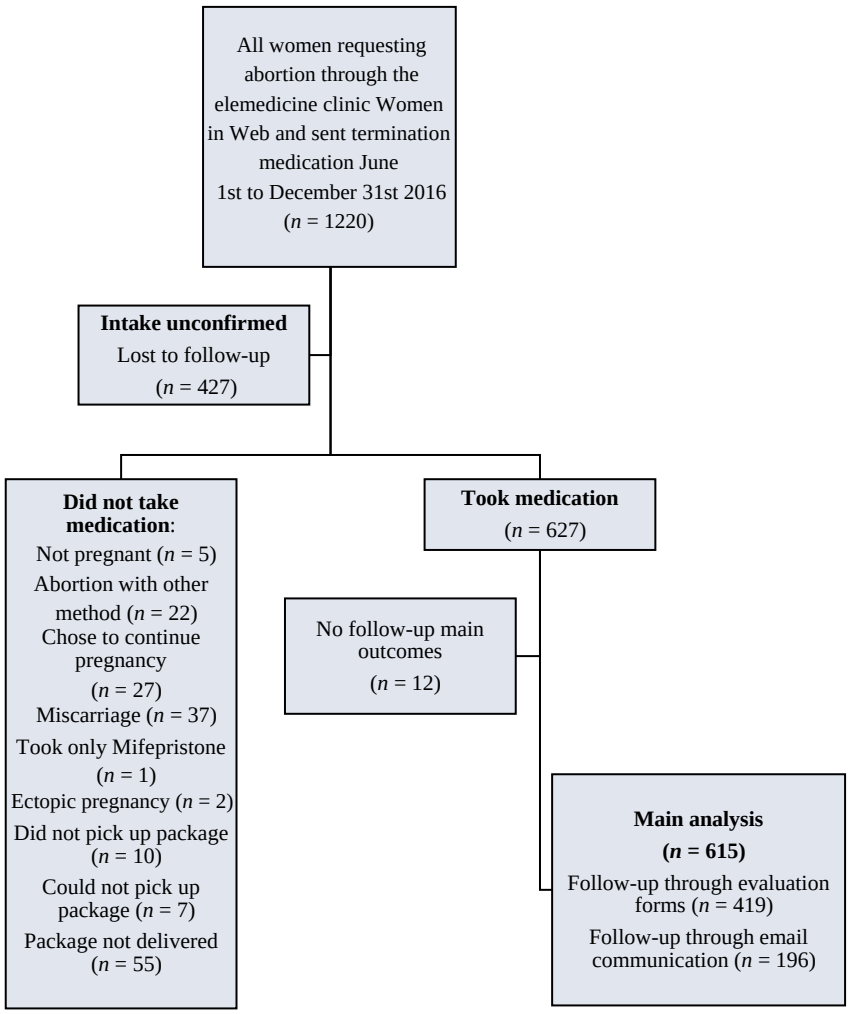

Figure 1. Flowchart of the inclusion of women to the study based on 1220 women requesting a abortion through telemedicine and sent termination medication from 1 June to 31 December 2016.

was associated with an increased rate of immediate clinical visits for concerns related to the termination procedure, and this rate increased with increasing gestational age. The rate of reported heavy bleeding was not increased but both the rate of surgical evacuation and the rate of other medical treatments during or after the abortion were increased among women at >9 weeks of gestation. Satisfaction levels and rates of met expectations were similar across gestational age groups.

Strengths and limitations

Women reported the timing of the abortion as either within or after a week of receiving their medication, and this was assumed to correspond to intake on the day of medication delivery or 1 week after delivery, respectively, so the gestational age at abortion in this study is the minimum gestational age at which the abortion could have been initiated. Theoretically, gestational age-specific adverse outcomes may therefore be overestimated and some women in the lower gestational group may be misclassified, which might underestimate the relative differences between groups. In the sensitivity analysis addressing this bias, however, the risks and significance level of heavy bleeding and hospital visits within 0–1 days for a complaint, associated with a gestational age of >9 weeks, were similar to those seen in the main analysis. The LTFU rate was high but was in line with previous studies on abortion, and was lower than other studies on abortion through telemedicine.[15,18–20] Women LTFU were more likely to be at >9 weeks of gestation at consultation and were more likely not to have made a donation to the clinic. Overall this may indicate lower financial means but also a lower likelihood of actual intake. The LTFU rate was slightly higher (35%) than what we had stipulated for our power calculation (30%), so it is possible that a larger sample would have shown significant differences in some outcomes. Symptoms were self-reported,

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Table 1. Background variables among 615 women in Poland having requested a medical abortion through telemedicine at ≤9 or >9 weeks of gestation, respectively, between 1 June and 31 December 2016

	Gestational age at abortion		*P* value[a]/OR (95% CI)
	≤9 weeks of gestation (*n* = 427)	>9 weeks of gestation (*n* = 188)	
Age in years at consultation, median (range)	28 (16–56)	26 (16–45)	*P* = 0.13
Gestational days at consultation, median (range)	37 (13–53)	49 (23–79)	*P* < 0.001
Gestational age at intake of termination medication, median (range)	53 (27–63)	70 (64–100)	*P* < 0.001
≤7 weeks (*n*, % of total)	158 (25.7)		
7^{+1}–9^{+0} weeks (*n*, % of total)	269 (43.7)		
9^{+1}–11^{+0} weeks (*n*, % of total)		148 (24.1)	
11^{+1}–14^{+2} weeks (*n*, % of total)		40 (6.5)	
Did not make donation for service, *n* (%)	2.1%	4.8%	2.34 (0.91–5.98)
Difficulty paying donation[b]			
No	165 (54.8%)	56 (47.5%)	Ref.
Yes	133 (44.2%)	60 (50.8%)	1.33 (0.87–2.04)
Missing	3 (1.0%)	2 (1.7%)	

[a]Difference between medians tested using an independent-samples median test.
[b]Based on evaluations only (301 women at <9 weeks of gestation and 118 women at >9 weeks of gestation).

which may not be representative of a clinical assessment. Data were extracted from standardised evaluation forms, however. The outcome data extracted from email communication was restricted to reported hospital visits for specific symptoms. The level or direction of subjectivity is therefore not expected to vary between groups, making relative comparisons valid.

The data upon which this study is based represent a patient population outside the formal health sector, for which there is otherwise little access to quantitative data. The data were collected prospectively, which reduces the risk of investigator bias.

Interpretation

In this study women at >9 weeks of gestation had an almost four-fold increased risk of clinical visits within 0–1 days of the abortion for a concern related to the termination, compared with women at ≤9 weeks of gestation. The rate of these immediate clinical visits increased with increasing gestational age, and increased nine-fold at >11 weeks of gestation compared with ≤9 weeks of gestation. The rate of heavy bleeding, strong and prolonged pain during the abortion, experiencing pain or bleeding more than expected, symptoms that may be expected to account for most emergency consultations, were however not significantly increased among women at >9 weeks of gestation. Some studies on abortion indicate that both blood loss and pain during medical abortion increase with gestational age at abortion up to 9 weeks of gestation,[21] even to the extent that it affects the acceptability to women,[22] but other studies have not supported this.[23,24] Although it is not possible to assess the clinical validity of the woman's decision to seek hospital care, it can be assumed that she herself found that her symptoms warranted assessment. It is possible that women at >9 weeks of gestation went to the hospital more readily because they assumed that their gestational age put them at higher risk of complications and wanted to pre-empt these. Although the categorical survey data show that there was no greater reporting of heavy bleeding amongst women at >9 weeks of gestation, it is possible that women at >9 weeks of gestation were more likely to have symptoms towards the extremes of heavy bleeding and pain, which mandated hospital assessment. Another possible explanation is that more women at >9 weeks of gestation, particularly those approaching 12 weeks of gestation, would have needed additional doses of misoprostol in order to complete the abortion at home. WoW routinely send four extra misoprostol tablets if a woman is at >9 weeks of gestation (i.e. 800 + 400 + 400 micrograms of misoprostol), but the service cannot always predict who will be at this gestational age at the time of the abortion. It may take into consideration whether additional online support might benefit women at higher gestational ages. Women in both gestational age groups reported a high rate of unexpected pain, which indicates that the information about what symptoms to expect during the abortion, as well as specific recommendations for pain relief, may need to be amended in the clinical guidance information provided.

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Table 2. Rates and risks of outcomes affecting patient safety and acceptability after medical abortion at ≤9 or >9 weeks of gestation, respectively, among women in Poland having requested a abortion through telemedicine between 1 June and 31 December 2016

Safety outcomes[a]	Gestational age at abortion		Unadjusted OR, 95% CI	Adjusted[d] OR, 95% CI
	≤9 weeks of gestation (*n* = 427) *n* (%)	>9 weeks of gestation (*n* = 188) *n* (%)		
Heavy bleeding[b]				
No	382 (89.5)	164 (88.8)	Ref.	Ref.
Yes	29 (6.8)	19 (10.1)	1.55 (0.88–2.99)	1.65 (0.90–3.04)
Missing	2 (0.5)	2 (1.1)		
Hospital visit for complaints within 0–1 days[c]				
No	391 (91.6)	161 (85.6)	Ref.	Ref.
Yes	14 (3.3)	22 (12.2)	**3.82 (1.91–7.65)**	**3.82 (1.90–7.69)**
Missing	22 (5.2)	5 (2.7)		
Acceptability outcomes[e]	**≤9 weeks of gestation (*n* = 295)**	**>9 weeks of gestation (*n* = 124)**		
Pain > expected[f]	107 (36.3)	49 (39.5)	1.15 (0.75–1.77)	1.11 (0.71–1.71)
Bleeding > expected[g]	69 (23.4)	35 (28.2)	1.29 (0.80–2.07)	1.26 (0.78–2.02)
Dissatisfaction[h]	7 (2.4)	2 (1.6)	0.67 (0.14–3.29)	0.69 (0.14–3.36)
Secondary outcomes[e]	**≤9 weeks of gestation (*n* = 295)**	**>9 weeks of gestation (*n* = 124)**		
Surgical intervention[i]	37 (12.5)	28 (22.6)	**2.03 (1.18–3.50)**	**2.04 (1.18–3.32)**
Any treatment[j]	54 (18.3)	36 (29.0)	**1.83 (1.12–2.97)**	**1.84 (1.13–3.00)**

n, number; OR, odds ratio; CI, confidence interval.
Bold indicates statistically significant values.
[a]Outcome data based on evaluations and email follow-up (total *n* = 615).
[b]'I was bleeding more than 2 maxi pads each hour for more than 2 hours' reported in follow-up form or blood-loss requiring clinical visit reported by email.
[c]Hospital visit on the same day as the abortion or the day after and (with reason for visit reported as 'yes, because I had complaints and was worried I might have a complication', 'I was bleeding more than 2 maxi pads each hour for more than 2 hours', or 'I had pain that continued several days after the abortion and did not go away').
[d]Adjusted for age at abortion and having paid the service fee; 4 and 27 women, respectively, with missing data were excluded from the regression analysis of heavy bleeding and hospital visits within 0–1 days.
[e]Outcome data based on follow-up evaluations only (total *n* = 419).
[f]Answered 'more than expected'/'much more than expected' to 'How much pain did you have?'.
[g]Answered 'no, more than expected'/'no, much more than expected' to 'Was the bleeding after taking the medication as expected?'.
[h]Answered 'no, I was dissatisfied'/'no, I was very dissatisfied' to 'Was medical abortion an appropriate method for you?'
[i]Vacuum aspiration or dilatation and curettage after abortion.
[j]Antibiotic or misoprostol treatment, fluid or blood transfusion, vacuum aspiration, or dilatation and curettage.

Despite an increased rate of clinical visits within the first 2 days, the satisfaction rate with the abortion procedure was 95.2% among women at >9 weeks of gestation, compared with 97.9% among women at ≤9 weeks of gestation. The high satisfaction rates suggest that it is unlikely that women in either gestational group experienced their physical or mental health to be in jeopardy.

Women at >9 weeks of gestation had a higher risk of medical treatment or interventions during or after the abortion, mainly with an increased rate of surgical evacuation. The increasing rate of surgical evacuation with gestational age at abortion is supported by previous studies.[15,20,25] Complete abortion without intervention has, however, been estimated to occur in 94.5–97.0% of medical abortion in the first trimester, which means that the rate of surgical evacuation in both gestational groups was higher than the expected.[26–30] Most women in this study who underwent surgical evacuation reported neither heavy nor prolonged bleeding. The rates of surgical evacuation found are in line with previous studies on telemedicine abortion in Poland, but are higher than reported in a recent study on telemedicine abortion in Australia.[18,19,31] It is possible

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Table 3. Subanalysis of the rate and risk of a hospital visit for complaints within 0–1 days of the abortion stratified by gestational age among 615 women in Poland having requested a abortion through telemedicine between 1 June and 31 December 2016

Gestational age	Hospital visit for complaints within 0–1 days[a]				
	No, *n* (%)	Yes, *n* (%)	Missing, *n* (%)	OR[c], 95% CI	aOR[b], 95% CI
≤9 weeks	391 (91.6)	14 (3.3)	22 (5.2)	Ref	Ref
9^{+1}–10^{+6} weeks	132 (89.2)	13 (8.8)	3 (2.0)	**2.75 (1.26–6.00)**	**2.76 (1.26–6.02)**
11^{+0}–14^{+2} weeks	29 (72.5)	9 (22.50)	2 (5.0)	**8.67 (3.46–21.72)**	**9.20 (3.58–23.60)**

Significant differences indicated in bold.
[a]Hospital visit on the same day as the abortion or on the day after (reason for visit reported as 'yes, because I had complaints and was worried I might have a complication', 'I was bleeding more than 2 maxi pads each hour for more than 2 hours', or 'I had pain that continued several days after the abortion and did not go away').
[b]Adjusted for age at abortion and having made a donation for the service.
[c]Regression analysis based on 588 women, with women with missing values on outcome data excluded (n = 27).

therefore that the high rates found in this and in previous studies reflect either clinical practice in the assessment of 'miscarriage' in Poland or existing financial incentives to performing surgical procedures, rather than clinical indications. This is supported by the comparatively low rate of post-abortion additional misoprostol treatment, which is an efficient and non-invasive treatment for incomplete abortion.[32] The rate of continuing pregnancy was similar between groups and is in line with previous studies.[33] A larger sample size would be expected to show an increasing rate of continuing pregnancy with increasing gestational age at abortion.

Our results are probably generalizable to study populations in similar socio-economic settings. A lack of access to safe abortion continues to be a major health impediment for women globally as a result of questions of legality, stigma, or infrastructural constraints.[1,2,34] Establishing whether medical abortion through telemedicine can be performed at gestational ages of >9 weeks, without risking safety and acceptability standards, is a step towards expanding this alternative model of abortion care to women who are otherwise at high risk of the consequences of unsafe abortion.

Conclusion

Medical abortion through telemedicine at >9 weeks of gestation is associated with a higher rate of clinical visits for complaints related to the termination procedure in the immediate days following the abortion, compared with abortion at ≤9 weeks of gestation. It is associated with an increased risk of post-abortion treatment and intervention, but not with a lower rate of satisfaction or unmet expectations. Abortion through telemedicine seems to be safe and acceptable to women at >9 weeks of gestation, but may necessitate adjustments to misoprostol doses, online information, and support.

Disclosure of interests

RG is the founder and current director of Women on Web, the source for the participant data in the study. Otherwise, all authors report no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could appear to have influenced the submitted work. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

RG had the original idea for the study. ME designed the study, performed the main analysis, wrote the first and final draft of the manuscript, and is the guarantor for the article. LB contributed substantially to the literature review and data analysis. RG and KGD contributed to the study design and interpretation of the results. KGD, RG, and LB contributed to manuscript revision.

Details of ethics approval

Women gave permission in their initial consultation for their anonymised data to be used for statistical and research purposes. Ethical permission for the study was granted through a broad ethics approval for studies on WoW data granted by the Local Ethics Committee at Karolinska Institutet, Stockholm, Sweden, on 27 January 2010 (dnr 2009/2072-31/2).

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Rates and risks of symptoms and intervention after medical abortion at ≤9 or >9 weeks of gestation, respectively, among 419* women in Poland having requested a abortion through telemedicine between 1 June and 31 December 2016.

Table S2. Sensitivity analysis 1.

Table S3. Sensitivity analysis 2.■

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Telemedicine: are we still falling short?

A Lavelanet

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Linked article This is a mini commentary on M Endler et al., pp. 609–618 in this issue. To view this article visit https://doi.org/10.1111/1471-0528.15553

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Telemedicine has transformed the way in which healthcare services are delivered. Telemedicine can connect multiple remote sites, reducing both direct and indirect costs for individuals, and serving as an asset for burdened or under-resourced health systems. Through telemedicine, inequities related to the geographical distribution of medical services are reduced, thereby improving access to communities that are traditionally underserved (World Health Organization. Telemedicine: opportunities and developments in Member States: report on the second global survey on eHealth, 2009). These benefits are magnified for abortion services, where access can be more difficult because of stigma and fear of persecution, especially in restricted settings.

Endler et al. assess the safety and acceptability of medical abortion provided through telemedicine beyond 9 weeks of gestation (Endler et al. *BJOG* 2019;126:609–18). The work of Endler et al. is important, especially as telemedicine for later gestational ages is being employed. Their results confirm what other studies show: abortion the late first trimester is safe (Kapp et al. *Contraception* 2018; https://doi.org/10.1016/j.contraception.2018.11.002).

Some of the author's conclusions warrant further discussion, however. Women with pregnancies of 9 weeks of gestation or longer have a higher rate of hospital visits for concerns related to the abortion, leading to an increased risk of post-abortion treatment and intervention. Women still find the procedure acceptable, which includes satisfaction with the procedure and whether expectations related to the experience are met. The authors correctly highlight that acceptability is about so much more than whether medical abortion is the right choice of method, but greater discussion could have been afforded to the acceptability of telemedicine itself and how telemedicine can better facilitate managing women's expectations as they go through the process of abortion. The authors state that information about what symptoms to expect during the abortion, at least in relation to pain and specific recommendations for pain relief, may need to be overseen in the clinical guidance information provided. This acknowledgment by the authors highlights that medical abortion provided through telemedicine is perhaps still falling short on managing women's expectations.

Dawson et al. (*BMC Health Serv Res* 2016;16:612) include acceptability as an important component of accessing comprehensive abortion services. Questions as to whether the information, explanation, and services provided accommodate social norms and values, and whether women find self-management easy to use, are important to assess. A qualitative evidence synthesis review by Wainwright et al, including research from legal and legally restricted contexts, demonstrates that women self-managing their abortion appreciate counselling that prepares them for variability in personal experiences. Women need pragmatic information related to managing expulsion at home (Wainwright et al. *Reproductive Health Matters* 2016;24:155–67). Increased opportunities for partners to be involved (where desired) are seen as a benefit to alleviate partner concerns related to pain or bleeding (Wainwright et al. *Reproductive Health Matters* 2016;24:155–67). Yet, although access to such counselling improved confidence and acceptability, anxieties related to managing complications persist.

Thus, as Endler et al. note, additional information and support may be needed by women, but it appears that greater guidance is still needed to those providing abortion services through telemedicine on how best to do this. Time and resources should be directed into collecting data related to how well we are responding to the needs of these women in order to maximise the benefits of telemedicine.

Disclosure of interests

None declared. A completed disclosure of interest form is available to view online as supporting information.

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Life and Family Initiative

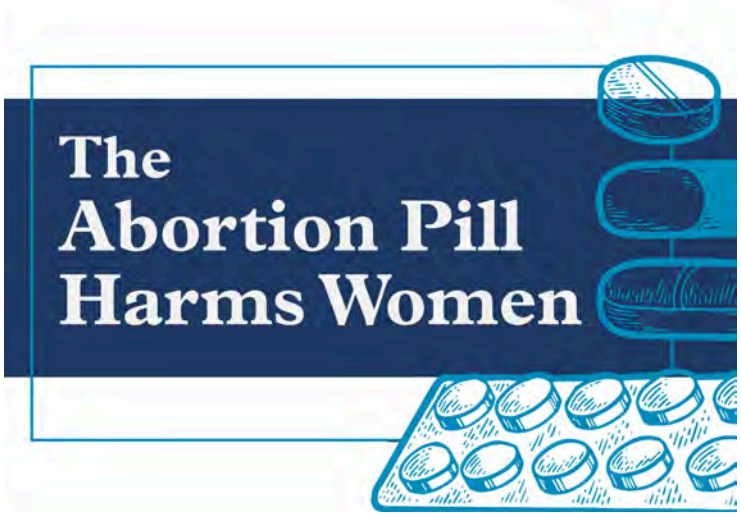
EPPC is committed both to ensuring the equal protection of unborn children in the law and to providing concrete support to families by advancing a pro-life, pro-family agenda that takes our duties in justice to the unborn and to families seriously.

Recognizing the duties of care owed by parents to their dependent children, and the rights those duties engender, we seek to order society toward the full flourishing of human beings by properly protecting both. A full account of reproductive justice must embrace the inherent dignity and value of each human being by giving pregnant women and caregiving families the societal support they deserve and require. It must also ask of expectant mothers that they offer their developing unborn children due care, and of fathers that they take up their shared duties of care toward both mother and child. And it must prevent abortionists from performing acts of lethal violence to vulnerable and dependent human beings.

EPPC's Life and Family Initiative brings together the longstanding pro-life efforts of many EPPC scholars—including Mary FioRito, Erika Bachiochi, Patrick T. Brown, Alexandra DeSanctis, and Nathanael Blake —and coordinates with our existing programs on HHS Accountability, Bioethics and American Democracy, The Constitution, the Courts, and the Culture, Catholic Studies, and Evangelicals in Civic Life to create an integrated, holistic response addressing both the necessary protections for unborn children and the necessary support for pregnant mothers and their families.

The Life and Family Initiative works nationwide to advance pro-life policies that protect unborn children by restricting abortion at the state and federal levels, via legislation, regulation, and litigation. We continue to advance cultural remedies and propose robust public policies that support families and offer necessary aid to women facing unexpected pregnancies. The Initiative builds on the heroic and critical work that maternity homes, pregnancy resource centers, and countless volunteers have carried out for more than fifty years. Strong families and communities are essential building blocks of a healthy society, and economic policy must keep that point front and center.

Building an authentic culture of life will require an energetic agenda to support mothers and children, to more fully engage fathers, and to call upon society at large to promote justice and the common good.



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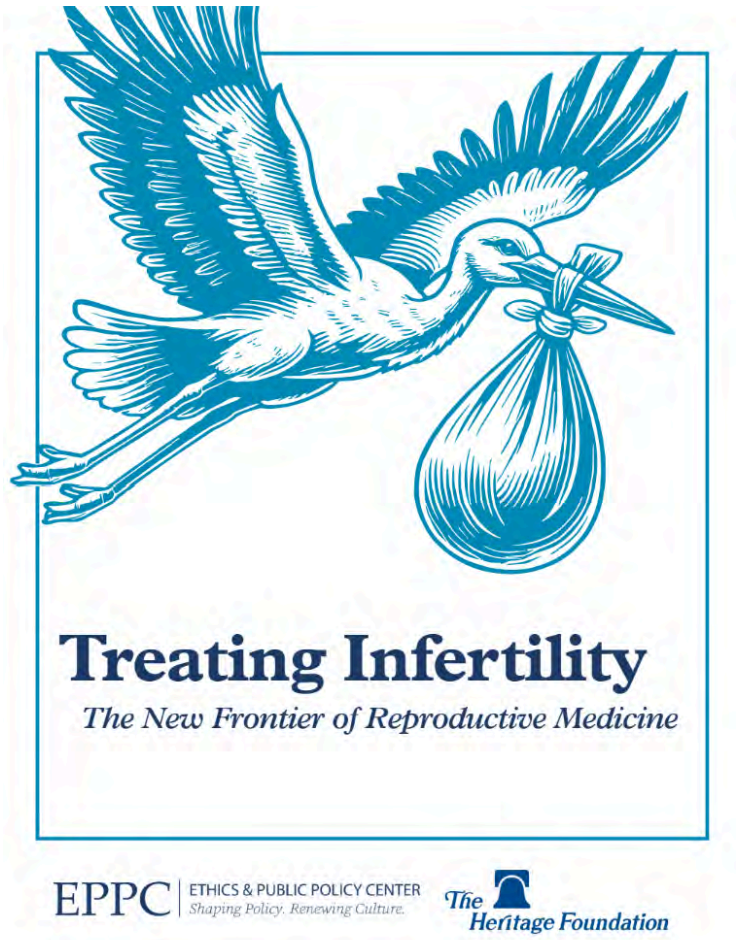

Treating Infertility: The New Frontier of Reproductive Medicine

In this series of briefs, medical professionals and scholars highlight misconceptions about in vitro fertilization (IVF), while making the case for restorative reproductive medicine (RRM) as a better treatment for infertility.

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LIFE AND FAMILY INITIATIVE

5 Things to Know About In Vitro Fertilization (IVF)

Patrick Brown, Ethics and Public Policy Center

ETHICS AND PUBLIC POLICY CENTER
Shaping Policy. Renewing Culture.

1 *Myth: Expanding public funding for IVF will boost birth rates*
Fact: Virtually no nation that has publicly subsidized IVF has seen a subsequent increase in birth rates
Countries like Japan, Hungary, and Australia have implemented public IVF funding, yet their overall fertility rates have continued to decline. This is partly because IVF gives some couples a false sense of security, leading them to delay trying to get pregnant, yet IVF success falls rapidly after age 35. The main exception is Israel, which compliments IVF funding with a broadly pro-family culture and generous spending on child benefits.

2 *Myth: Expanding public funding for IVF is uncontroversial*
Fact: The U.S.' light-touch regulations around assisted reproduction raises questions about patient safety and bioethics concerns
The U.S. has some of the fewest restrictions around IVF in the world; the last major regulation was passed in 1992, and most nations require much higher standards of patient care from fertility clinics. Additionally, the U.S. permits practices, such as eugenic embryo screening and sex selection, which raise serious concerns and are impermissible in many other countries.

3 *Myth: Expanding public funding for IVF is inexpensive*
Fact: Depending on the way it's implemented, expanding public subsidy for IVF could lead to higher health care costs or raise federal expenditures
The average cost of an IVF cycle is around $15,000, and many need more than one cycle to successfully become pregnant. If insurers are required to cover this cost without co-payments for all who want it, it will lead to a perceptible increase in health insurance premiums for workers and families. If the federal government were to assume those costs, the fiscal impact would be at least $80 billion over a ten-year budget window.

4 *Myth: Expanding public funding for IVF is the best way to help couples with infertility*
Fact: Many couples have higher success with restorative reproductive health approaches, such as those championed by the MAHA movement
Many couples struggling with infertility achieve better outcomes through restorative reproductive medicine, such as NaProTechnology or hormonal therapies. This fits the Make America Healthy Again agenda, which emphasizes holistic solutions and long-term well-being over high-intervention treatments. And while the IRS does currently limit tax-deductibility of IVF expenses to married couples, many fertility clinics apply the concept of "social infertility" to provide IVF services to single parents or third-parties.

5 *Myth: Expanding public funding for IVF is a political winner*
Fact: While polls do show helping couples face fertility is broadly popular, most polls do not put that top-line support in context
Polls tend to show broad support for IVF in theory, but few have polled the question against a backdrop of ethical concerns or higher costs. Polling for public benefits often falls when voters are informed about the impact it will have on their cost of living. Additionally, despite the attempts to attack President Trump over the politics of reproduction into an albatross in 2024, very few polls suggest his discussion of IVF costs were a top issue for many voters.

5 Things to Know About In Vitro Fertilization (IVF)

Patrick Brown explains the facts about in vitro fertilization refuting common myths and misconceptions about IVF and its results.

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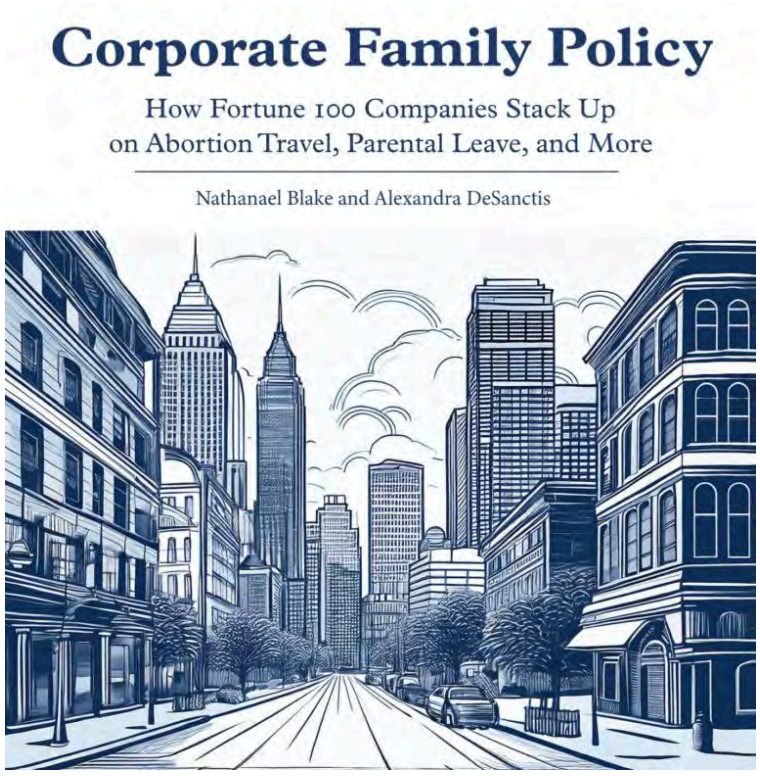

Corporate Family Policy Report

A new investigative report by Ethics and Public Policy Center (EPPC) scholars Alexandra DeSanctis and Nathanael Blake offers a detailed analysis of each Fortune 100 company's family, parental leave, and abortion policies. Its findings are clear: major American corporations have a long way to go to truly support mothers and fathers in their workplaces.

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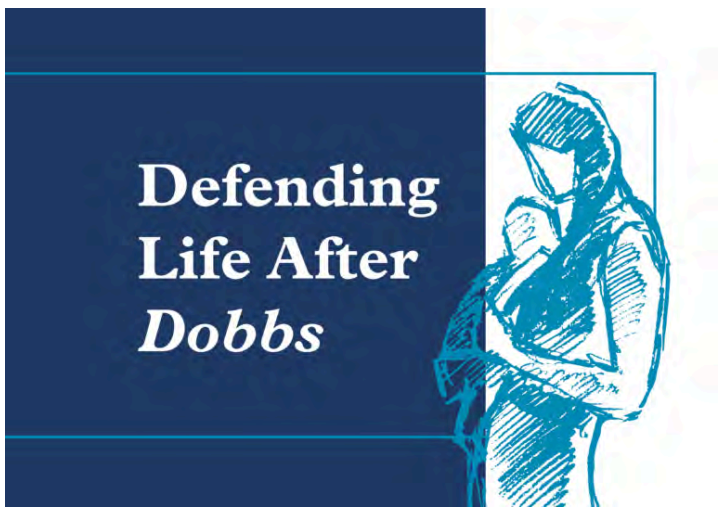

Defending Life After *Dobbs*

A team of scholars at EPPC has prepared this series of papers to equip lawmakers, staffers, lawyers, and scholars to defend unborn life in this new landscape. Based on the best available scholarship, the papers in this series are deliberately brief distillations of complex issues, accessible to non-specialists who may lack the time or expertise to wade through lengthy law review articles or philosophical papers in the scholarly literature. Each article deals with a different issue or argument now in play in the state courts and legislatures and includes a brief bibliography for further reading.

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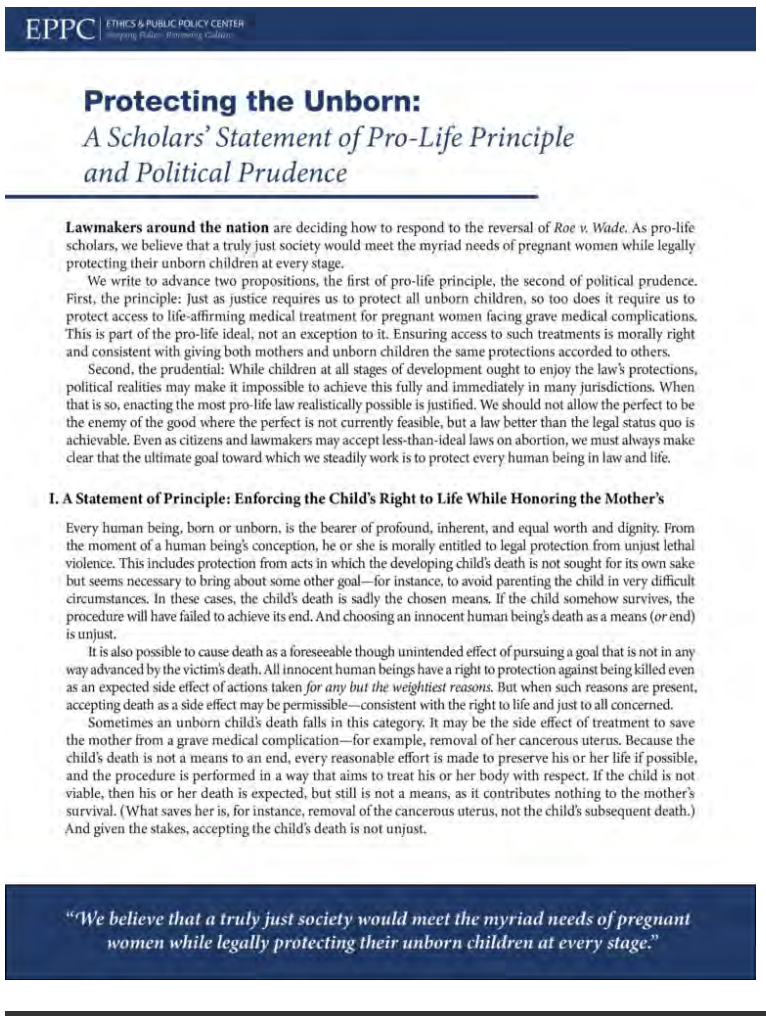
Five Pro-Family Priorities for the 118th Congress and Beyond

Policies and Public Opinion on Putting Families First

The family is the primary social institution oriented towards the bearing and rearing of children. An agenda to strengthen that institution should protect families from the economic and cultural forces that can undermine them. This report, a collaboration between the Institute for Family Studies and the Ethics and Public Policy Center, offers five policy ideas for an authentically pro-family Congress to champion.

Read the Report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Protecting the Unborn:
A Scholars' Statement of Pro-Life Principle and Political Prudence

Lawmakers around the nation are deciding how to respond to the reversal of *Roe v. Wade*. As pro-life scholars, we believe that a truly just society would meet the myriad needs of pregnant women while legally protecting their unborn children at every stage.

We write to advance two propositions, the first of pro-life principle, the second of political prudence. First, the principle: Just as justice requires us to protect all unborn children, so too does it require us to protect access to life-affirming medical treatment for pregnant women facing grave medical complications. This is part of the pro-life ideal, not an exception to it. Ensuring access to such treatments is morally right and consistent with giving both mothers and unborn children the same protections accorded to others.

Second, the prudential: While children at all stages of development ought to enjoy the law's protections, political realities may make it impossible to achieve this fully and immediately in many jurisdictions. When that is so, enacting the most pro-life law realistically possible is justified. We should not allow the perfect to be the enemy of the good where the perfect is not currently feasible, but a law better than the legal status quo is achievable. Even as citizens and lawmakers may accept less-than-ideal laws on abortion, we must always make clear that the ultimate goal toward which we steadily work is to protect every human being in law and life.

I. A Statement of Principle: Enforcing the Child's Right to Life While Honoring the Mother's

Every human being, born or unborn, is the bearer of profound, inherent, and equal worth and dignity. From the moment of a human being's conception, he or she is morally entitled to legal protection from unjust lethal violence. This includes protection from acts in which the developing child's death is not sought for its own sake but seems necessary to bring about some other goal—for instance, to avoid parenting the child in very difficult circumstances. In these cases, the child's death is sadly the chosen means. If the child somehow survives, the procedure will have failed to achieve its end. And choosing an innocent human being's death as a means (*or* end) is unjust.

It is also possible to cause death as a foreseeable though unintended effect of pursuing a goal that is not in any way advanced by the victim's death. All innocent human beings have a right to protection against being killed even as an expected side effect of actions taken *for any but the weightiest reasons*. But when such reasons are present, accepting death as a side effect may be permissible—consistent with the right to life and just to all concerned.

Sometimes an unborn child's death falls in this category. It may be the side effect of treatment to save the mother from a grave medical complication—for example, removal of her cancerous uterus. Because the child's death is not a means to an end, every reasonable effort is made to preserve his or her life if possible, and the procedure is performed in a way that aims to treat his or her body with respect. If the child is not viable, then his or her death is expected, but still is not a means, as it contributes nothing to the mother's survival. (What saves her is, for instance, removal of the cancerous uterus, not the child's subsequent death.) And given the stakes, accepting the child's death is not unjust.

"We believe that a truly just society would meet the myriad needs of pregnant women while legally protecting their unborn children at every stage."

Protecting the Unborn: A Scholars' Statement of Pro-Life Principle and Political Prudence

"Protecting the Unborn: A Scholars' Statement of Pro-Life Principle and Political Prudence," signed by EPPC's Ryan T. Anderson, Erika Bachiochi, Alexandra DeSanctis, Aaron Kheriaty, Carl R. Trueman, Ed Whelan, and George Weigel with a coalition of leading intellectuals, articulates an ethically sound foundation for pro-life efforts and offers guidance for political leaders in prudent decision-making in the post-*Roe* political landscape.

Read the Statement


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Envisioning a Pro-Family Policy Agenda:
A Statement of Principles

Strong families are the foundation of a healthy society. Especially at a time when cultural, political, and economic trends have pushed marriage and fertility rates to record lows, it is crucial for policymakers to have a clear vision of how public policy might better support family life. One of the primary aims of our politics should be empowering mothers and fathers to better live out their obligations to each other, to their children, and to their communities.

In its ideal form, the family is the social institution by which children are brought into existence, raised, and prepared to take on responsibilities as they grow into maturity. Though no family is perfect, they are small, cohesive communities that should be respected as having both a social and economic role and function. Parents bear the primary and ultimate responsibility to nurture, shape, and educate their children. As such, they should be afforded space, shielded from inappropriate state intrusion or undue market pressures, to fulfill their responsibilities and live out their irreplaceable function.

As scholars, writers, and legal experts, we offer the following eleven principles to advance an authentically pro-family approach to public policy. To safeguard and foster families' essential work, policymakers should:

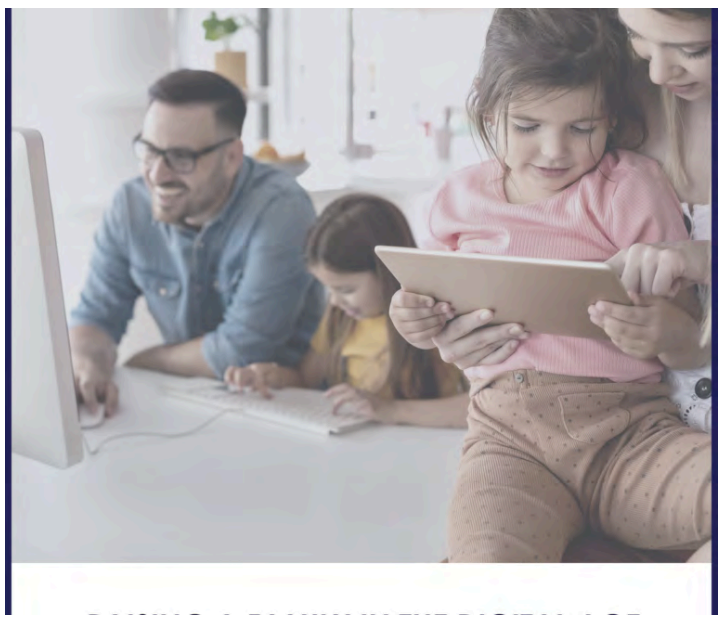
- Seek to strengthen the bond of marriage and the enduring relationship between mothers, fathers, and their children that forms the core of family life.
- Ensure that unborn children are protected in law, and that mothers and their infants receive the care and social support they deserve to ensure a healthy start to life.
- Acknowledge the out-of-pocket and opportunity costs associated with becoming a parent, and advance policies that would make having children more affordable and achievable.
- Pursue approaches to paid leave that provide a baseline of protection for new parents from the demands of the workplace.
- Create an approach to early childhood that embraces parents' different values and needs, eschewing credentialization and over-regulation for authentic pluralism, while ensuring that families with a parent working part-time or at home are treated equitably.
- Develop labor policies that create flexibility for parents without jeopardizing their financial security, allowing more families to find the work-life balance that is right for them.
- Reinforce the dignity of work by expecting and empowering at least one parent to participate in the labor force, both to contribute to society and to model the virtues of consistency, conscientiousness, and self-sufficiency.
- Appreciate how increases in the cost of living burden parents, particularly those living on a single income, and seek to lower costs in sectors like housing, health care, and higher education by removing artificial barriers to entry and encouraging innovation.

"In its ideal form, the family is the social institution by which children are brought into existence, raised, and prepared to take on responsibilities as they grow into maturity."

Envisioning a Pro-Family Policy Agenda: A Statement of Principles

"Envisioning a Pro-Family Policy Agenda: A Statement of Principles" was signed by EPPC's Ryan T. Anderson, Erika Bachiochi, and Patrick T. Brown, as well as other leading intellectuals. The document suggests eleven tenets that should guide a pro-life, pro-family approach to policymaking.

Read the Statement



Raising a Family in the Digital Age

Raising a Family in the Digital Age: A Technology Guide for Parents, by Clare Morell, Patrick Brown, Noelle Mering, and Mary Hasson, is a 20-page resource designed to help educate parents about the harms and dangers of today's technologies and equip them with practical tools to protect their children.

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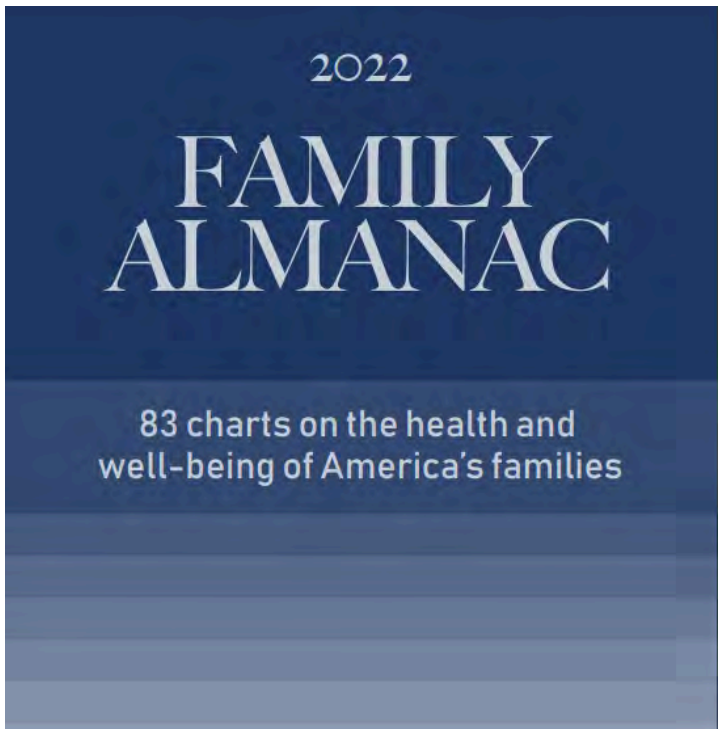

EPPC's 2022 Family Almanac

The 2022 Family Almanac, compiled by Patrick Brown, contains a wealth of data about the state of the American family, comprehensively assessing what families look like, why they matter, and where their biggest pain points are. This resource proves a vital tool for readers and policymakers in understanding the challenge and opportunities for conservative family policy.

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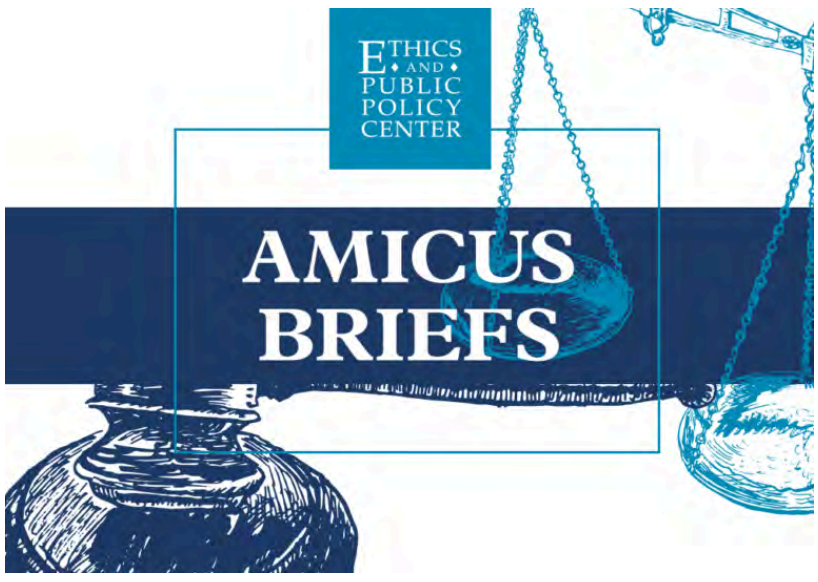

Amicus Briefs

EPPC and our scholars regularly file amicus briefs in key cases to promote a true and full account of human nature and human flourishing in the context of American constitutional law. Compiled on this page are some of our amicus briefs in cases addressing the right to life, marriage, gender ideology, religious freedom, free speech, and the rule of law.

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Verifying the effectiveness of medical abortion; ultrasound versus hCG testing

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Abstract

Objectives: The combination of mifepristone and misoprostol is an established method for termination of pregnancy. However, there is no general agreement about how best to evaluate the treatment outcome.

Study design: In 217 women with an unwanted pregnancy below 49 days of amenorrhoea, ultrasound examination and serum hCG test were performed before treatment and at follow-up.

Results: Treatment was successful in 98.2%. At follow-up their hCG dropped to a mean of 3% (S.D. 3) of initial levels and the endometrium measured a mean of 10 mm (S.D. 4). Interpretation of endometrium was difficult in some cases because of inhomogeneous structure. Using hCG was reliable in 98.5% of successful abortions. For ultrasound the corresponding figure was 89.8% for the cases with a confirmed intrauterine pregnancy before treatment but only 66% if all pregnancies were included.

Conclusion: Measuring serum hCG before treatment and at follow-up is more effective than ultrasound to confirm a successful medically induced abortion in early pregnancy.
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Keywords: Medical abortion; Mifepristone; hCG; Ultrasound; Verification of expulsion

1. Introduction

Treatment with a combination of mifepristone (Mifegyne®, Exelgyn, France) and the prostaglandin analogue, misoprostol (Cytotec®, Searle AG, USA), both administered orally, has been shown to be a safe, effective method for termination of early pregnancy [1–7]. Medical abortion with mifepristone and misoprostol is licensed for use in about 30 countries including most of Europe, USA, Russia and China.

The method is highly effective up to 49 days of amenorrhoea. The estimation of duration of pregnancy before treatment is therefore of importance and is in most cases based on medical history, gynaecological examination and an ultrasound examination. For the evaluation of the outcome of treatment, complete abortion, incomplete abortion, missed abortion or continuing pregnancy various methods are used. Beside clinical events and a gynaecological examination either measurement of serum hCG or an ultrasound examination is performed at a follow-up visit 1–3 weeks following start of treatment [8,9].

The aim of the present study was to compare the usefulness of hCG measurement and ultrasound examination before and after medical abortion in determining the outcome of treatment.

2. Material and methods

Two-hundred and seventeen women with an unwanted pregnancy up to 49 days of amenorrhoea, requesting medical abortion, were treated between 26 April and 10 November 1999. The treatment was performed on an outpatient basis at a general public hospital in Austria. A vaginal ultrasound (Toshiba Powervision 6000, vaginal probe 7.5 MHz) was performed to confirm pregnancy gestation in all women. A crown-rump length (CRL) of 10 mm was used as upper limit for treatment, consistent with 49 days amenorrhoea [10,11]. Furthermore serum hCG levels were determined in all women. All patients gave an informed consent for the abortion.

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The patients received 600 mg mifepristone orally at the hospital. They returned 48 h later to take 400 μg misoprostol orally once or twice. A second dose of 400 μg misoprostol orally after 3 h was given, according to routine, if bleeding had not started at that time or if bleeding was less than on the first day of menstruation [1].

The first follow-up to assess the treatment outcome was performed on day 6–18. The ultrasound examination and hCG testing was repeated at this time. If there was a continuing pregnancy, vacuum aspiration was performed. Surgical intervention was also performed if there was heavy bleeding or if requested by the patient. If it was unclear whether the woman had aborted completely a further follow-up visit was scheduled. The treatment was regarded as successful only if no surgical treatment was necessary up to the first menstruation.

Women who wanted combined oral contraceptives (OC) were advised to start on day 3 (day 1 being the day of mifepristone treatment). If there was suspected retention or heavy bleeding at follow-up, women on OC were asked to stop taking the pill after the fourteenth tablet.

The hCG levels at follow-up are given as the percentage of the value before the treatment and presented as mean and (S.D.). Measurements of endometrial thickness are given in mm and presented as mean and (S.D.).

3. Results

All patients completed the treatment and returned for follow-up.

The distribution of the gestational age of the pregnancies before treatment based on the ultrasound findings is shown in Table 1.

The hCG levels ranged from as low as 28 in the earliest up to 190,750 mU/ml in the most advanced pregnancy. The correlation between ultrasound findings and the hCG levels before treatment is shown in Table 2. Examples of ultrasound images of the endometrium are shown in Figs. 1–6.

A second dose of misoprostol was given to 28 women (12.9%) who had not started to bleed or had a minimal bleeding within 3 h following the first dose. One hundred and eight (49.7%) women obtained OC on day 3 following start of treatment.

Table 1
Ultrasound findings before treatment, $n = 217$

No gestational sac	6 (2.7%)	(see patient 1, Fig. 1)
Gestational sac but no yolk sac or foetal pole	44 (20.3%)	(see patient 2, Fig. 2)
Gestational sac with yolk sac but no foetus or CRL <2 mm	105 (48.4%)	(see patient 3, Fig. 3)
CRL >2 mm	62 (28.6%)	(see patient 4, Fig. 4)

CRL: crown-rump length.

Table 2
Correlation between ultrasound findings and serum hCG level before treatment

No gestational sac	28–1,752 mU/ml, (median 558 mU/ml)
Gestational sac, no yolk sac	802–54,443 mU/ml, (median 4.072 mU/ml)
Yolk sac	2,700–107,400 mU/ml, (median 17.295 mU/ml)
CRL >2 mm	22,900–190,750 mU/ml, (median 63.600 mU/ml)

CRL: crown-rump length.

Treatment was successful without the need for surgical intervention in 98.2% of cases. A total of four vacuum aspirations had to be performed; two for continuing pregnancy and two for haemorrhage.

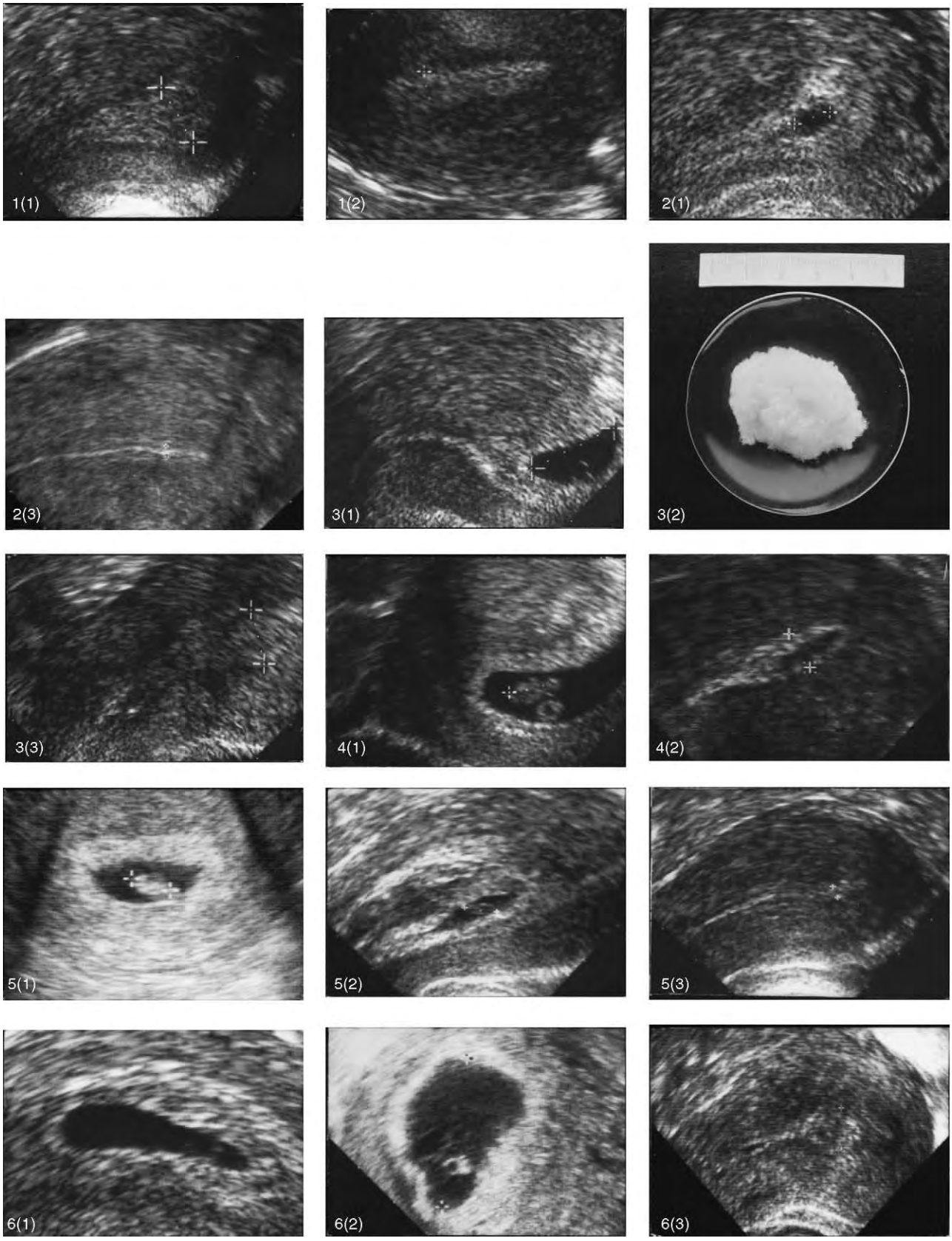
The hCG levels dropped to a mean of 3% (S.D. 3) of the value before treatment, ranging from 1 to 44% of the initial value in the cases of successful abortion (Fig. 7). The hCG value was above 17%, range 27–44%, in only three cases. Expulsion was confirmed by ultrasound in all of them, without the need for further follow-up. The two women with a continuing pregnancy had elevated hCG levels, 159% on day 10 and 7900% on day 8, respectively. Two patients were found to have a missed abortion. In each a gestational sac was seen on ultrasound which failed to grow from treatment to the time of the first follow-up at days 8 and 9 respectively. The drop in hCG was 91% in one and 3%, in the other woman. At a second follow-up visit, 8 and 15 days later respectively, both subjects had expelled the gestational sac without further treatment.

When 20% of the initial hCG value was used as cut-off, a positive predictive value for successful expulsion of 0.995 was obtained (Table 3).

If the reduction of the hCG level is less than 80%, the negative predictive value is 0.5 and further evaluation using ultrasound examination and repeated hCG measurements are needed to confirm the outcome of treatment.

The date of follow-up had been scheduled between day 6–18 according to the preferences of the patients. Due to the wide variation between treatment and follow-up, any cut off value of the hCG level has to be interpreted with caution. Nevertheless we found the cut-of at 20% valid, as all cases with complete abortion and early follow-up were far below this value.

Verification of successful abortion by ultrasound was possible only for the cases where the initial ultrasound examination had shown the presence of an intrauterine pregnancy (yolk sac or CRL). This was the case in 167 women (77%). Endometrium at follow-up measured 10 mm (mean, S.D. 4) in cases of successful abortion, ranging from 1 to 24 mm (Fig. 8). The content of the uterine cavity was inhomogeneous in some cases, making interpretation difficult (see Figs. 3 and 5). Complete abortion could not be verified at first follow-up (performed on days 7–12) by ultrasound alone in 17 of these cases (10.2%) due to the inhomogeneous picture. A further follow-up was scheduled in these cases (Fig. 5).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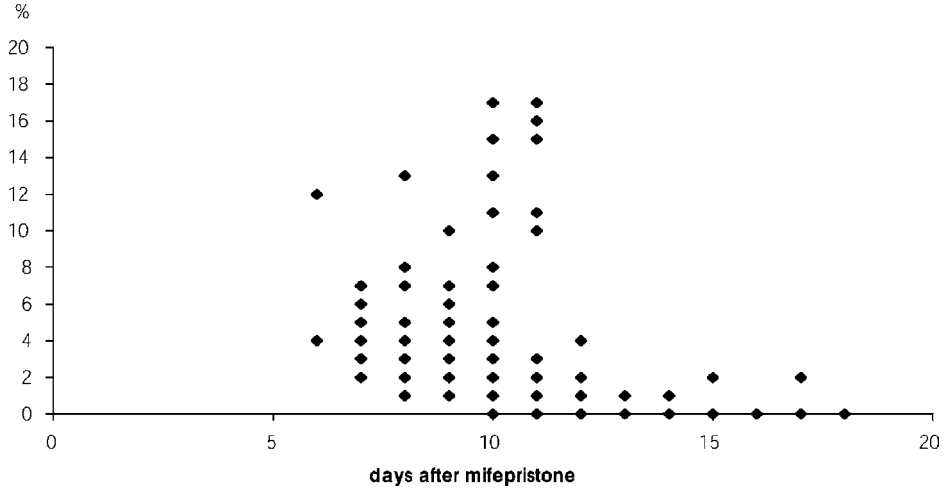

Fig. 7. S-hCG at follow-up in percentage of initial value, $n = 213$. Mean level 3% (0.1–44) of the hCG values before treatment.

Table 3
Positive and negative predictive value for expulsion at follow-up using a cut-off value of 20% of the initial value in hCG decrease

	True expulsion	True non-expulsion	Total	
hCG <20% per expulsion	210	1	211	Positive predictive value = 0.995
hCG>20% per non-expulsion	3	3	6	Negative predictive value = 0.5
Total	213	4	217	

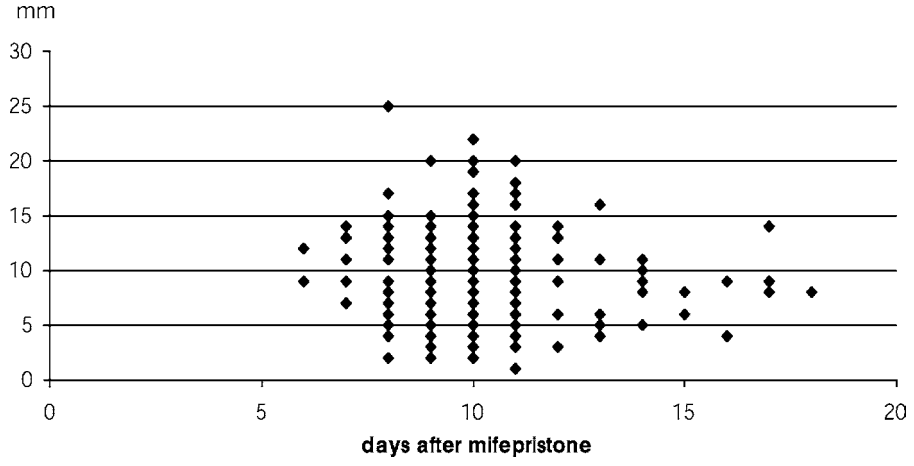

Fig. 8. Endometrial thickness at follow-up, $n = 213$. Mean 10 mm (1–24).

←

Figs. 1–6. Examples of patients with various duration of pregnancies up to 49 days counted from last menstrual period (LMP). Ultrasound images of the endometrium and S-hCG levels before and after treatment with 600 mg mifegyne (day 1) followed by 0.4 mg of misoprostol orally, 48 h later (day 3).

(1) Day 1 S-hCG 269 mU/ml. Day 9 S-hCG 20 mU/ml.
(2) Day 1 gestational sac 5 mm. S-hCG 862 mU/ml. Day 3 expelled gestational sac. Day 7 thin endometrium. S-hCG 7 mU/ml.
(3) Day 3 expelled gestational sac. Day 7 endometrium 12 mm. S-hCG 837 mU/ml.
(4) Day 1 CRL 1/4 10 mm. S-hCG 83439 mU/ml. Day 8 endometrium 8 mm. S-hCG 312 mU/ml.
(5) Day 1 CRL 1/4 6 mm. S-hCG 104 900 mU/ml. Started OC on Day 3. Day 10 endometrium 20 mm. S-hCG 16 841 mU/ml. Day 21 withdrawal bleeding. Day 28 S-hCG 100 mU/ml.
(6) Day 1 gestational sac and yolk sac. S-hCG 11947 mU/ml. Started OC on Day 3. Day 9 ultrasound image consistent with a missed abortion. S-hCG 10819 mU/ml. Day 18 withdrawal bleeding (stopped OC on day 16). Day 19 endometrium 8 mm. S-hCG 718 mU/ml.

4. Discussion

Treatment with 600 mg mifepristone and 0.4 mg misoprostol orally followed 3 h later by a second dose of 0.4 mg misoprostol if the woman had not started to bleed was found to be a highly effective method to terminate pregnancy in women with a duration of amenorrhoea up to 49 days. Out of the 217 women treated, 213 aborted without surgical intervention giving an overall success rate of 98.2%. Vacuum aspiration was performed in four women due to continuing pregnancy (two women) or heavy bleeding (two women). The outcome corresponds well with previous results using the same treatment [1].

The success of treatment is dependant on gestational age. If the duration of amenorrhoea is more than 49 days the efficacy of mifepristone and oral misoprostol is less effective [12]. The duration of pregnancy can usually be determined by menstrual history and a gynaecological examination. However, in some subjects these parameters are not sufficient and an ultrasound examination can be of considerable value.

There is no general agreement on how to verify the outcome of medical abortion. Some centres use ultrasound before administration of mifepristone and at follow-up, others rely on serum hCG levels or use a less sensitive urine pregnancy test (500 mU/ml) at follow-up. Whether ultrasound examination or serum hCG measurement is more suitable depends on several factors (Table 4). Ultrasound is not reliable in very early pregnancy before the yolk sac is visible. It could be useful to exclude a persisting extra uterine pregnancy after treatment but not in all cases. On the other hand it gives an immediate result in most cases and is inexpensive where available. Also, it can sometimes be of great relief for women in early pregnancy to see for herself that no foetal heart rate can be demonstrated.

The use of ultrasound to determine the outcome of medical abortion and possible need for surgical intervention clearly requires knowledge of the ultrasound finding following medical abortion. In the present study follow-up was performed according to the wish of the patient between days 6 and 18. Ultrasound at follow-up was sometimes difficult to interpret. The endometrium was often thick and sometimes inhomogeneous resembling an incomplete abortion (Figs. 3 and 5). It might be difficult to abstain from surgical intervention in such cases. However, no negative consequences were observed whilst waiting for the next menstrual bleeding to occur. Thus, the need for curettage in cases with missed abortion or a thick endometrium at follow-up could be reduced by refraining from immediate surgical intervention. An increasing hCG level at follow-up on the other hand, indicates a need for surgical intervention.

Table 4
Comparing ultrasound and hCG measurement to verify the effectiveness of the treatment

Advantages	Disadvantages
Ultrasound	
Usually done before starting the treatment	No reliable result in very early pregnancy
Easy to perform	Sometimes difficult to interpret at follow-up
Immediate result	
Great relief for the woman when there is no foetal structure visible	Vaginal ultrasound necessary
hCG	
Always a definite result	Not possible to exclude a gestational age >49 days LMP
Easy to perform	Some time needed to obtain the result

To measure serum hCG levels is especially helpful in early pregnancy. Measuring hCG is also reliable in detecting a persistent pregnancy or incomplete expulsion, even when extra uterine. Successful expulsions were consistent with a marked decline in hCG value at follow-up. Using 20% of the initial value as cut-off at follow-up gave a high sensitivity. It allowed correct diagnosis in 98.5% of the patients with successful expulsion. Only one patient with missed abortion at follow-up discovered by ultrasound had a marked decrease of hCG. She expelled the gestational sac with time without complications. There is probably a high frequency of spontaneous expulsion until or during the next menstruation in such cases. Measuring hCG can easily be done in most places and might be more convenient for the woman than an ultrasound examination. Furthermore there is no need to have it performed in the same institution that provided the medical abortion.

Even following medical abortion an ovulation could occur before the first menstruation. It is therefore of importance to provide the woman with an effective contraceptive method immediately after treatment. It has previously been demonstrated that OC can be given immediately after treatment without influencing outcome or bleeding [13].

In conclusion, hCG levels are a safe and effective way to verify complete abortion following medical treatment. Performing hCG is recommended especially in very early pregnancy. It's advantage over ultrasound is less pronounced at a later gestational age, as soon as an intrauterine pregnancy can be diagnosed by ultrasound. Plasma hCG level at follow-up compared to the initial value gave a reliable result in 98.5% of successful abortions, when using 20% of the initial value as cut-of. In contrast the reliability of ultrasound examination in diagnosing successful expulsion was 89.8% in the cases with a prior diagnosis of an intrauterine pregnancy. Ultrasound at follow-up showed a thick endometrium in many cases, sometimes with an inhomogeneous structure even when the abortion was complete. The ultrasound findings might be difficult to interpret and may lead to unnecessary surgical interventions. Conservative management i.e. waiting for the menstruation or an withdrawal bleeding proved to be safe. Surgical intervention was performed only in cases of continuous evolving pregnancy or

heavy bleeding. Thus if ultrasound is used alone to verify outcome of treatment, caution should be made to avoid unnecessary interventions.

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Research Letter | Obstetrics and Gynecology

Telehealth vs In-Clinic Medication Abortion Services

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Introduction

Abortion is a common health care service, yet federal and state regulations continue to restrict care options, with disproportionate impacts on underserved communities.[1-3] Due to limited in-clinic access throughout the country, telehealth medication abortion services (tele-MAB), including online consultations and medications delivered directly to patients, can make abortion care more convenient and accessible.[4]

Other areas of health care have documented disparities in telehealth access, although less is known about tele-MAB services.[5] We sought to understand differences in patient characteristics

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Table 1. Description of Study Sample

Patient demographic characteristic	Patients receiving medication abortion services, April 23, 2020 to January 31, 2022, No. (%)			*P* value[a]
	Total (N = 1241)	In-clinic (n = 858)	Telehealth (n = 383)	
Age, y				
Mean, range	30 (13-52)	30 (13-52)	31 (15-47)	.002
<20	92 (7.4)	63 (7.3)	29 (7.6)	
21-25	244 (19.7)	193 (22.5)	51 (13.3)	
26-30	339 (27.3)	236 (27.5)	103 (26.9)	
31-35	312 (25.1)	201 (23.4)	111 (29.0)	
≥36	254 (20.5)	165 (19.2)	89 (23.2)	
Self-declared gender				
Women	1209 (97.4)	841 (98.0)	368 (96.1)	.08
Men	1 (0.1)	1 (0.1)	0	
Missing data	31 (2.5)	16 (1.9)	15 (3.9)	
Self-declared race and ethnicity				
Asian, Native Hawaiian, or Other Pacific Islander	220 (17.7)	167 (19.5)	53 (13.8)	<.001
Black or African American	232 (18.7)	186 (21.7)	46 (12.0)	
Hispanic or Latino	176 (14.2)	123 (14.3)	53 (13.8)	
White	361(29.1)	246 (28.7)	115 (30.0)	
Multiracial or other race	150 (12.1)	52 (6.1)	98 (25.6)	
Declined to specify or no response	102 (8.2)	84 (9.8)	18 (4.7)	
Primary language				
English	1163 (93.7)	782 (91.1)	381 (99.5)	<.001
Other	78 (6.3)	76 (8.9)	2 (0.5)	
Living children				
Mean, range	1 (0-7)	1 (0-7)	1 (0-7)	.22
0	472 (38.0)	339 (39.5)	133 (34.7)	
≥1	743 (59.9)	509 (59.3)	234 (61.1)	
Missing data	26 (2.1)	10 (1.2)	16 (4.2)	
Type of payment for visit				
Cash self-pay	279 (22.5)	179 (20.9)	100 (26.1)	.12
Public insurance	595 (48.0)	419 (48.8)	176 (46.0)	
Private insurance	367 (29.6)	260 (30.3)	107 (27.9)	

(continued)

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Table 1. Description of Study Sample (continued)

Patient demographic characteristic	Patients receiving medication abortion services, April 23, 2020 to January 31, 2022, No. (%)			*P* value[a]
	Total (N = 1241)	In-clinic (n = 858)	Telehealth (n = 383)	
Social Vulnerability Index rank				
Low	889 (71.6)	635 (74.0)	254 (66.3)	<.001
Medium	316 (25.5)	211 (24.6)	105 (27.4)	
High	33 (2.7)	9 (1.1)	24 (6.3)	
Missing	3 (0.2)	3 (0.4)	0	
Distance to Cedar River Clinic locations, mi				
<5	267 (21.5)	203 (23.6)	64 (16.7)	<.001
5-10	410 (33.0)	300 (35.0)	110 (28.7)	
10-25	428 (34.5)	294 (34.3)	134 (35.0)	
25-50	73 (5.9)	44 (5.1)	29 (7.6)	
>50	55 (4.4)	12 (1.4)	43 (11.2)	
Missing	8 (0.6)	5 (0.6)	3 (0.8)	
Past and current health conditions				
Mean, range	1 (0-14)	1 (0-14)	0 (0-9)	<.001
0	790 (63.7)	489 (57.0)	301 (78.6)	
1	194 (15.6)	164 (19.1)	30 (7.8)	
≥2	227 (18.3)	196 (22.8)	31 (8.1)	
Missing data	30 (2.4)	9 (1.1)	21 (5.5)	
Prior abortions				
Mean, range	0.87 (0-11)	0.87 (0-11)	0.85 (0-9)	.06
0	691 (55.7)	499 (58.2)	192 (50.1)	
≥1	521 (42.0)	350 (40.8)	171 (44.7)	
Missing data	29 (2.3)	9 (1.1)	20 (5.2)	
Gestational duration, d				
Mean, range	45 (13-70)	45 (22-70)	46 (13-70)	.08
≤42	521 (42.0)	370 (43.1)	151 (41.0)	
43-56	535 (43.1)	378 (44.1)	157 (39.4)	
57-70	152 (12.3)	94 (11.0)	58 (15.1)	
Missing data	33 (2.7)	16 (1.9)	17 (4.4)	
Eligibility for telehealth medication abortion and patient was asked to come into clinic				
Eligible	375 (30.2)	NA	375 (97.9)	NA
Ineligible	8 (<0.1)	NA	8 (2.1)	

Abbreviation: NA, not applicable.

[a] *P* values were calculated using χ^2 tests.

between those using telehealth vs in-clinic for medication abortion care and to explore the role of tele-MAB in serving diverse patient populations.

Methods

This cross-sectional study follows the STROBE reporting guideline[6] and was approved by the University of Washington and University of California, Los Angeles institutional review boards with exemption from informed consent because data were deidentified in accordance with 45 CFR § 46. We analyzed electronic medical record data from tele-MAB and tele-MAB–eligible patients who received in-clinic medication abortion services at Cedar River Clinics, a reproductive health care clinic in Washington State, between April 23, 2020, and January 31, 2022 (eFigure in Supplement 1). A sensitivity analysis was completed excluding in-clinic patients with missing information on tele-MAB eligibility (208 patients [17%]). Using bivariable and multivariable logistic regressions, we examined associations of patient characteristics (eTable in Supplement 1) with odds of receiving

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tele-MAB vs in-clinic services. We used 2-sided tests with an α criterion of .05, using Stata IC statistical software version 16.1 (StataCorp). Data analysis was conducted from September to December 2022.

Table 2. Unadjusted and Adjusted ORs for Receiving Tele-MAB Compared With In-Clinic Medication Abortion Services

Patient characteristic	Likelihood of receiving tele-MAB vs in-clinic medication abortion services, OR (95% CI)			
	Unadjusted model (N =1241)	*P* value[a]	Adjusted multivariable model (n = 1156)[b]	*P* value[a]
Age, y				
<20	0.83 (0.51-1.37)	.003	0.49 (0.26-0.92)[c]	<.001
21-25	0.48 (0.33-0.70)[d]		0.35 (0.22-0.57)[d]	
26-30	0.79 (0.57-1.10)		0.60 (0.40-0.90)[c]	
31-35	1 [Reference]		1 [Reference]	
≥36	0.98 (0.69-1.38)		0.98 (0.64-1.40)	
Self-declared race and ethnicity				
Asian, Native Hawaiian, or Other Pacific Islander	0.68 (0.46-0.99)[c]	<.001	0.87 (0.56-1.37)	<.001
Black or African American	0.53 (0.36-0.78)[e]		0.61 (0.39-0.95)[c]	
Hispanic or Latino	0.92 (0.62-1.36)		0.88 (0.5-1.43)	
White	1 [Reference]		1 [Reference]	
Multiracial or other race	4.03 (2.70-6.03)[c]		4.52 (2.78-7.34)[c]	
Declined to specify or no response	0.46 (0.26-0.80)[e]		0.476(0.25-0.88)[c]	
Preferred language				
English	1 [Reference]	<.001	1 [Reference]	<.001
Other	0.05 (0.01-0.22)[d]		0.06 (0.02-0.26)[e]	
No. of living children				
0	1 [Reference]	.22	NA	NA
≥1	1.17 (0.91-1.51)		NA	
Type of payment for visit				
Public insurance	1 [Reference]	.12	NA	NA
Private insurance	0.98 (0.74-1.30)		NA	
Cash self-pay	1.33 (0.98-1.80)		NA	
Social Vulnerability Index rank				
Low	1 [Reference]	<.001	1 [Reference]	.70
Medium	1.24 (0.94-1.64)		1.14 (0.81-1.61)	
High	6.67 (3.06-14.5)[d]		1.31 (0.37-4.69)	
Distance to Cedar River Clinic location, mi	1.02 (1.02-1.03)[d]	<.001	1.02 (1.01-1.03)[d]	<.001
Past and current health conditions, No.				
0	1 [Reference]	<.001	1 [Reference]	<.001
1	0.30 (0.20-0.45)[c]		0.24 (0.15-0.38)[c]	
≥2	0.26 (0.17-0.39)[d]		0.19 (0.12-0.31)[d]	
Prior abortions, No.				
0	1 [Reference]	.058	1 [Reference]	.002
≥1	1.27 (0.99-1.63)		1.63 (1.20-2.22)[e]	
Gestational duration, d				
≤42	0.98 (0.75-1.28)	.08	0.83 (0.60-1.13)	.22
43-56	1 [Reference]		1 [Reference]	
57-70	1.49 (1.02-2.16)[c]		1.21 (0.77-1.90)	

Abbreviations: NA, not available; OR, odds ratio; tele-MAB, telehealth medication abortion services.

[a] Reported *P* values from Wald test.

[b] Variables statistically significant in the χ^2 bivariate analyses ($P < .10$) were included in the multivariable model. For the multivariable model, 85 observations were dropped due to missingness (5 for distance and 80 missing on multiple covariates).

[c] $P < .05$.

[d] $P < .001$.

[e] $P < .01$.

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Results

Of the 1241 patients (mean [range] age, 30 [13-52] years) included in the study, 858 individuals (69%) received in-clinic appointments for medication abortion services and 383 (31%) received tele-MAB services (**Table 1**). In the unadjusted analysis, number of living children and payment type were not different between tele-MAB and in-clinic patients. In the adjusted model, individuals who lived further from a clinic and had at least 1 prior abortion were more likely to receive tele-MAB (**Table 2**). Compared with White individuals, patients who self-reported as multiracial or other race were also more likely to receive tele-MAB, whereas Black individuals were more likely to be seen in-clinic. Younger individuals, non-English speakers, and those with at least 1 health condition were also less likely to receive tele-MAB vs in-clinic services. The association of gestational duration (GD) with appointment type was not significant in the multivariable model but was significant in the sensitivity analysis, with those at 57 to 70 days GD more likely to choose tele-MAB than those at 43 to 56 days (adjusted odds ratio, 1.75; 95% CI, 1.06-2.89). The sensitivity analysis found all other associations to be robust.

Discussion

Our findings suggest that tele-MAB facilitates abortion care access for those further from brick-and-mortar abortion facilities and, thus, may mitigate the impacts of travel logistics and costs. Additionally, tele-MAB may better meet the needs of those with prior abortion experience, perhaps due to greater familiarity with the abortion process. Further research is needed to better understand patients who identified as multiracial or other race and how identity, including prior experiences of racism in health care settings, may impact patient preference for tele-MAB services. Additional research is also needed to determine whether those at later GD are more likely to choose tele-MAB, perhaps anticipating initiation of their termination.

Our findings also suggest some groups with limited access to abortion care (ie, younger individuals, those with limited English proficiency, and those with health conditions) are less likely to use tele-MAB services. Efforts to educate patients about telehealth procedures and improve availability of language support are needed to make tele-MAB feasible for diverse populations. Limitations of this study are that findings may not be generalizable to asynchronous or less-integrated telemedicine models, or other care settings.

Patients face many barriers to accessing abortion care, and tele-MAB services facilitate more convenient and timely care. Tele-MAB services reach some communities traditionally underserved by clinic-based services, addressing some disparities in receipt of care. As access to abortion care continues to be restricted in the US, innovative models of care delivery are needed to accommodate the sustained demand for services and to meet the needs of diverse patient populations.

ARTICLE INFORMATION

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Correction: This article was corrected on September 22, 2023, to fix numerical errors in Table 1 and Table 2.

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Author Contributions: Drs Fiastro and Godfrey had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Fiastro, Ruben, Godfrey.

Acquisition, analysis, or interpretation of data: Fiastro, Zheng, Gipson.

Drafting of the manuscript: Fiastro.

Critical review of the manuscript for important intellectual content: All authors.

Statistical analysis: Fiastro, Zheng.

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Administrative, technical, or material support: Fiastro, Ruben.

Supervision: Fiastro, Gipson, Godfrey.

Conflict of Interest Disclosures: Dr Godfrey reported receiving personal fees from Organon Nexplanon outside the submitted work. No other disclosures were reported.

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Data Sharing Statement: See Supplement 2.

Additional Information: Preliminary findings were included in Dr Fiastro's dissertation research as part of a public health doctoral program at the University of California, Los Angeles, submitted in June 2023.

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SUPPLEMENT 1.

eFigure. Description of Eligible Study Sample From All Who Received Medication Abortion Services During the Study Period (April 23, 2020 – January 31, 2022)
eTable. Definitions of Patient Characteristics
eReferences

SUPPLEMENT 2.

Data Sharing Statement

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Original Investigation | Obstetrics and Gynecology

Trends in Maternal Mortality and Severe Maternal Morbidity During Delivery-Related Hospitalizations in the United States, 2008 to 2021

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Abstract

IMPORTANCE Maternal mortality and severe maternal morbidity (SMM) are important focus areas in public health. Further understanding trends, health disparities, and risk factors for these adverse outcomes is vital to public health decision-making.

OBJECTIVE To describe trends and risk factors for delivery-related maternal deaths and SMM in the United States.

DESIGN, SETTING, AND PARTICIPANTS This is a retrospective cross-sectional study using data from a large, geographically diverse, all-payer hospital administrative database. Hospital discharges from January 2008 to December 2021 with any Medicare Severity Diagnosis Related Group, *International Classification of Diseases, Ninth Revision, Clinical Modification*, or *International Classification of Diseases, Tenth Revision, Clinical Modification* delivery diagnosis or procedure code were included. Data analysis took place from February 2021 to March 2023.

EXPOSURES Year, quarter (Q), age, race and ethnicity, delivery method.

MAIN OUTCOMES AND MEASURES Maternal mortality, SMM during delivery-related hospitalization.

RESULTS Overall, 11 628 438 unique hospital discharges were analyzed, with a mean (SD) age of 28 (6) years. There were 437 579 (3.8%) Asian, 92 547 (0.8%) American Indian, 1 640 355 (14.1%) Black, 1 762 392 (15.2%) Hispanic, 83 189 (0.7%) Pacific Islander, and 6 194 139 (53.3%) White patients. Regression-adjusted maternal mortality per 100 000 discharges declined from 10.6 deaths in Q1 2008 to 4.6 deaths in Q4 2021. Mortality was significantly higher among patients with advanced maternal age (eg, age 35-44 years vs 25-34 years: adjusted odds ratio [aOR], 1.49; 95% CI, 1.22-1.84). Other significant risk factors for mortality included cesarean delivery, comorbid conditions, complications, and COVID-19 diagnosis (eg, cesarean delivery: aOR, 2.28; 95% CI, 1.87-2.79). The prevalence of any SMM increased from 146.8 per 10 000 discharges in Q1 of 2008 to 179.8 per 10 000 discharges in Q4 of 2021. SMM risk factors included age 24 years or younger or age 35 years or older, belonging to a racial or ethnic minority group, cesarean delivery, Medicaid insurance, and having 1 or more comorbidities (eg, age 10-19 years: aOR, 1.39; 95% CI, 1.36-1.42).

CONCLUSIONS AND RELEVANCE This cross-sectional study found that delivery-related mortality in US hospitals decreased for all racial and ethnic groups, age groups, and modes of delivery during 2008 to 2021, likely demonstrating the impact of national strategies focused on improving maternal quality of care provided during delivery-related hospitalizations. SMM prevalence increased for all patients, with higher rates for racial and ethnic minority patients of any age. Advanced maternal age,

(continued)

Key Points

Question What were trends of and risk factors associated with maternal mortality and severe maternal morbidity (SMM) among women giving birth in US hospitals during 2008 to 2021?

Findings In this cross-sectional study of more than 11.6 million delivery-related hospitalizations, regression-adjusted in-hospital maternal delivery-related mortality per 100 000 discharges declined from 10.6 to 4.6, while the prevalence of SMM per 10 000 discharges increased from 146.8 to 179.8 during 2008 to 2021. Differences were found across racial and ethnic groups, age, mode of delivery, and comorbidities for mortality and SMM.

Meaning In this study, in-hospital maternal mortality improved between 2008 and 2021 despite increases in SMM prevalence and presence of comorbidities for the overall population.

+ Supplemental content

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Abstract (continued)

racial or ethnic minority group status, cesarean delivery, and comorbidities were associated with higher odds of mortality and SMM.

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Introduction

Complications from pregnancy and childbirth are leading contributors to mortality and severe morbidities, resulting in significant burden on pregnant patients and their babies. Among developed countries, the United States has the highest maternal mortality ratio.[1] In 2019, there were 3 747 540 births in the United States, with an estimated birth rate of 11.4 per 1000 population.[2] According to US Pregnancy Mortality Surveillance System (PMSS) data, the pregnancy-related mortality ratio in the United States had increased since 1987 from 7.2 deaths per 100 000 live births to 17.3 deaths per 100 000 live births in 2017, although the trend slowed substantially after 2008.[3]

Maternal mortality has been described as the "tip of the iceberg" and maternal morbidity as a larger problem, "the base."[4] For every individual who dies as a result of their pregnancy, it is estimated that 20 or 30 more experience significant lifelong complications that affect their health and well-being.[5,6] Severe maternal morbidity (SMM), which the US Centers for Disease Control and Prevention (CDC) defines as "unexpected outcomes of labor and delivery that result in significant short- or long-term consequences to a woman's health,"[1] has steadily increased in the United States in recent years and is estimated to affect more than 50 000 patients annually.

Causes of maternal deaths and SMM at the time of delivery are multifactorial and are not well documented.[7] Measuring specific outcomes occurring during delivery and hospitalization could improve understanding of how to predict, manage, and mitigate maternal outcomes. In addition, enhanced understanding of the causes of delivery-related death and SMM can inform potential strategies to improve overall maternal health outcomes in the United States. This study aimed to provide evidence to enhance understanding of patterns, trends, and risk factors associated with delivery-related deaths and SMM in US hospitals using a large maternal sample in the hospital setting.

Methods

Study Design

This retrospective cross-sectional study was conducted to examine trends associated with delivery-related maternal in-hospital mortality and SMM between January 2008 and December 2021, using data from the Premier PINC AI Healthcare Database (PHD). All data were statistically deidentified and adherent to the Health Insurance Portability and Accountability Act. Based on US Title 45 Code of Federal Regulations, Part 46, this study was exempted from institutional review board approval and informed consent. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Data Source

The PHD is a large, all-payer (including Medicaid), geographically diverse administrative database comprising more than 1200 US hospitals and health systems.[8] This database represents approximately 25% of all US inpatient admissions. All data were validated at both facility and patient levels. The CDC, the National Institute of Health, and academic and industry researchers have used PHD data for studies in a variety of disease areas.[9-15]

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Study Population

This study reviewed inpatient hospitalizations between January 1, 2008, and December 31, 2021, with any Medicare Severity Diagnosis Related Group (MS-DRG) or *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis or procedure codes (on or before September 30, 2015) or *International Classification of Diseases and Related Health Problems, Tenth Revision, Clinical Modification* (*ICD-10-CM*) codes (on or after October 1, 2015) indicating delivery (eTable 1 in Supplement 1). Hospitalizations for patients younger than 10 years at time of admission and those with evidence of abortive outcomes were excluded from the study. The index date was defined as the discharge date for the qualifying hospitalization. Missing data for categorical variables were included in the other or unknown group. Only a small percentage of patients had missing data, which should not have affected the trend analysis.

Study Variables

SMM

Complications or procedures indicative of SMMs were examined during the delivery-related hospitalization; these included acute myocardial infarction, acute kidney failure, amniotic fluid embolism, aneurysm, cardiac arrest or ventricular fibrillation, cardioversion, disseminated intravascular coagulation, eclampsia, heart failure or arrest during procedure, puerperal cerebrovascular disorders, acute heart failure or pulmonary edema, severe anesthesia complications, sepsis, shock, sickle cell anemia with crisis, air and thrombotic embolism, blood transfusion, hysterectomy, temporary tracheostomy, and ventilation. The diagnosis and procedure codes to identify the complications are listed in eTable 2 in Supplement 1. The presence of any SMM was used as a measure for the adverse event occurring during delivery. Morbidities were reported as number of patients with each SMM or any SMM of interest per 10 000 eligible discharges.

In-Hospital Delivery-Related Mortality

Death was defined as having delivery-related hospitalization discharge status as deceased. In-hospital mortality was reported as the number of patients who died during index hospitalization per 100 000 eligible discharges.

Patient, Hospital, and Visit Characteristics

Patient characteristics included age (10-19, 20-24, 25-34, 35-44, ≥45 years), race and ethnicity (categorized as American Indian, Asian, Black, Hispanic, Pacific Islander, White, and other or unknown), and primary insurance payer. The other or unknown category captures all patients who selected other category for race, had missing data for race or ethnicity, or had a hospital-reported race that could not be matched to the standard race categories used in this article. Race and ethnicity were reported by the hospital. For the purposes of this study, we defined racial or ethnic minority patients as those with race or ethnicity classifications other than White. Hospital characteristics included population served (urban, rural), teaching status, US census divisions (ie, Middle Atlantic, Mountain, East North Central, East South Central, New England, Pacific, South Atlantic, West North Central, and West South Central), and hospital size (1-299, 300-499, and ≥500 beds). Visit information, such as index year, quarter (Q), admission type (elective, emergency, urgent, or trauma center), and an indicator for pre–*ICD-10-CM* or post–*ICD-10-CM* coding system change on October 1, 2015, were also examined.

Clinical Characteristics

The individual conditions in the Maternal Comorbidity Index (MCI)[16] were assessed as potential risk factors of maternal mortality or morbidity, including pulmonary hypertension, placenta previa, sickle cell disease, gestational hypertension, mild or unspecified preeclampsia, severe preeclampsia, chronic kidney disease, preexisting hypertension, chronic ischemic heart disease, congenital heart disease, systemic lupus erythematosus, HIV, multiple gestation, substance use disorder, alcohol

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abuse, tobacco use, cardiac valvular disease, chronic congestive heart failure, asthma, preexisting diabetes, gestational diabetes, obesity, cystic fibrosis, and previous cesarean delivery (eTable 3 in Supplement 1). The type of delivery (vaginal, cesarean) and COVID-19 status were also examined.

All SMMs were included as covariates for the mortality analysis. Because of overlap across comorbid conditions, certain SMMs were grouped together. Per CDC recommendations, cardiac conditions (including acute myocardial infarction, cardiac arrest or ventricular fibrillation, conversion of cardiac rhythm, heart failure or arrest during surgery or procedure, and pulmonary edema or acute heart failure) were grouped into 1 binary variable called cardiovascular complications for multivariable modeling. Acute respiratory conditions (including acute respiratory distress syndrome, temporary tracheostomy, and ventilation) were grouped into a binary variable called respiratory complications.[17] Hemorrhage and blood transfusion were combined into bleeding complications with 3 categories: no bleeding, hemorrhage with no blood transfusion, and blood transfusion. Eclampsia, severe preeclampsia without eclampsia, mild or unspecified preeclampsia without eclampsia, or severe preeclampsia, and no preeclampsia or eclampsia were grouped into one 4-level covariate.

Statistical Analysis

Descriptive analysis was performed to assess the distribution of demographics and hospital and clinical characteristics for each year. Categorical variables were expressed as counts and percentages. Owing to space limitations, we only included specific descriptive results for 2008, 2014 (ie, the year before the *ICD-9-CM* to *ICD-10-CM* coding change), 2016 (ie, the year after the *ICD-9-CM* to *ICD-10-CM* coding change), 2019 (ie, the year before the COVID-19 pandemic), 2020, and 2021 (ie, years during the COVID-19 pandemic), rather than for all years in this study.

Two separate multivariable logistic regression models were created to assess the independent associations of potential risk factors with delivery-related maternal mortality and SMM, adjusting for confounders. For both models, patient demographics, hospital and visit characteristics, and MCI conditions were included as covariates. In the mortality regression, the SMM complications were added to the model to account for disease conditions that happened during the delivery-related hospitalization before the occurrence of mortality. In addition, a logistic regression of mortality without SMMs as covariates was performed as a sensitivity analysis. Backward selection with $P < .05$ was used to select final models, with the exception that patient age, race and ethnicity, delivery type, and study year and Q were kept in the model regardless of *P* values. For the mortality model, SMM conditions that were closely related to each other were combined. Combined variables included bleeding complications, cardiovascular complications, respiratory complications, and an eclampsia or preeclampsia category. In the regression of SMM, eclampsia was 1 component of the SMM outcome, while the preeclampsia conditions were used as separate covariates in the model.

Adjusted mortality and SMM rates for the overall study population were calculated using recycled prediction methods[16,18] based on estimates from the regressions. Adjusted mortality and SMM rates were also reported by age group, race and ethnicity, and type of delivery, based on additional regression models that included interaction terms between year and the variable of interest.

All analyses were conducted using Python Scikit-Learn package version 0.22.1 (Python Software Foundation). Analysis of the data took place from February 2021 through March 2023. *P* values were 2-sided, and statistical significance was set at $P < .05$.

Results

Patient Characteristics

Among the 11 628 438 eligible discharges related to delivery, more than half (6 498 217 [55.9%]) were among patients aged 25 to 34 years, 1 885 571 (16.2%) were among patients aged 35 years or older, and 759 301 (6.5%) were among patients aged 10 to 19 years. There were 437 579 (3.8%) Asian patients, 92 547 (0.8%) American Indian patients, 1 640 355 (14.1%) Black patients, 1 762 392

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(15.2%) Hispanic patients, 83 189 (0.7%) Pacific Islander patients, and 6 194 139 (53.3%) White patients. Medicaid was identified as the primary payer for 4 958 174 discharges (42.6%). The census region distribution reflected the geographic distribution of the PHD patient population. Approximately one-third of the sample underwent cesarean delivery. The proportion of discharges in younger age groups decreased while the proportion in older age groups increased over the study period. The distribution of race and ethnicity, primary payer type, census region, and delivery type did not differ significantly across years (**Table 1**).

Maternal Comorbid Conditions

As shown in Table 1, obesity (91.0 per 1000 discharges), gestational diabetes (74.3 per 1000 discharges), and tobacco use (58.2 per 1000 discharges) were the most common comorbidities, followed by gestational hypertension, asthma, preeclampsia, preexisting hypertension, and substance use disorder. Compared with the prevalence in 2008, higher prevalence of sickle cell disease, gestational hypertension, severe preeclampsia, preexisting hypertension, substance use disorder, asthma, gestational diabetes, obesity, and hemorrhage were observed in 2021 (Table 1).

Prevalence and Trend of SMMs

The unadjusted prevalence of any SMM was estimated to be 163.3 per 10 000 discharges for the overall sample from 2008 to 2021, with higher prevalence observed in 2021 (206.1 per 10 000 discharges) compared with 2008 (135.2 per 10 000 discharges). Blood transfusion was the most common SMM observed, with a prevalence of 108.4 per 10 000 discharges. Other relatively common SMMs included disseminated intravascular coagulation (24.7 per 10 000 discharges), hysterectomy (11.0 per 10 000 discharges), acute respiratory distress syndrome (9.8 per 10 000 discharges), acute kidney failure (9.7 per 10 000 discharges), sepsis (7.4 per 10 000 discharges), eclampsia (7.2 per 10 000 discharges), shock (6.1 per 10 000 discharges), and acute heart failure or pulmonary edema (5.6 per 10 000 discharges). Prevalence of acute kidney failure, acute respiratory distress syndrome, sepsis, shock, mechanical ventilation, blood transfusion, and hysterectomy were higher in 2021 than in 2008 (Table 1).

As seen in **Figure 1**A, the adjusted prevalence of any SMM increased from Q1 2008 (146.8 per 10 000 discharges) to Q4 2021 (179.8 per 10 000 discharges). The increasing trend was observed in all age groups with the greatest change observed in patients aged 45 years or older and those aged 10 to 19 years (Figure 1B). Consistent increasing trend was also observed in all racial and ethnic groups, with the biggest increase observed among Pacific Islander patients (from 132.0 per 10 000 discharges in Q1 2008 to 298.8 per 10 000 discharges in Q4 2021), American Indian patients (from 156.5 per 10 000 discharges in Q1 2008 to 245.0 per 10 000 discharges in Q4 2021), and Asian patients (from 133.4 per 10 000 discharges in Q1 2008 to 238.2 per 10 000 discharges in Q4 2021) (Figure 1C). A significant increase in adjusted SMM prevalence was observed in patients undergoing cesarean delivery (from 252.4 per 10 000 discharges in Q1 of 2008 to 312.1 per 10 000 discharges in Q4 of 2021), and a similarly increasing trend was seen in patients with vaginal delivery (from 84.4 per 10 000 discharges in Q1 of 2008 to 108.4 per 10 000 discharges in Q4 of 2021) (Figure 1D).

Unadjusted and Adjusted Trend of In-Hospital Delivery-Related Mortality

As shown in **Figure 2**A, a downward trend was observed for in-hospital mortality among deliveries after adjusting for changes in patient demographic, visit, hospital, and clinical characteristics. From Q1 of 2008 to Q4 of 2021, the adjusted in-hospital mortality decreased from 10.6 per 100 000 discharges to 4.6 per 100 000 discharges. Each subsequent year after 2008 had an 11% decrease in odds of death compared with the previous year (adjusted odds ratio [aOR], 0.89; 95% CI, 0.87-0.92) (**Table 2**). There was an increase in mortality from Q2 of 2020 through Q4 of 2021 that may be associated with the COVID-19 pandemic. However, after controlling for COVID-19 diagnosis, the adjusted trend decreased consistently across the full study period. The downward trend for in-hospital mortality was observed in all age groups, with the biggest decrease occurring in patients

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Table 1. Demographic and Clinical Characteristics of Hospital Inpatient Discharges for Newborn Delivery From 2008 to 2021

Characteristic	Overall (2008-2021) (N = 11 628 438)	2008 (n = 545 297)	2014 (n = 959 874)	2016 (n = 947 865)	2019 (n = 895 086)	2020 (n = 816 259)	2021 (n = 737 241)
Demographic characteristics, No. (%)							
Age group, y							
10-19	759 301 (6.5)	54 859 (10.1)	61 862 (6.4)	50 844 (5.4)	43 283 (4.8)	37 984 (4.7)	31 551 (4.3)
20-24	2 485 349 (21.4)	131 265 (24.1)	214 382 (22.3)	193 547 (20.4)	172 562 (19.3)	155 545 (19.1)	135 711 (18.4)
25-34	6 498 217 (55.9)	280 481 (51.4)	537 605 (56.0)	546 059 (57.6)	517 947 (57.9)	472 928 (57.9)	430 853 (58.4)
35-44	1 863 674 (16.0)	77 861 (14.3)	144 381 (15.0)	155 624 (16.4)	159 443 (17.8)	147 978 (18.1)	137 560 (18.7)
≥45	21 897 (0.2)	831 (0.2)	1644 (0.2)	1791 (0.2)	1851 (0.2)	1824 (0.2)	1566 (0.2)
Race and ethnicity							
American Indian	92 547 (0.8)	3614 (0.7)	7400 (0.8)	7031 (0.7)	7078 (0.8)	6452 (0.8)	5998 (0.8)
Asian	437 579 (3.8)	97 (<0.1)	40 970 (4.3)	45 423 (4.8)	38 467 (4.3)	37 268 (4.6)	33 805 (4.6)
Black	1 640 355 (14.1)	76 464 (14.0)	127 521 (13.3)	130 219 (13.7)	130 805 (14.6)	121 362 (14.9)	107 857 (14.6)
Hispanic	1 762 392 (15.2)	71 490 (13.1)	133 203 (13.9)	127 114 (13.4)	149 926 (16.7)	146 098 (17.9)	142 558 (19.3)
Pacific Islander	83 189 (0.7)	2 (<0.1)	7432 (0.8)	7584 (0.8)	7236 (0.8)	6745 (0.8)	5991 (0.8)
White	6 194 139 (53.3)	267 502 (49.1)	516 803 (53.8)	539 920 (57.0)	483 398 (54.0)	437 934 (53.7)	396 643 (53.8)
Other or unknown	1 418 237 (12.2)	126 128 (23.1)	126 545 (13.2)	90 574 (9.6)	78 176 (8.7)	60 400 (7.4)	44 389 (6.0)
Payer							
Medicaid	4 958 174 (42.6)	225 608 (41.4)	408 037 (42.5)	395 360 (41.7)	382 978 (42.8)	352 971 (43.2)	314 442 (42.7)
Commercial	5 828 008 (50.1)	276 056 (50.6)	481 244 (50.1)	485 290 (51.2)	451 857 (50.5)	409 232 (50.1)	376 045 (51.0)
Charity or indigent	18 816 (0.2)	1076 (0.2)	1792 (0.2)	1711 (0.2)	1240 (0.1)	964 (0.1)	706 (0.1)
Other	823 440 (7.1)	42 557 (7.8)	68 801 (7.2)	65 504 (6.9)	59 011 (6.6)	53 092 (6.5)	46 048 (6.2)
Census region							
West North Central	706 715 (6.1)	31 165 (5.7)	62 499 (6.5)	64 931 (6.9)	58 928 (6.6)	48 407 (5.9)	45 065 (6.1)
South Atlantic	3 134 865 (27.0)	154 102 (28.3)	241 336 (25.1)	244 261 (25.8)	234 747 (26.2)	217 066 (26.6)	184 555 (25.0)
East South Central	782 615 (6.7)	24 419 (4.5)	74 856 (7.8)	69 372 (7.3)	65 104 (7.3)	62 533 (7.7)	60 427 (8.2)
East North Central	1 639 978 (14.1)	62 432 (11.4)	135 177 (14.1)	134 357 (14.2)	145 291 (16.2)	135 827 (16.6)	127 165 (17.2)
Middle Atlantic	1 385 382 (11.9)	75 875 (13.9)	94 350 (9.8)	107 311 (11.3)	118 432 (13.2)	101 991 (12.5)	85 193 (11.6)
Pacific	1 585 909 (13.6)	100 431 (18.4)	136 760 (14.2)	153 325 (16.2)	79 905 (8.9)	74 353 (9.1)	68 644 (9.3)
West South Central	1 411 885 (12.1)	59 814 (11.0)	122 417 (12.8)	108 469 (11.4)	112 469 (12.6)	97 420 (11.9)	85 263 (11.6)
Mountain	705 575 (6.1)	25 806 (4.7)	68 574 (7.1)	44 687 (4.7)	63 908 (7.1)	62 070 (7.6)	63 692 (8.6)
New England	275 514 (2.4)	11 253 (2.1)	23 905 (2.5)	21 152 (2.2)	16 302 (1.8)	16 592 (2.0)	17 237 (2.3)
Delivery type							
Vaginal	7 748 427 (66.6)	359 909 (66.0)	641 973 (66.9)	629 087 (66.4)	604 494 (67.5)	547 666 (67.1)	493 125 (66.9)
Cesarean	3 830 448 (32.9)	184 583 (33.8)	316 392 (33.0)	306 935 (32.4)	285 510 (31.9)	263 072 (32.2)	239 587 (32.5)
Unknown	49 563 (0.4)	805 (0.1)	1509 (0.2)	11 843 (1.2)	5082 (0.6)	5521 (0.7)	4529 (0.6)
Maternal comorbid conditions, No. (rate per 1000 discharges)							
Pulmonary hypertension	2692 (0.2)	115 (0.2)	205 (0.2)	177 (0.2)	232 (0.3)	220 (0.3)	233 (0.3)
Placenta previa	70 431 (6.1)	2976 (5.5)	5537 (5.8)	5894 (6.2)	5934 (6.6)	5639 (6.9)	5177 (7.0)
Sickle cell disease	48 352 (4.2)	720 (1.3)	1922 (2.0)	5461 (5.8)	6375 (7.1)	6256 (7.7)	5536 (7.5)
Gestational hypertension	584 415 (50.3)	17 728 (32.5)	39 796 (41.5)	47 693 (50.3)	60 811 (67.9)	60 194 (73.7)	60 685 (82.3)

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Table 1. Demographic and Clinical Characteristics of Hospital Inpatient Discharges for Newborn Delivery From 2008 to 2021 (continued)

Characteristic	Overall (2008-2021) (N = 11 628 438)	2008 (n = 545 297)	2014 (n = 959 874)	2016 (n = 947 865)	2019 (n = 895 086)	2020 (n = 816 259)	2021 (n = 737 241)
Mild preeclampsia or unspecified preeclampsia	329 904 (28.4)	14 760 (27.1)	28 488 (29.7)	22 786 (24.0)	26 110 (29.2)	24 839 (30.4)	23 182 (31.4)
Severe preeclampsia	342 672 (29.5)	9888 (18.1)	23 600 (24.6)	27 187 (28.7)	36 222 (40.5)	35 129 (43)	35 278 (47.9)
Chronic kidney disease	23 557 (2.0)	1293 (2.4)	2815 (2.9)	1101 (1.2)	1113 (1.2)	1101 (1.3)	1031 (1.4)
Preexisting hypertension	310 054 (26.7)	10 242 (18.8)	23 948 (24.9)	27 794 (29.3)	26 953 (30.1)	27 114 (33.2)	27 119 (36.8)
Congenital heart disease	10 250 (0.9)	395 (0.7)	875 (0.9)	728 (0.8)	837 (0.9)	846 (1.0)	852 (1.2)
Systemic lupus erythematosus	15 092 (1.3)	498 (0.9)	1283 (1.3)	1172 (1.2)	1228 (1.4)	1292 (1.6)	1213 (1.6)
HIV	9612 (0.8)	487 (0.9)	695 (0.7)	762 (0.8)	667 (0.7)	687 (0.8)	584 (0.8)
Multiple gestation	214 087 (18.4)	10 360 (19.0)	18 208 (19.0)	17 476 (18.4)	15 604 (17.4)	13 606 (16.7)	12 751 (17.3)
Drug abuse	250 039 (21.5)	6353 (11.7)	18 887 (19.7)	21 921 (23.1)	25 035 (28.0)	25 489 (31.2)	24 114 (32.7)
Alcohol abuse	10 591 (0.9)	501 (0.9)	1066 (1.1)	731 (0.8)	649 (0.7)	622 (0.8)	634 (0.9)
Tobacco use	676 360 (58.2)	31 371 (57.5)	61 885 (64.5)	52 893 (55.8)	49 195 (55.0)	43 355 (53.1)	36 879 (50.0)
Cardiac valvular disease	24 109 (2.1)	2697 (4.9)	1974 (2.1)	1336 (1.4)	1167 (1.3)	1129 (1.4)	1060 (1.4)
Chronic congestive heart failure	10 250 (0.9)	395 (0.7)	875 (0.9)	728 (0.8)	837 (0.9)	846 (1)	852 (1.2)
Asthma	532 746 (45.8)	17 054 (31.3)	41 758 (43.5)	44 603 (47.1)	49 168 (54.9)	49 847 (61.1)	48 420 (65.7)
Preexisting diabetes	116 122 (10.0)	4688 (8.6)	10 306 (10.7)	9512 (10.0)	8702 (9.7)	8650 (10.6)	7241 (9.8)
Gestational diabetes	864 546 (74.3)	29 409 (53.9)	66 520 (69.3)	71 338 (75.3)	77 422 (86.5)	80 041 (98.1)	76 955 (104.4)
Obesity	1 057 844 (91.0)	18 550 (34.0)	76 178 (79.4)	91 702 (96.7)	116 107 (129.7)	122 908 (150.6)	121 771 (165.2)
Cystic fibrosis	959 (0.1)	36 (0.1)	55 (0.1)	92 (0.1)	54 (0.1)	130 (0.2)	126 (0.2)
Previous cesarean delivery	2 027 278 (174.3)	86 087 (157.9)	170 848 (178.0)	168 750 (178.0)	160 945 (179.8)	145 359 (178.1)	131 693 (178.6)
Other clinical conditions							
Hemorrhage	551 647 (47.4)	18 108 (33.2)	38 522 (40.1)	50 010 (52.8)	52 302 (58.4)	50 408 (61.8)	49 398 (67.0)
Severe maternal morbidities, No. (rate per 10 000 discharges)							
Acute myocardial infarction	370 (0.3)	7 (0.1)	18 (0.2)	24 (0.3)	40 (0.4)	54 (0.7)	40 (0.5)
Acute kidney failure	11 304 (9.7)	262 (4.8)	702 (7.3)	905 (9.5)	1275 (14.2)	1350 (16.5)	1426 (19.3)
Acute respiratory distress syndrome	11 430 (9.8)	245 (4.5)	820 (8.5)	899 (9.5)	994 (11.1)	1272 (15.6)	1695 (23.0)
Amniotic fluid embolism	571 (0.5)	25 (0.5)	36 (0.4)	51 (0.5)	55 (0.6)	44 (0.5)	37 (0.5)
Aneurysm	289 (0.2)	5 (0.1)	20 (0.2)	30 (0.3)	30 (0.3)	31 (0.4)	21 (0.3)
Cardiac arrest or ventricular fibrillation	1065 (0.9)	38 (0.7)	87 (0.9)	102 (1.1)	70 (0.8)	86 (1.1)	137 (1.9)
Cardioversion	1040 (0.9)	35 (0.6)	73 (0.8)	78 (0.8)	85 (0.9)	94 (1.2)	103 (1.4)
Disseminated intravascular coagulation	28 722 (24.7)	1418 (26.0)	2709 (28.2)	1848 (19.5)	1789 (20)	1594 (19.5)	1614 (21.9)
Eclampsia	8367 (7.2)	448 (8.2)	571 (5.9)	969 (10.2)	602 (6.7)	562 (6.9)	530 (7.2)
Heart failure or arrest during procedure	677 (0.6)	84 (1.5)	72 (0.8)	7 (0.1)	13 (0.1)	7 (0.1)	12 (0.2)
Puerperal cerebrovascular disorders	3492 (3.0)	186 (3.4)	260 (2.7)	287 (3.0)	274 (3.1)	268 (3.3)	291 (3.9)
Acute heart failure or pulmonary edema	6567 (5.6)	264 (4.8)	426 (4.4)	575 (6.1)	601 (6.7)	580 (7.1)	576 (7.8)
Severe anesthesia complications	1111 (1.0)	103 (1.9)	107 (1.1)	71 (0.7)	59 (0.7)	40 (0.5)	42 (0.6)
Sepsis	8594 (7.4)	249 (4.6)	606 (6.3)	760 (8.0)	858 (9.6)	871 (10.7)	973 (13.2)
Shock	7112 (6.1)	161 (3.0)	488 (5.1)	633 (6.7)	745 (8.3)	726 (8.9)	784 (10.6)
Sickle cell anemia with crisis	1131 (1.0)	56 (1.0)	82 (0.9)	86 (0.9)	99 (1.1)	88 (1.1)	68 (0.9)

(continued)

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Table 1. Demographic and Clinical Characteristics of Hospital Inpatient Discharges for Newborn Delivery From 2008 to 2021 (continued)

Characteristic	Overall (2008-2021) (N = 11 628 438)	2008 (n = 545 297)	2014 (n = 959 874)	2016 (n = 947 865)	2019 (n = 895 086)	2020 (n = 816 259)	2021 (n = 737 241)
Air and thrombotic embolism	2877 (2.5)	90 (1.7)	179 (1.9)	271 (2.9)	291 (3.3)	258 (3.2)	300 (4.1)
Blood transfusion	125 999 (108.4)	4746 (87.0)	10 498 (109.4)	9347 (98.6)	9971 (111.4)	9704 (118.9)	9727 (131.9)
Hysterectomy	12 738 (11.0)	476 (8.7)	977 (10.2)	1033 (10.9)	1121 (12.5)	1134 (13.9)	944 (12.8)
Temporary tracheostomy	324 (0.3)	14 (0.3)	26 (0.3)	15 (0.2)	17 (0.2)	27 (0.3)	57 (0.8)
Ventilation	4154 (3.6)	39 (0.7)	128 (1.3)	524 (5.5)	506 (5.7)	519 (6.4)	675 (9.2)
Any severe maternal morbidity	189 908 (163.3)	7374 (135.2)	15 366 (160.1)	14 410 (152)	15 250 (170.4)	14 961 (183.3)	15 192 (206.1)

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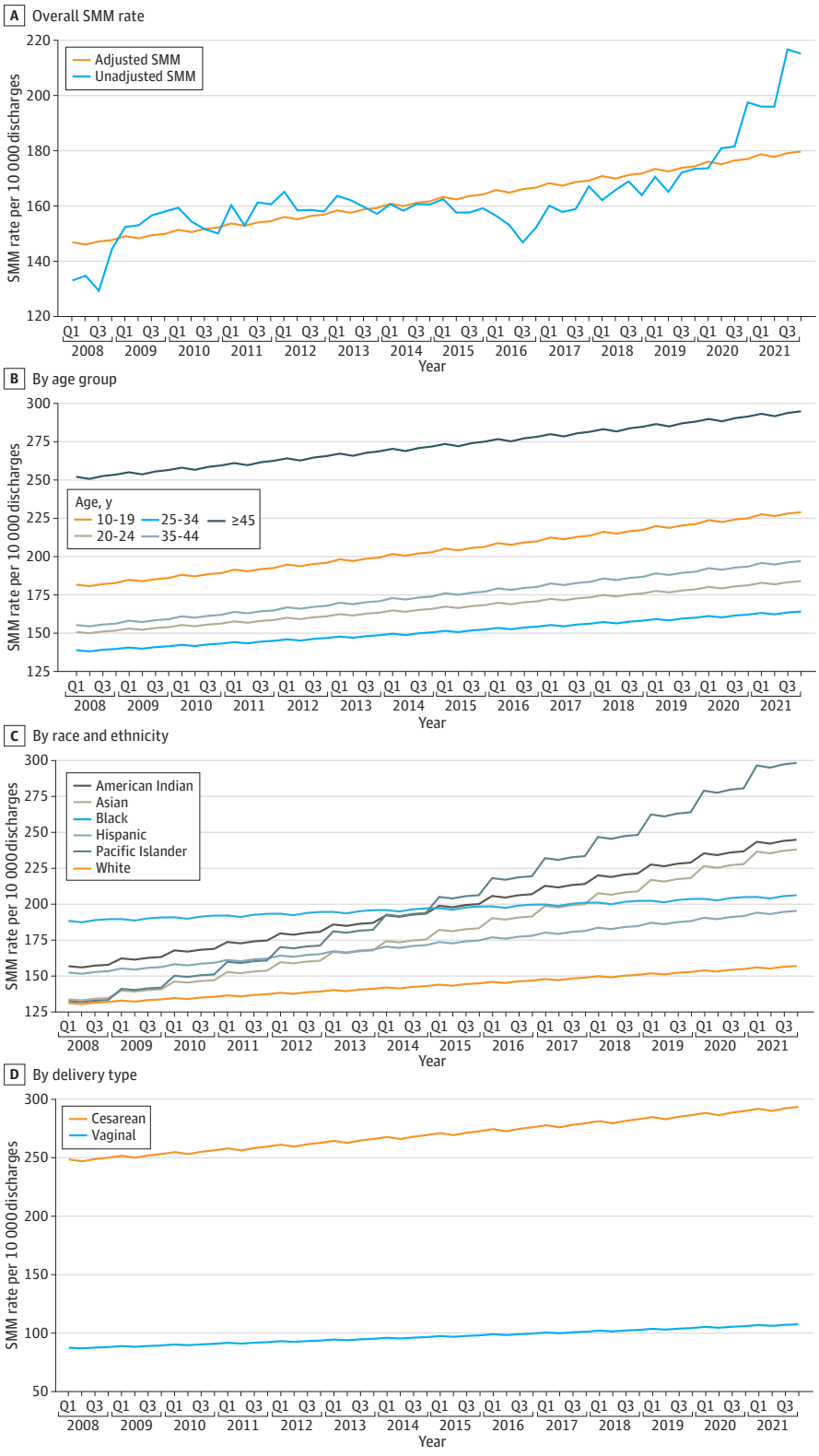
Figure 1. Trend of Unadjusted and Regression-Adjusted Severe Maternal Morbidity (SMM) Rates Among Hospital Inpatient Discharges for Newborn Delivery, 2008 to 2021, Overall and by Age Group, Race and Ethnicity, and Delivery Type



Q indicates quarter.

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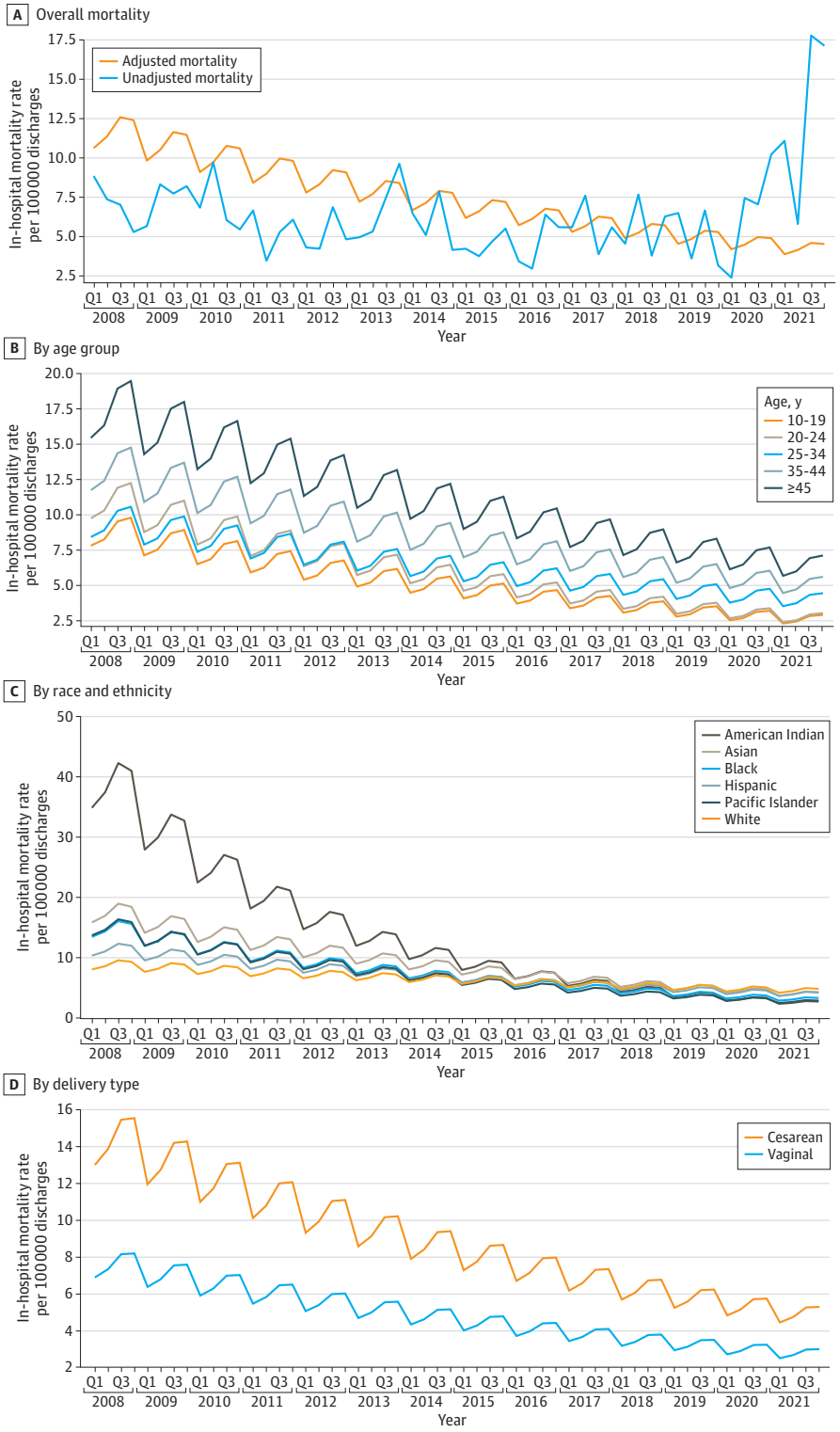
Figure 2. Trend of Unadjusted and Regression-Adjusted In-Hospital Mortality Among Hospital Inpatient Discharges for Newborn Delivery, 2008 to 2021, Overall and by Age Group, Race and Ethnicity, and Delivery Type



Q indicates quarter.

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Table 2. Estimates From the Multivariable Logistic Regression of In-Hospital Mortality and Any SMM Among Hospital Inpatient Discharges for Newborn Delivery, 2008 to 2021

Variable	Adjusted OR (95% CI)		
	In-hospital mortality[a]	In-hospital mortality sensitivity analysis[b]	Any SMM[c]
Age group, y			
10-19	0.74 (0.48-1.14)	0.61 (0.42-0.89)	1.39 (1.36-1.42)
20-24	0.90 (0.70-1.15)	0.70 (0.56-0.86)	1.10 (1.08-1.11)
25-34	1 [Reference]	1 [Reference]	1 [Reference]
35-44	1.49 (1.22-1.84)	2.16 (1.83-2.54)	1.17 (1.16-1.19)
≥45	1.95 (0.83-4.55)	6.01 (3.16-11.41)	1.76 (1.65-1.88)
Year	0.89 (0.87-0.92)	0.95 (0.93-0.97)	1.02 (1.01-1.02)
Diagnosis code version (*ICD-10-CM* vs *ICD-9-CM*)	NE	NE	0.92 (0.90-0.94)
Race			
White	1 [Reference]	1 [Reference]	1 [Reference]
American Indian	1.86 (0.95-3.64)	1.93 (1.10-3.39)	1.41 (1.35-1.48)
Asian	1.37 (0.88-2.14)	1.61 (1.11-2.34)	1.33 (1.30-1.36)
Black	1.09 (0.86-1.37)	1.78 (1.47-2.15)	1.39 (1.38-1.41)
Hispanic	1.06 (0.81-1.39)	1.04 (0.83-1.31)	1.22 (1.20-1.24)
Other or unknown	1.02 (0.77-1.35)	1.19 (0.94-1.51)	1.21 (1.19-1.22)
Pacific Islander	0.89 (0.29-2.76)	1.25 (0.48-3.26)	1.53 (1.45-1.61)
Quarter			
First	0.80 (0.62-1.04)	0.91 (0.74-1.13)	0.99 (0.98-1.01)
Second	0.88 (0.68-1.14)	0.91 (0.74-1.13)	0.99 (0.98-1.00)
Third	1.02 (0.80-1.31)	1.03 (0.85-1.26)	1.00 (0.98-1.01)
Fourth	1 [Reference]	1 [Reference]	1 [Reference]
Urbanicity of hospital population served (rural vs urban)	NE	NE	0.88 (0.87-0.90)
Primary payer			
Commercial	1 [Reference]	1 [Reference]	1 [Reference]
Charity or indigent	1.51 (0.27-8.53)	2.36 (0.78-7.09)	1.57 (1.42-1.73)
Medicaid	1.73 (1.41-2.13)	1.66 (1.4-1.97)	1.22 (1.20-1.23)
Other	1.72 (1.25-2.36)	1.69 (1.31-2.20)	1.23 (1.21-1.25)
Teaching hospital (vs nonteaching)	NE	NE	1.18 (1.17-1.20)
Hospital region			
South Atlantic	1 [Reference]	1 [Reference]	1 [Reference]
East North Central	0.91 (0.67-1.24)	0.87 (0.68-1.11)	0.94 (0.93-0.95)
East South Central	1.42 (1.00-2.02)	1.29 (0.96-1.72)	0.90 (0.88-0.92)
Middle Atlantic	0.93 (0.68-1.27)	0.91 (0.70-1.18)	1.15 (1.13-1.16)
Mountain	1.04 (0.70-1.54)	1.31 (0.95-1.79)	0.87 (0.85-0.89)
New England	0.73 (0.35-1.53)	0.62 (0.32-1.18)	1.09 (1.06-1.12)
Pacific	0.66 (0.48-0.92)	0.66 (0.50-0.88)	0.84 (0.83-0.86)
West North Central	1.36 (0.90-2.07)	1.28 (0.91-1.80)	0.88 (0.86-0.90)
West South Central	1.07 (0.80-1.45)	1.11 (0.88-1.42)	1.09 (1.08-1.11)
Admission type			
Elective	1 [Reference]	1 [Reference]	1 [Reference]
Emergent	3.17 (2.48-4.04)	5.17 (4.26-6.26)	1.50 (1.48-1.52)
Urgent	1.20 (0.96-1.49)	1.55 (1.29-1.87)	1.08 (1.06-1.09)
Trauma center	16.65 (9.89-28.04)	16.21 (10.36-25.35)	1.40 (1.31-1.50)
Other or unknown	1.46 (0.90-2.36)	1.43 (0.96-2.15)	1.28 (1.25-1.31)
Delivery type			
Vaginal	1 [Reference]	1 [Reference]	1 [Reference]
Cesarean	2.28 (1.87-2.79)	3.94 (3.34-4.64)	3.00 (2.97-3.03)
Comorbidities (yes vs no)			
COVID-19 diagnosis	13.31 (8.95-19.79)	41.63 (31.7-54.67)	4.44 (4.23-4.66)

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Table 2. Estimates From the Multivariable Logistic Regression of In-Hospital Mortality and Any SMM Among Hospital Inpatient Discharges for Newborn Delivery, 2008 to 2021 (continued)

Variable	Adjusted OR (95% CI)		
	In-hospital mortality[a]	In-hospital mortality sensitivity analysis[b]	Any SMM[c]
Placenta previa	NE	NE	6.32 (6.17-6.47)
Sickle cell disease	NE	NE	2.93 (2.82-3.05)
Gestational hypertension	NE	NE	1.29 (1.26-1.31)
Mild or unspecified preeclampsia	NE	NE	1.93 (1.89-1.97)
Severe preeclampsia	NE	NE	4.55 (4.48-4.62)
Chronic kidney disease	NE	NE	5.21 (4.99-5.44)
Preexisting hypertension	NE	NE	1.54 (1.50-1.57)
Chronic ischemic heart disease	NE	NE	3.92 (3.50-4.39)
Congenital heart disease	0.07 (0.01-0.34)	1.8 (0.46-7.08)	2.43 (2.23-2.66)
Systemic lupus erythematosus	3.68 (1.70-7.97)	7.63 (4.28-13.62)	1.95 (1.81-2.10)
HIV	3.94 (1.30-11.92)	3.03 (1.29-7.13)	1.47 (1.33-1.63)
Multiple gestation	NE	NE	2.20 (2.16-2.24)
Substance use disorder	1.38 (1.00-1.91)	3.44 (2.67-4.43)	1.71 (1.67-1.75)
Alcohol abuse	NE	NE	1.68 (1.52-1.85)
Cardiac valvular disease	0.19 (0.10-0.33)	6.73 (4.07-11.14)	3.50 (3.32-3.69)
Asthma	NE	NE	1.26 (1.24-1.28)
Preexisting diabetes	1.70 (1.20-2.42)	3.69 (2.81-4.86)	1.22 (1.18-1.25)
Gestational diabetes	NE	NE	0.96 (0.95-0.98)
Cystic fibrosis	40.17 (7.22-223.56)	35.97 (9.32-138.81)	1.76 (1.22-2.52)
Previous cesarean delivery	NE	NE	0.88 (0.87-0.89)
SMM (yes vs no)			
Acute kidney failure	1.30 (1.01-1.67)	Not included	Not included
Amniotic fluid embolism	7.67 (5.28-11.14)	Not included	Not included
Aneurysm	25.07 (7.40-84.91)	Not included	Not included
Disseminated intravascular coagulation	2.21 (1.69-2.88)	Not included	Not included
Puerperal cerebrovascular disorder	9.09 (6.11-13.51)	Not included	Not included
Sepsis	1.90 (1.45-2.51)	Not included	Not included
Shock	3.81 (2.96-4.91)	Not included	Not included
Air and thrombotic embolism	2.63 (1.79-3.86)	Not included	Not included
Sickle cell anemia with crisis	4.96 (2.17-11.33)	Not included	Not included
Bleeding complications (hemorrhage with no blood transfusion vs no bleeding)	2.73 (2.06-3.61)	Not included	Not included
Bleeding complications (blood transfusion vs no bleeding)	3.87 (3.05-4.91)	Not included	Not included
Hysterectomy	1.69 (1.24-2.318)	Not included	Not included
Respiratory complications[d]	5.92 (4.56-7.69)	Not included	Not included
Cardiovascular complications[e]	111.11 (86.69-142.42)	Not included	Not included

Abbreviations: *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; *ICD-10-CM*, *International Statistical Classification of Diseases, Tenth Revision, Clinical Modification*; NE, not entered in final model; OR, odds ratio; SMM, severe maternal morbidity.

[a] Overall, 728 deaths among 11 628 380 inpatient hospitalizations were included in the analysis; 58 patients reported by hospitals with in-hospital mortality followed by readmission were excluded from the regression of mortality. Additional covariates included in the regression of mortality are described in the Statistical Analysis section.

[b] A logistic regression of mortality without SMMs as covariates was performed as a sensitivity analysis.

[c] A total of 189 908 discharges with SMM (of 11 628 438 inpatient hospitalizations) were included in the analysis. Additional covariates included in the regression of severe maternal morbidity are described in the Statistical Analysis section.

[d] Respiratory complications included acute respiratory distress syndrome, temporary tracheostomy and ventilation as defined by the US Centers for Disease Control and Prevention.

[e] Cardiovascular complications included any of the following severe maternal morbidities: acute myocardial infarction, cardiac arrest or ventricular fibrillation, conversion of cardiac rhythm, heart failure or arrest during surgery or procedure, and pulmonary edema or acute heart failure as defined by the US Centers for Disease Control and Prevention.

aged 45 years or older (Figure 2B). A decreasing trend for in-hospital mortality was observed in all racial and ethnic groups. In particular, the greatest decrease in adjusted mortality was observed for American Indian patients: from 34.8 per 100 000 discharges in Q1 of 2008 to 2.7 per 100 000 discharges in Q4 of 2021 (Figure 2C; the 95% CI for mortality among American Indian patients is

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provided in eTable 4 in Supplement 1). In-hospital mortality consistently decreased during the study period for patients with cesarean delivery (from 12.6 per 100 000 discharges in Q1 of 2008 to 5.2 per 100 000 discharges in Q4 of 2021) and also for patients with vaginal delivery (from 6.6 per 100 000 discharges in Q1 of 2008 to 3.0 per 100 000 discharges in Q4 of 2021) (Figure 2D).

Risk Factors for In-Hospital Mortality and SMM

Compared with patients aged 25 to 34 years, those between 35 and 44 years had higher odds of dying during the index hospitalization (aOR, 1.49; 95% CI, 1.22-1.84). Although the association between race and mortality was not statistically significant in the regression in which SMMs were included as covariates, a sensitivity analysis showed that American Indian (aOR, 1.93, 95% CI, 1.10-3.39), Black (aOR, 1.78; 95% CI, 1.47-2.15), and Asian patients (aOR, 1.61, 95% CI, 1.11-2.34) had increased risk of death compared with White patients, suggesting that the racial disparity was partly attributable to the difference in the SMM rates across racial and ethnic groups. The mortality of Pacific Islander patients and Hispanic patients was not statistically significantly different from White patients in the sensitivity analysis. Patients with cesarean delivery had 2-fold higher odds of death than those with vaginal delivery (aOR, 2.28; 95% CI, 1.87-2.79). Patients with a COVID-19 diagnosis had a 13-fold increased odds of mortality compared with those without COVID-19 (aOR, 13.31; 95% CI, 8.95-19.79). Among comorbidity and acute complications assessed, cardiac complications, cystic fibrosis, aneurysm, trauma, and puerperal cerebrovascular disorder were among the risk factors associated with death during delivery-related hospitalization (Table 2).

As seen in Table 2, after adjusting for other risk factors and compared with patients aged 25 to 34 years, both patients younger than 24 years (eg, age 10-19 years: aOR, 1.39; 95% CI, 1.36-1.42) and older than 35 years (eg, age ≥45 years: aOR, 1.76; 95% CI, 1.65-1.88) had increased odds of SMM. All minority racial and ethnic groups were associated with increased odds of experiencing any SMM (Pacific Islander: aOR, 1.53; 95% CI, 1.45-1.61; American Indian: aOR, 1.41; 95% CI, 1.35-1.48; Black: aOR, 1.39; 95% CI, 1.38-1.41; Asian: aOR, 1.33; 95% CI, 1.30-1.36; Hispanic: aOR, 1.22; 95% CI, 1.20-1.24). Cesarean delivery (aOR, 3.00; 95% CI, 2.97- 3.03) and COVID-19 diagnosis (aOR, 4.44; 95% CI, 4.23-4.66) were also associated with substantially higher adjusted odds of SMM. Among all the chronic comorbidities assessed, placenta previa (aOR, 6.32; 95% CI, 6.17-6.47), chronic kidney disease (aOR, 5.21; 95% CI, 4.99-5.44), severe preeclampsia (aOR, 4.55; 95% CI, 4.48-4.62), cardiac valvular disease (aOR, 3.50; 95% CI, 3.32-3.69), chronic ischemic heart disease (aOR, 3.92; 95% CI, 3.50-4.39), and sickle cell disease (aOR, 2.93; 95% CI, 2.82-3.05) were associated with the highest odds of experiencing SMM (Table 2).

Discussion

This cross-sectional study examined rates of delivery-related in-hospital maternal mortality and SMM in a large national inpatient database. In this sample encompassing more than 11 million inpatient discharges, delivery-related in-hospital mortality was found to decrease significantly over a period of 14 years. The adjusted mortality per 100 000 discharges decreased by more than 50% from Q1 of 2008 to Q4 of 2021, likely demonstrating the impact of national strategies focused on improving the maternal quality of care provided by the hospitals during delivery-related hospitalizations. In contrast, the rates of overall SMM increased over time for the overall population, which may be attributable to preexisting conditions and the increasing trend in the age of delivering patients in the past decade. The increasing trend of adjusted SMM rates was seen in all racial and ethnic minority groups and was most prominent in Asian, American Indian, and Pacific Islander patients. The fact that many of the comorbid conditions are risk factors for mortality and SMM indicates that it is essential to consider comorbid conditions when assessing SMM and mortality and that better management of patients' comorbid conditions during pregnancy may help reduce SMM occurrence and ultimately decrease mortality risk. Further improvement in patient outcomes could be achieved if patients with known risk factors could access improved care during pregnancy and during hospital delivery.

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Delivery-related in-hospital maternal mortality in this study was lower than that reported in PMSS data, which defined pregnancy-related death as death during pregnancy or within 1 year of the end of pregnancy, from a cause related to pregnancy or its management.[3] PMSS data showed an increasing trend in pregnancy-related mortality during 1987 to 2017, which differs from our findings. A plausible explanation for these differences is that the timeframe for assessing mortality was substantially different between our study and the PMSS. Our study focused on mortality during delivery-related hospitalizations, which was associated with the change in quality of care for all patients in a hospital setting. In contrast, the PMSS estimates cover the entire pregnancy and postpartum period, which are associated with the overall burden of deaths among pregnant patients. Because a proportion of pregnancy-related deaths occur during delivery hospitalization, the differences between our findings and the PMSS estimates reinforced the importance of examining mortality separately for different stages of pregnancy and postpartum.

The study found that mortality risk was associated with several factors, including advanced maternal age, Medicaid as primary insurance, cesarean delivery, comorbid conditions, and severe complications during delivery. Similarly, a maternal age younger than 19 years or older than 35 years; being Asian, American Indian, Black, Hispanic, Pacific Islander; cesarean delivery; Medicaid enrollment; and maternal comorbid conditions were associated with higher risk of developing SMM during delivery. The racial and ethnic differences observed in delivery-related maternal mortality seem to be at least partly attributable to the racial and ethnic variation observed in SMM based on the main and sensitivity analyses of this study. Therefore, further research and understanding on the causes of both mortality and SMM, including the impact of comorbidities on maternal outcomes, is needed. Additionally, developing a national hospital measure to more clearly identify and reduce SMMs will likely have a beneficial impact on improving national quality strategies aimed at improving maternal health outcomes in the United States.

Limitations

The study has limitations. The PHD is a hospital administrative database and does not include as much clinical details as electronic health records. Identifying clinical conditions and procedures relied on the accuracy of hospital-reported diagnosis and procedure codes. Coding errors may lead to misclassification of variables. The definition of mortality was based on in-hospital death during the visit for delivery, without accounting for death before delivery admission or after discharge.

Maternal comorbid conditions were defined based on diagnosis during the visit for delivery. Conditions occurring before admission may not have been captured. Since the study spanned 14 years, there were changes in how hospitals collected and reported race and ethnicity. Hispanic was reported as a race category before 2011, while ethnicity was listed as a separate field in the patient admission form in later years. Hispanic race or ethnicity as defined in this study included patients who reported Hispanic as their race before 2011 and those who reported Hispanic as their ethnicity in 2012 and later, regardless of their reported race.

Conclusions

This large national study found a decreasing trend of in-hospital delivery-related maternal mortality during 2008 to 2021, regardless of racial or ethnic group, age, or mode of delivery, likely demonstrating the impact of national and local strategies focused on improving the maternal quality of care provided by hospitals during delivery-related hospitalizations. Risk factors for in-hospital delivery-related mortality included cesarean delivery, COVID-19 diagnosis, and comorbidities and acute complications. Analysis indicated that American Indian, Black, and Asian patients had a statistically significant increased risk of death compared with White patients only when not controlling for SMMs, suggesting that the racial difference in mortality could be at least partly attributable to the differences in SMM rates across racial groups (analysis of Pacific Islander and Hispanic patients were not statistically significant).

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From 2008 to 2021, there was an increasing trend of SMM rates, and chronic comorbid conditions were associated with higher rates. SMMs are known risk factors of maternal deaths and impose substantial social and economic burdens. Notably, disparities in both mortality and SMM remained across age, delivery mode, and racial and ethnic groups. These characteristics should be considered when designing maternal care quality improvement programs. As current national strategies increasingly focus on improving delivery-related maternal outcomes among high-risk groups, including racial and ethnic minority groups, it will become important to evaluate the effectiveness of these strategies in reducing occurrences of maternal mortality and SMM.

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Author Contributions: Messers Lipkin and Perigard had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPLEMENT 1.

eTable 1. *ICD-9-CM* and *ICD-10-CM* Diagnosis and Procedure Codes Used for Patient Inclusion and Exclusion
eTable 2. *ICD-9-CM* and *ICD-10-CM* Diagnosis and Procedure Codes Used to Identify Severe Maternal Morbidities
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SUPPLEMENT 2.

Data Sharing Statement

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Original research article

Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days☆,☆☆

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Abstract

Objective: The aim of this study was to report on the safety and efficacy of an evidence-based medical abortion regimen utilizing 200 mg of mifepristone orally followed by home use of 800 mcg misoprostol buccally 24–48 h later through 63 days estimated gestational age.

Study design: We analyzed outcomes in women presenting for medical abortion between April 1, 2006, and May 31, 2011, using an evidence-based alternative to the United States Food and Drug Administration (FDA)-approved regimen. Cases were identified for this descriptive study from our electronic practice management (EPM) database, and our electronic database on adverse events was queried for information on efficacy and safety. The primary outcome was successful abortion. Logistic regression was used to identify predictors of successful abortion.

Results: Among the 13,373 women who completed follow-up, efficacy of the regimen was 97.7%. Efficacy was highest at 29 to 35 days (98.8%) and 36 to 42 days (98.8%) of gestation and lowest at 57 to 63 days (95.5%). The odds of needing aspiration for any reason were greatest at higher gestational ages. Rates of infection requiring hospitalization and rates of transfusion were 0.01 and 0.03%, respectively.

Conclusions: An evidence-based regimen of 200 mg of mifepristone orally followed by home use of 800 mcg of buccal misoprostol 24–48 h later is safe and effective through 63 days estimated gestational age. Further, the need for aspiration for any reason was low, and hospitalization was rare.

Implications: This study reinforces the safety and efficacy of the evidence-based regimen for medical abortion (200 mg mifepristone orally followed by home use of 800 mcg of misoprostol buccally 24–48 h later) through 63 days estimated gestational age, and contributes to the existing evidence against restrictions requiring use of the FDA-approved regimen.

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Keywords: Medical abortion; Mifepristone; First-trimester abortion; Evidence-based regimen; Buccal misoprostol; Efficacy

1. Introduction

The United States Food and Drug Administration (FDA) approved the use of mifepristone and misoprostol for pregnancy termination in 2000. The regimen, labeled for use through 49 days estimated gestational age, required a minimum of three visits to the healthcare provider. Six hundred milligrams of mifepristone was taken orally at Visit 1, followed in 2 days by misoprostol 400 mcg, also taken orally. A third follow-up visit was required in 14 days to ensure that the abortion was complete. The efficacy of this regimen ranged from 92 to 97% [1–3]. Publications soon followed providing an evidence base for alterations to the regimen. Alterations included a lower dose of mifepristone, different routes of administration of misoprostol, variations in the timing of misoprostol administration, home use of misoprostol, and increasing the gestational age limit for the regimen [4–11]. A recent publication confirmed the low rate of significant adverse events with use of the evidence-based regimen [11].

In 2008, a prospective study was published describing the use of 200 mg of mifepristone followed in 24 to 36 h by 800 mcg of buccal misoprostol for pregnancy termination to 63

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days of gestation with a success rate for the regimen of 96.2% [8]. Despite the growing literature supporting evidence-based provision of medical abortion, some providers are required by law to limit the provision of medical abortion to that regimen, which was FDA-approved more than a decade ago [12]. The goal of the current study was to assess, in a much larger cohort of patients, the safety and efficacy of an evidence-based medical abortion regimen utilizing 200 mg of mifepristone orally followed by home use of 800 mcg of misoprostol buccally 24–48 h later through 63 days estimated gestational age.

2. Materials and methods

2.1. Medical abortion protocols and monitoring

Our large network of urban healthcare centers includes 19 health centers providing approximately 15,000 abortions per year, of which about 30% are medical abortions. Demographic information, treatment dates, and diagnostic codes for all patients were retrieved using the electronic practice management (EPM) billing system. Some clinical information was retrieved from an electronic medical records (EMR) system, which was gradually implemented across all study sites between 2008 and 2010. All patients undergo an ultrasound examination for pregnancy dating prior to abortion. The clinician administering the medication abortion performed and interpreted the ultrasound. All clinicians had undergone the same standardized training and were monitored regularly to ensure accuracy and to maintain consistency. Ultrasound machines using a Hadlock scale calculated gestational age in days; herein, we analyze and report gestational age in 7-day increments (e.g., 22 to 28 days). Since April 2006, our medical abortion regimen has consisted of 200 mg of mifepristone taken orally at the health center followed by 800 mcg of buccal misoprostol used by the patient at home 24 to 48 h later. Medical protocols during the study period allowed for repeat doses of misoprostol for patients who had an incomplete medical abortion. Data on which patients received a repeat dose are not available from the EPM system, but only in the EMR system; therefore, for patients seen at sites that had not yet implemented EMR at the time of treatment, information on whether a repeat dose of misoprostol was given is not available. For the first 3 years of the study period, the upper gestational age limit for this regimen was 56 days. In February 2009, based on newly published data, the upper limit was increased to 63 days [8]. All patients were scheduled to return in 7 to 14 days for a postabortion evaluation. Beginning in 2007, all patients also received routine antibiotic coverage beginning on the day of the mifepristone administration. The standard antibiotic regimen was a 7-day course of doxycycline (100 mg twice a day), with an alternative regimen of one dose of azithromycin (1 g) for cases in which doxycycline was contraindicated.

Our EPM database contains information on all patients undergoing medical abortion, including patient demographics and the ultrasound-determined gestational age. We also maintain a separate electronic database of adverse events including ongoing pregnancy, aspiration for symptoms and/or retained products of conception, infection requiring hospitalization, and hemorrhage requiring transfusion.

2.2. Statistical methods

Bivariate and multivariate logistic regression were used to assess predictors of successful medical abortion. Covariates available in our data set were poverty level, race/ethnicity, gestational age, and patient age; other patient-level data were not available. Results were considered statistically significant at $p < .05$. Statistical analysis was performed using Stata/SE 11.2 (College Station, TX).

The primary outcome of interest was successful abortion. A successful abortion was defined as expulsion of the pregnancy without the need for aspiration. Patients who required aspiration for an ongoing pregnancy or symptoms such as pain or bleeding were considered to have had unsuccessful medical abortions. We queried our adverse events database to identify continuing pregnancies (those pregnancies with documented fetal growth or cardiac activity seen at the follow-up), all cases of aspiration, and hospitalization for either infection or transfusion. We cross-checked this against the list of postprocedure visits in our EPM system in order to ensure that all cases had been identified.

Institutional review board (IRB) approval was obtained from the Ethical and Independent Review Service of Independence, MO, and an exemption for analysis of the existing data was granted by the Princeton University IRB.

3. Results

3.1. Sample description

For this descriptive study, we queried our EPM database and identified 15,890 patients who had a medical abortion between April 1, 2006, and May 31, 2011. During the period under review, medical abortions were provided at 14 different clinic sites belonging to our network in one urban area, all using the same evidence-based protocol. There were 2470 (15.5%) patients who failed to return for a follow-up visit and were excluded from analysis. An additional 20 patients were excluded from the analysis due to missing data on gestational age, and a further 27 patients were excluded because they did not complete the medical abortion (these patients either changed their mind and chose a surgical abortion, were ineligible for a medical abortion because they were beyond the 63-day gestational limit, or began the regimen but did not take all of the medications). This left 13,373 patients for analysis.

Demographic characteristics of the 13,373 women who had a medical abortion between April 1, 2006, and May 31, 2011, and who returned for follow-up are shown in Table 1. Half of the women were between the ages of 18 and 24, and small proportions were under the age of 18 (4.5%) or 40 or

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Table 1
Demographic characteristics of women having a medical abortion with mifepristone 200 mg and misoprostol 800 mcg buccally (*N*=13,373)

	n	%
Gestational age (days)		
22–28	554	4.1
29–35	1080	8.1
36–42	2495	18.7
43–49	4816	36.0
50–56	3142	23.5
57–63	1286	9.6
Poverty level (% FPL)		
0–100	9679	72.4
>100	3694	27.6
Race/ethnicity		
Hispanic/Latino	6215	46.5
White	3235	24.2
African American	1263	9.5
Asian	1172	8.8
Other/declined	1487	11.1
Patient age (years)		
<18	605	4.5
18–24	6684	50.0
25–29	3317	24.8
30–34	1613	12.1
35–39	855	6.4
40+	299	2.2

older (2.2%). Nearly half of women identified as Hispanic or Latino, and 72% reported an income at or below the poverty line. The most frequent gestational age in our data set was 43 to 49 days (36.0%), and the least frequent was 22 to 28 days (4.1%).

3.2. Frequency and predictors of successful abortion

Termination of pregnancy with 200 mg of oral mifepristone followed by 800 mcg of buccal misoprostol 24–48 h later was successful among 97.7% of women who completed follow-up. Only 307 (2.3%) of the 13,373 women included in this study underwent aspiration for any reason. Specifically, 70 (0.5%) women had a continuing pregnancy, and 237 (1.8%) women required aspiration for reasons other than continuing pregnancy, most commonly due to reported symptoms of pain and/or bleeding. Data on the need for a repeat dose of misoprostol were available from a subset of women from clinics in which the EMR system was used, which included 7335 women (54.8% of the total sample). Of these 7335 women, 87 (1.2%) received a repeat dose of misoprostol.

Table 2 shows the proportion of patients requiring aspiration for ongoing pregnancy or for symptoms, such as heavy bleeding, by gestational age. The proportion with ongoing pregnancy ranged from 0.15% for those at 36 to 42 days of gestation to 1.63% at 57 to 63 days of gestation. Compared with the reference category (43 to 49 days), odds of ongoing pregnancy were greater for those at the highest gestational age. The proportion of women treated with aspiration for symptoms, not ongoing pregnancy, ranged from 0.65 to 2.49%. The incidence of hospitalization for infection or hemorrhage requiring transfusion was very low (Table 3). In total, six women required hospitalization for any reason (two women were hospitalized for infection, and four were hospitalized for transfusion), and incidence was at or below 0.1% among all gestational ages.

In a multivariate logistic regression model (Table 4), poverty level and race/ethnicity were not significant predictors of successful abortion. Certain categories of gestational age were significantly associated with success; compared with the reference category (43 to 49 days), those at 36 to 42 days of gestation had greater odds of success, whereas those at 50 to 56 days and 57 to 63 days had lower odds of success. Compared with the reference category (18 to 24), those in the middle three age groups had significantly lower odds of success, but differences for those in the youngest (17 and under) and highest (40 and older) age groups were not significant.

3.3. Loss to follow-up

A comparison of patients who completed follow-up and those who were lost to follow-up is presented in Table 5. Compared with patients at 43 to 49 days of gestation, patients at higher gestational ages were more likely to be lost to follow-up. For patients with incomes at or below the Federal Poverty Level (FPL), the odds of being lost to follow-up were greater than those above FPL. Odds of being lost to follow-up were greater for those younger than 18 (compared with those 18 to 24) and lower for those aged 40 and older.

4. Discussion

4.1. General implications

This study demonstrates that the evidence-based regimen for medical abortion (mifepristone 200 mg orally followed by home use of misoprostol 800 mcg buccally 24–48 h later) is highly effective through 63 days estimated gestational age, with an overall success rate of 97.7%. This is higher than the efficacy rates reported in two pivotal trials used in submission for FDA approval of mifepristone,[1,2] yet utilizes one-third the dose of mifepristone (200 mg rather than 600 mg) and buccal administration and home use of misoprostol rather than oral administration in the clinic. Repeat dosing of misoprostol was administered in only 1.2% of patients for whom this information is available, and given the way in which the EMR system was implemented across study sites, we can assume that this rate would be representative of the entire sample. Although efficacy is lower at later gestational ages, even in the 57- to 63-day range, this evidence-based regimen was still more effective than rates reported in the FDA-approved regimen, which sets the upper gestational age limit at 49 days. Furthermore, the rates of unsuccessful abortion in this study are lower than the rates reported in the two trials that were initially submitted to the FDA for approval of mifepristone.

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Table 2
Aspiration for ongoing pregnancy, symptoms or any indication among those who completed follow-up, by gestational age.

Gestational age	Aspiration for ongoing pregnancy n (%)	OR	95% CI	Aspiration for symptoms n (%)	OR	95% CI	Aspiration for any reason * n (%)	OR	95% CI
22–28 days	4 (0.72)	2.69	0.87–8.27	11 (1.99)	1.39	0.73–2.65	15 (2.71)	1.39	0.80–2.43
29–35 days	5 (0.46)	1.72	0.61–4.83	7 (0.65)	0.45	0.21–0.98	13 (1.20)	0.61	0.34–1.10
36–42 days	4 (0.16)	0.59	0.19–1.82	25 (1.00)	0.70	0.44–1.10	30 (1.20)	0.61	0.40–0.92
43–49 days	13 (0.27)	ref		69 (1.43)	ref		94 (1.95)	ref	
50–56 days	23 (0.73)	2.72	1.38–5.39	64 (2.04)	1.43	1.01–2.02	97 (3.09)	1.60	1.20–2.13
57–63 days	21 (1.63)	6.13	3.06–12.28	32 (2.49)	1.76	1.15–2.80	58 (4.51)	2.37	1.70–3.31
Totals	70 (0.5)			237 (1.8)			307 (2.3)		

OR: odds ratio; CI: confidence interval
* This column includes 29 cases wherein reason for aspiration is unknown.

This study adds to the growing literature supporting provision of medical abortion using evidence-based regimens, and supports the conclusion that legislative efforts to restrict medical abortion to the FDA regimen are based on political goals to restrict abortion services, not efficacy or patient safety.

4.2. Limitations

Our study has some limitations. It is retrospective in nature and relies on the accuracy of our EPM database. However, review of our EPM system has shown a high degree of accuracy when compared with patient records [13]. In addition, we are not a closed system, and it is possible and even likely that some patients who experienced complications did not return to us for care. However, since many patients need to pay for aftercare obtained outside our system, but not within our system, it is more likely than not that the patients who did not return for follow-up did so because they did not feel that they needed follow-up, rather than that they were experiencing a complication. In that case, excluding them from our analysis would have tended to overestimate, rather than underestimate, the need for aspiration in our population. We based our analysis of efficacy only on those patients who did return for a follow-up visit, so we cannot exclude the possibility of additional visits or treatment elsewhere.

Loss to follow-up is common in studies of medical abortion, as many patients may determine on their own that their abortion is complete and that follow-up is not needed. The rate of loss to follow-up in this study (15.5%) is lower than loss to follow-up found in other clinical medical abortion studies, which report loss of follow-up of 18 to 45% [14–17]. We found that loss to follow-up was significantly more common among those at higher gestational ages; given that odds of success are lower among those with more advanced pregnancies, it is possible that this study underestimates the true odds of unsuccessful abortion. Loss to follow-up was significantly higher among the youngest age group and lower among the oldest age group, but as these age categories were unrelated to whether the abortion was successful, we do not believe that these differences would systematically bias our results.

Table 3
Hospitalizations for infection or transfusion in women having a medical abortion with mifepristone 200 mg and misoprostol 800 mcg buccally (*N*=13,373)

Gestational age	Patients *n*	Infections *n* (%)	Transfusions *n* (%)
22–28 days	554	0 (0.00)	1 (0.18)
29–35 days	1080	1 (0.09)	0 (0.00)
36–42 days	2495	0 (0.00)	0 (0.00)
43–49 days	4816	1 (0.02)	0 (0.00)
50–56 days	3142	0 (0.00)	3 (0.10)
57–63 days	1286	0 (0.00)	0 (0.00)
Total	13,373	2 (0.01)	4 (0.03)

4.3. Conclusion

In summary, an evidence-based regimen of mifepristone 200 mg orally followed by misoprostol 800 mcg buccally

Table 4
Factors associated with successful medical abortion in women using mifepristone 200 mg and misoprostol 800 mcg buccally (N=13,373)

	Successful *n* (%)	Unsuccessful *n* (%)	OR	95% CI
Gestational age (days)				
22–28	539 (97.3)	15 (2.7)	0.72	0.41–1.25
29–35	1067 (98.8)	13 (1.2)	1.68	0.94–3.01
36–42	2465 (98.8)	30 (1.2)	1.65	1.09–2.50
43–49	4722 (98.1)	94 (2.0)	Ref	
50–56	3045 (96.9)	97 (3.1)	0.62	0.47–0.83
57–63	1228 (95.5)	58 (4.5)	0.42	0.30–0.58
Total patients	13,066 (97.7)	307 (2.3)		
Poverty level (% FPL)				
0–100	9466 (97.8)	213 (2.2)	0.95	0.74–1.23
>100	3600 (97.5)	94 (2.5)	Ref	
Race/ethnicity				
Hispanic/Latino	6074 (97.7)	141 (2.3)	Ref	
White	3163 (97.8)	72 (2.2)	1.02	0.76–1.37
African American	1228 (97.2)	35 (2.8)	0.90	0.62–1.31
Asian	1146 (97.8)	26 (2.2)	1.02	0.67–1.57
Other/declined	1454 (97.8)	33 (2.2)	1.08	0.74–1.59
Patient age (years)				
<18	597 (98.7)	8 (1.3)	1.44	0.70–2.98
18–24	6560 (98.1)	124 (1.9)	Ref	
25–29	3233 (97.5)	84 (2.5)	0.72	0.54–0.96
30–34	1556 (96.5)	57 (3.5)	0.51	0.37–0.70
35–39	829 (97.0)	26 (3.0)	0.58	0.37–0.89
40+	291 (97.3)	8 (2.7)	0.68	0.33–1.40

OR, odds ratio; CI, confidence interval.

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Table 5
Loss to follow-up analysis among women having a medical abortion with mifepristone 200 mg and misoprostol 800 mcg buccally (N=13,373)

	Completed follow-up *n* (%)	Lost to follow-up *n* (%)	OR[a]	95% CI
Gestational age (days)				
22–28	554 (85.1)	97 (14.9)	1.00	0.79–1.25
29–35	1080 (86.3)	172 (13.7)	0.91	0.76–1.08
36–42	2495 (85.6)	419 (14.4)	0.96	0.84–1.09
43–49	4816 (85.1)	845 (14.9)	Ref	
50–56	3142 (83.0)	645 (17.0)	1.17	1.05–1.31
57–63	1286 (81.7)	288 (18.3)	1.28	1.10–.48
Poverty level (% FPL)				
0–100	9679 (83.7)	1887 (16.3)	1.24	1.12–1.38
>100	3694 (86.5)	579 (13.6)		
Race/ethnicity				
Hispanic/Latino	6215 (84.1)	1173 (15.9)		
White	3235 (83.4)	643 (16.6)	1.05	0.95–1.17
African American	1263 (82.8)	262 (17.2)	1.10	0.95–1.27
Asian	1172 (91.1)	115 (8.9)	0.52	0.43–0.64
Other/declined	1487 (84.5)	273 (15.5)	0.97	0.84–1.12
Patient age (years)				
<18	605 (80.0)	152 (20.0)	1.42	1.17–1.71
18–24	6684 (84.9)	1186 (15.1)		
25–29	3317 (83.7)	646 (16.3)	1.10	0.99–1.22
30–34	1613 (84.8)	289 (15.2)	1.01	0.88–1.16
35–39	855 (84.6)	156 (15.4)	1.03	0.86–1.23
40+	299 (89.0)	37 (11.0)	0.70	0.49–0.99

OR, odds ratio; CI, confidence interval.
[a] OR represents odds of being lost to follow-up.

48–72 h later is safe and effective through 63 days estimated gestational age. Further, need for aspiration for any reason was low, the chance of needing aspiration increased with gestational age at the time of medical abortion, and the frequency of hospitalization was rare. This study reinforces the safety and efficacy of the evidence-based regimen for medical abortion, and contributes to the evidence against restrictions that require use of the FDA-approved regimen.

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Patient Perspectives Regarding Clinician Communication During Telemedicine Compared With In-Clinic Abortion

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Abstract

OBJECTIVE: To explore patient perspectives regarding patient–clinician communication during telemedicine medication abortion compared to traditional, facility-based, in-clinic visits.

METHODS: We conducted semi-structured interviews with participants who received either live, face-to-face telemedicine or in-clinic medication abortion from a large, reproductive healthcare facility in Washington State. Using Miller's conceptual framework for patient-doctor communication in telemedicine settings, we developed questions exploring participants' experiences of the medication abortion consultation, including the clinician's verbal and non-verbal interpersonal approach and communication of relevant medical information, and the setting where care was received. We used inductive-deductive constant comparative analysis to identify major themes. We summarize patient perspectives using patient–clinician communication terms outlined in Dennis' quality abortion care indicator list.

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RESULTS: Thirty participants completed interviews (aged 20–38 years), 20 of whom had medication abortion by telemedicine and 10 who received in-clinic services. Participants receiving telemedicine abortion services reported high-quality patient–clinician communication, which came from their freedom to choose their consultation location and feeling more relaxed during clinical encounters. In contrast, most in-clinic participants portrayed their consultations as lengthy, chaotic, and lacking comfort. In all other domains, both telemedicine and in-clinic participants reported similar levels of interpersonal connection to their clinicians. Both groups appreciated medical information about how to take the abortion pills and relied heavily on clinic-based printed materials and independent online resources to answer questions during the at-home termination process. Both telemedicine and in-clinic participant groups were highly satisfied with their care.

CONCLUSION: Patient-centered communication skills used by clinicians during facility-based, in-clinic care translated well to the telemedicine setting. However, we found that patients receiving medication abortion through telemedicine favorably ranked their patient–clinician communication overall as compared to those in traditional, in-clinic settings. In this way, telemedicine abortion appears to be a beneficial patient-centered approach to this critical reproductive health service.

Précis:

Telemedicine appears to be a beneficial patient-centered approach to critically needed first-trimester abortion services.

Today, medication abortion makes up more than half of all abortions occurring in the United States (U.S.).[1] Abortion by telemedicine became more prevalent during the COVID-19 Public Health Emergency (PHE) when the U.S. Food and Drug Administration (FDA) temporarily, and then permanently suspended the mifepristone in-clinic dispensing requirement.[2] Requests for direct-to-patient telemedicine medication abortion services, in which patients choose where they receive care are expected to increase following the 2022 U.S. Supreme Court case Dobbs decision.[3,4]

Despite its growing use, data regarding best practices for patient-clinician communication when providing abortion care through telehealth are lacking. Patient-clinician communication is considered a critical element of patient-centered care, and has been associated with valuable health system outcomes, including increased patient trust, improved treatment adherence, overall positive patient experience, improved healthcare efficiency, and lower cost.[5–7]

For abortion care, however, patient-clinician communication considerations are unique because of both stigma and the systemic access issues that often compromise the ability for care to be patient-centered.[8] Unlike other aspects of reproductive health care, patients often obtain abortion care from someone other than their usual clinician, further compromising comfort and trust.[9–11] By interviewing participants who received direct-to-patient telemedicine medication abortion services, we explored the setting and how clinicians' interpersonal and communication behaviors affected the patient experience of patient–clinician communication compared to traditional, in-clinic medication abortion care.

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METHODS

We conducted a cross-sectional, in-depth, semi-structured interview study of patients who had recently received an in-clinic or telemedicine medication abortion. This study received institutional review board (IRB) approval by the University of Washington (UW) Human Subjects Division (ID: STUDY00013954) and is reported using the Consolidated Criteria for Reporting Qualitative Research (COREQ) guidelines.[12]

The team consists of a Principal Investigator (PI) who is a Complex Family Planning Fellowship-trained physician with master-level training in qualitative research (EMG), a PhD candidate in public health with experience working in abortion policy and qualitative research (AEF), a medical anthropologist and a master's level qualitative methods consultant (EAJ), a research coordinator with a masters of public health in maternal/child health (MRR), a medical student (EVY) and a family physician who provides abortion care with research expertise in implementation science (IMB). Throughout the study period, we enlisted a Community Advisory Board that represented Latina, young adult, and rural communities, two abortion advocacy organizations and a staff member from the clinic where we recruited participants.

We used Miller's conceptual framework for the evaluation of patient-clinician communication in telemedicine settings (Fig. 1).[13] We chose this model because it incorporates core components of patient-centered communication that have been widely quoted in the literature. The Miller framework also includes a category with factors related to the medium (e.g., telemedicine) used for the patient–clinician encounter, a key aspect we sought to evaluate among our participants.

This study used convenience sampling of all patients who had been given the option to receive medication abortion either by telemedicine or in-clinic from a Washington State independent, high-volume reproductive healthcare clinic organization, Cedar River Clinics (CRC). CRC is certified by several networks, including the National Abortion Federation. CRC began offering telemedicine medication abortion services using live, face-to-face video conferencing software in April 2020, in addition to continuing traditional in-person, clinic appointments. Telemedicine appointments require a known last menstrual period within 7 days, regular periods, no symptoms or risk factors for ectopic pregnancy and verbal confirmation of a positive pregnancy test, without requiring an ultrasound exam for gestational dating. Washington State permits nurse practitioners to provide medication abortion services, thus participants' clinical encounters involved either a physician or nurse practitioner.

To be eligible, participants had to speak and understand English, be at least 18 years old, had either telemedicine or in-clinic medication abortion in the prior month, and agree to an audio-recorded interview. Because we were most interested in evaluating patient–clinician communication with novel telehealth abortion, we purposively enrolled more telemedicine than in-clinic participants. To recruit participants, CRC staff asked every eligible patient to indicate their interest in being contacted by the UW study team when they signed their consent for abortion services. On a weekly basis, CRC staff provided contact information of

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interested patients to the research coordinator, who then attempted to contact each interested participant up to three times by email, text, or call over a two-week period. Contacted participants completed an eligibility survey in a secure REDCap database,[14] provided informed consent and scheduled an interview using an online calendar platform or by phone. Each participant received a $50 electronic gift card by email following their interview.

The qualitative methods consultant conducted semi-structured, in-depth interviews using HIPAA-compliant conferencing software at a time and place of the participant's choosing between September 2021-January 2022.

The research team developed the interview guide based on Miller's conceptual framework. Questions included the decision about the medication abortion service type (telemedicine vs. in-clinic), scheduling and attending their appointment, the clinician encounter, the setting where the encounter occurred, satisfaction with the care and clinical outcomes. Prior to initiating the interview, the qualitative methods consultant provided a brief description of the study team and assured participants their information would not be reported back to CRC. Each interview ranged between 35–60 minutes, was audio-recorded and transcribed. The interviewer recorded field notes after each interview, reflecting on data collection, personal biases, and patterns. No interviews were repeated. After the research team completed all the interviews, CRC provided the team with requested participant characteristic information (Table 1). Although an imperfect measure, we chose to list race/ethnicity as a proxy of shared lived experience to highlight the voices that informed this study.[15]

We used descriptive statistics to report participant characteristics. We used inductive-deductive constant comparative analysis to identify major themes and summarize patient perspectives consistent with Miller's conceptual model.[16] The analysts (EAJ and AEF) both coded the first ten interviews, meeting regularly to discuss coding discrepancies until they agreed on the codebook. After that point, they coded independently. The analysts created memos as they coded to track and synthesize thematic discussion and generate consensus. We defined data saturation as the point at which no relevant new themes related to the areas of focus were identified.[17] The analysts presented iterative summaries of the interviews to the larger research team and the community advisory board during the study's data collection and analysis phases. Dedoose software (version 9.0.62) was used to organize and manage the data . To increase the applicability of our findings to the abortion care setting specifically, we summarize patient perspectives using patient–clinician communication terms used in Dennis' quality abortion care indicator list (Fig 1).[18]

RESULTS

Of 42 patients who enrolled and scheduled interviews, our final study sample consisted of 30 individuals; 20 who received telemedicine and 10 who received in-clinic services (see Fig 2). Table 1 lists the selected sociodemographic characteristics of the study population. Twenty-three participants received their care from nurse practitioners and seven from physicians.

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We identified four separate domains of patient-clinician communication. Within these domains, we identified 8 relevant categories and 17 factors representing the perceptions of patients who received either telemedicine or in-clinic care. Domains, categories, factors, and illustrative quotations are listed in Table 2. Based on our findings, we summarize best practices for patient–clinician communication for medication abortion services (Box 1).

Domain 1: Medical Consultation Settings

Factors related to the medical consultation setting includes: (1) geographic accessibility of the appointment with the clinician, (2) efficiency of services and (3) perception of space where care was received in terms of privacy and comfort, all of which affected participants' attitudes about the consultation visit. Factors related to telemedicine consultation settings contrasted considerably with in-clinic (Table 2, Domain 1).

Participants who received telemedicine reported feeling like the care was accessible and efficient. They appreciated choosing where their medical consultation occurred. Examples of telemedicine consultation settings included one's own bedroom, a friend's home, or their car. Participants chose these spaces because they were quiet, familiar, convenient, away from kids or workplaces, providing a more controlled and relaxed consultation compared to the in-clinic setting. Many emphasized that telemedicine allowed them to talk more freely and openly, and feel more confident about the privacy of their abortion decision. For example, one participant shared, "I definitely felt at greater ease doing a telemedicine appointment when it came to going over the information…just because I was more comfortable in my own environment versus having to go to a doctor's office" (Participant 15, Telemedicine).

In contrast, participants described in-clinic visits as less accessible, inefficient, chaotic, and lacking privacy. Many struggled with transportation, traveling several hours to get to and from the clinic and expressed concern about potentially encountering someone they might know at the clinic. Compared to the shorter time spent with telemedicine, in-clinic appointments required a full day off work, with many describing having to wait for 4–6 hours, being moved to different waiting rooms and seeing multiple clinicians. In-clinic participants reported the setting as confusing, redundant and inefficient, with "lots of shuffling around." One participant shared feeling indifferent about the in-clinic setting, and thus did not connect with their clinician, stating: "I really didn't care who I spoke with. Honestly, I just wanted to get out…Get it done." (Participant 23, In-clinic). Many in-clinic participants expressed frustration about perceived COVID-19 restrictions of not being allowed to bring snacks, a support person, or their children, which would have made them more comfortable.

Domain 2: Patient–Clinician Interactions and Decision Making

This domain includes factors related to patient screening, how patients are treated by clinicians and staff, and respect for patients' ability to make decisions about their care. We did not detect major differences within this domain between participants who received their care through telemedicine versus in-clinic (Table 2, Domain 2).

Participants were given thoughtful, thorough and complete answers from their clinicians and felt respected and heard. Participants described emotionally empathetic, attentive,

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and non-judgmental interactions facilitated by clinicians with strong interpersonal skills. Telemedicine and in-clinic patients valued clinicians who personally customized the medical information to meet participant needs, concerns, and histories. A few participants preferred encounters that were brief and direct. In those instances, clinicians pivoted to that communication preference: “The doctor had a very straight to the point, matter-of-fact tone, and for me personally, that was helpful” (Participant 01, Telemedicine).

Domain 3: Clinician information provision, Postabortion Contraceptive Care, and Technical Competence

Within this domain, we compare factors related to participants receiving complete information about the medication abortion process and post-abortion contraceptive care, where to call if questions or complications arise, and quality of pain management. We did not detect differences within this domain between participants who received their care through telemedicine versus in-clinic (Table 2, Domain 3).

Most participants valued highly clinicians’ thorough explanation of the medication abortion process and symptom management. They appreciated when clinicians clearly and chronologically walked through the steps of medication abortion, including how to take the pills, when to expect symptoms to begin and end, and how to manage typical and atypical symptoms. They valued realistic, detailed information about how much blood to expect, especially compared to what is “normal,” intensity and length of pain, frequency of vomiting or diarrhea, and when symptoms typically subside. Most participants also appreciated clinicians’ suggestions regarding how to set up a supportive environment, such as requesting time off work, reassigning childcare responsibilities, and identifying a support person. Participants overwhelmingly applauded knowing about the clinic’s 24/7 nurse hotline for abortion-related questions, although few utilized it. “I didn’t feel as if I needed to (call) because I went online and I found my answers pretty easily…and everything seemed to be fine” (Participant 01, Telemedicine).

Many patients reported appreciating that the visit was not just about the abortion itself but included information about post-abortion contraceptive options: “We spent the bulk of the time talking about birth control…I said I wasn’t super worried about the abortion. I was more worried about birth control options because that’s something that I have struggled to figure out” (Participant 37, In-clinic). Participants expressed clinicians who took “extra” time to set up a contraceptive plan helped them feel confident that they would not need to pursue future abortions.

Clinicians seemed to lack technical competence related to adequate pain control, regardless of service type. Telemedicine and in-clinic participants equally made a point to mention the pain control recommendation given by clinicians was something they would have changed about their service. Participants appreciated hearing their options to treat the pain and cramping associated with pregnancy expulsion, such as heating pads, massage and over-the-counter medications and some conveyed adequate pain control. Nonetheless, a number of participants in both groups wished they had better access to pain relief (Table 2, Domain 3).

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Domain 4: Outcomes Related to Patient Knowledge and Attitudes

Health outcomes include participants' feeling like they understood the information provided, overall satisfaction, and having trust and confidence in the clinicians (Table 2, Domain 4).

Participants in both groups reported they had sufficient and accurate information that allowed them to comply with the medication regimen. They also reported the ability to recall clinician-shared information to manage symptoms at home and remain autonomous throughout their abortion. When asked if they felt prepared regarding pill taking and abortion side effects, most participants felt their clinicians provided sufficient levels of detail and they were, in turn, able to describe those details during the interviews, while others used clinic handouts or conducted web-searches. Regardless, some telemedicine and in-clinic participants reported being unprepared for amount and duration of vaginal bleeding and pelvic pain.

Overall, telemedicine and in-clinic participants shared high levels of satisfaction of care. Telemedicine participants overwhelmingly reported being satisfied with their abortion visit, many stating that they would pursue it again or recommend it. In-clinic participants, on the other hand, reported that patients should have the option to decide between telemedicine and in-clinic services, with about half stating "next time" they would choose telemedicine. Both telemedicine and in-clinic participants also shared similar attitudes about trusting the clinic to provide high-quality abortion care. Feelings of trust were especially evident with a telemedicine participant who became stressed about waiting online for her clinician who was running 30 minutes behind schedule but had not been notified by the clinic about this delay. Despite feeling uncertain, the participant's attitude toward the clinic as a place to trust made her satisfied about this particular encounter: "What stuck out to me [as I was waiting for the clinician] is that I felt really confident…like everything was going to be fine and that they were really there to support my choice…" (Participant 32, Telemedicine).

DISCUSSION

Our results show that both telemedicine and in-clinic participants felt respected, heard, understood, and valued by their clinician who provides abortion. The ability to choose the consultation location allowed telemedicine participants to feel like their encounter was more controlled and relaxed, while most in-clinic participants portrayed it as lengthy, chaotic, and lacking comfort. Because this study occurred when COVID-19 infection was still widespread, we surmise that many of the in-clinic participant experiences were due to unpredictable staff absences and social distancing requirements limiting clinic capacity. These in-clinic constraints ultimately compromised overall patient-clinician communication.

Both telemedicine and in-clinic participants had less favorable views about the clinic's pain control regimen, with several expressing they felt unprepared for the pain associated with medication abortion. This is unsurprising given the limited high-quality evidence regarding adequate pain management during medication abortion.[19] While participants stated they knew about the 24/7 nurse line, for reasons we did not thoroughly explore, participants who felt unprepared about the pain asserted they wish they had more pain medications at the moment of their abortion. This suggests that even if they had phoned the 24/7 line, they

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would have had to wait for a prescription to be called into a pharmacy for pick up, which may not have met their needs. Future studies should define patient characteristics associated with the need for additional pain medication to better inform clinic protocols.

Patient satisfaction with telemedicine over in-clinic care is consistent with other telemedicine abortion studies.[20,] Similar to other comparative telehealth and in-clinic studies, our telehealth participants appreciated reduced appointment times.[21,22] In contrast to a prior qualitative study in which some telemedicine participants stated they felt reduced personal interactions with their clinician than if they had seen them in-clinic, we detected no such difference.[23] This present study found that many of the patient–clinician interactions were consistent with behaviors and attributes associated with patient-centered communication. In essence, we showed that patient-centered communication qualities traditionally provided in the in-person abortion care setting can readily be translated to live, face-to-face video telemedicine.

The present study has several strengths. Based on our recruitment methods, each participant had had a medication abortion within the prior month. We also sampled to saturation and enrolled a relatively diverse participant population. Nonetheless, our study was limited by a convenience sample of participants who sought medication abortion within a single healthcare entity in Washington State, when the nation and state were still under a COVID-19 PHE. Thus, our findings may not be generalizable to all abortion care settings or to a time-period when the nation/state is not under a PHE. Our study evaluated participants who had live, face-to-face video telemedicine abortion care, which may not be applicable to asynchronous, online abortion care. Although we chose a conceptual framework that includes core components of patient-centered communication, we recognize it is a multifaceted construct, making it difficult to succinctly measure.[6,24,25] Ideally, patient–clinician communication is evaluated more comprehensively, using combinations of direct observations of clinical encounters or with standardized patients, validated survey measures that patients complete after the clinician encounter, post-visit patient interviews, and peer-colleague assessments.[6] Given the stigmatizing nature of abortion services, direct observations between clinicians and patients proved infeasible. Additionally, while there is a growing interest to develop and validate a person-centered abortion scale, such a scale has not been implemented for patients receiving abortion services through telemedicine.[26]

In conclusion, telemedicine is a beneficial patient-centered approach to critically needed first-trimester abortion services. To be patient-centered clinics should provide telemedicine abortion in the setting of the patient's choice and apply principles of patient-centered communication, including clinicians being non-judgmental, demonstrating respect and trust, tailoring to meet patients' needs, and explaining medication abortion processes and post-abortion contraceptive care as understood by patients. Clinics should also provide printed information with instructions about abortion pill use and where to call for questions and emergencies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1: Best practices for patient–physician communication for medication abortion encounters based on 30 in-depth interviews at a single healthcare facility

Patient–physician interactions:

- First minutes of the visit, create a non-judgmental, supportive, safe communication space
- Customize visits to meet patients' emotional/social needs. Some patients require straightforward facts and others need more emotional support
- Listen, pause
- Allow time/space for the patient to ask questions
- Express trust, validation and empowerment toward the fact this is the patient's decision to make
- Use check-back, have the patient summarize what was discussed

Provide the patient necessary information:

- Obtain baseline knowledge of what the patient knows and doesn't know about medication abortion
- Create awareness around the fact that most patients have already done extensive research
- Many patients already had an abortion, so consider asking about that first and tailor the visit accordingly
- Co-create a plan, order of events and ensure the patient knows what to expect in terms of passing the pregnancy at home
- Communicate first, yet flexible timing of events and symptoms [example, "Typical bleeding occurs between x # of days and y # of days but can also happen between z # of days and a # of days. If it is beyond a #, call the clinic."]
- Ensure the patient understands the details of taking the pills
- Ensure the patient has all the supplies potentially needed, especially for pain relief
- Post-abortion care is important- discuss birth control information and future fertility with the patient

Support:

- Ensure the patient knows how to get their questions answered
- Ensure the patient has social/emotional support in place
- Ensure the patient has a support person present at home during the procedure
- Reinforce that even though this is a home-based service, adequate time off work and childcare is needed
- High pain levels often necessitate last-minute medication or supplies so ensure someone can run to the pharmacy if needed

Setting:

- If telemedicine:
  - Send patients clear instructions about what programs to download before the telemedicine appointment and how to log onto the appointment
- If in-clinic:
  - Send patients clear directions that include how to find the clinic and get into the clinic Consider instructions with pictures
  - Communicate to patients what to expect inside the clinic (wait times, # of rooms/flow of visit, # of providers they will see)

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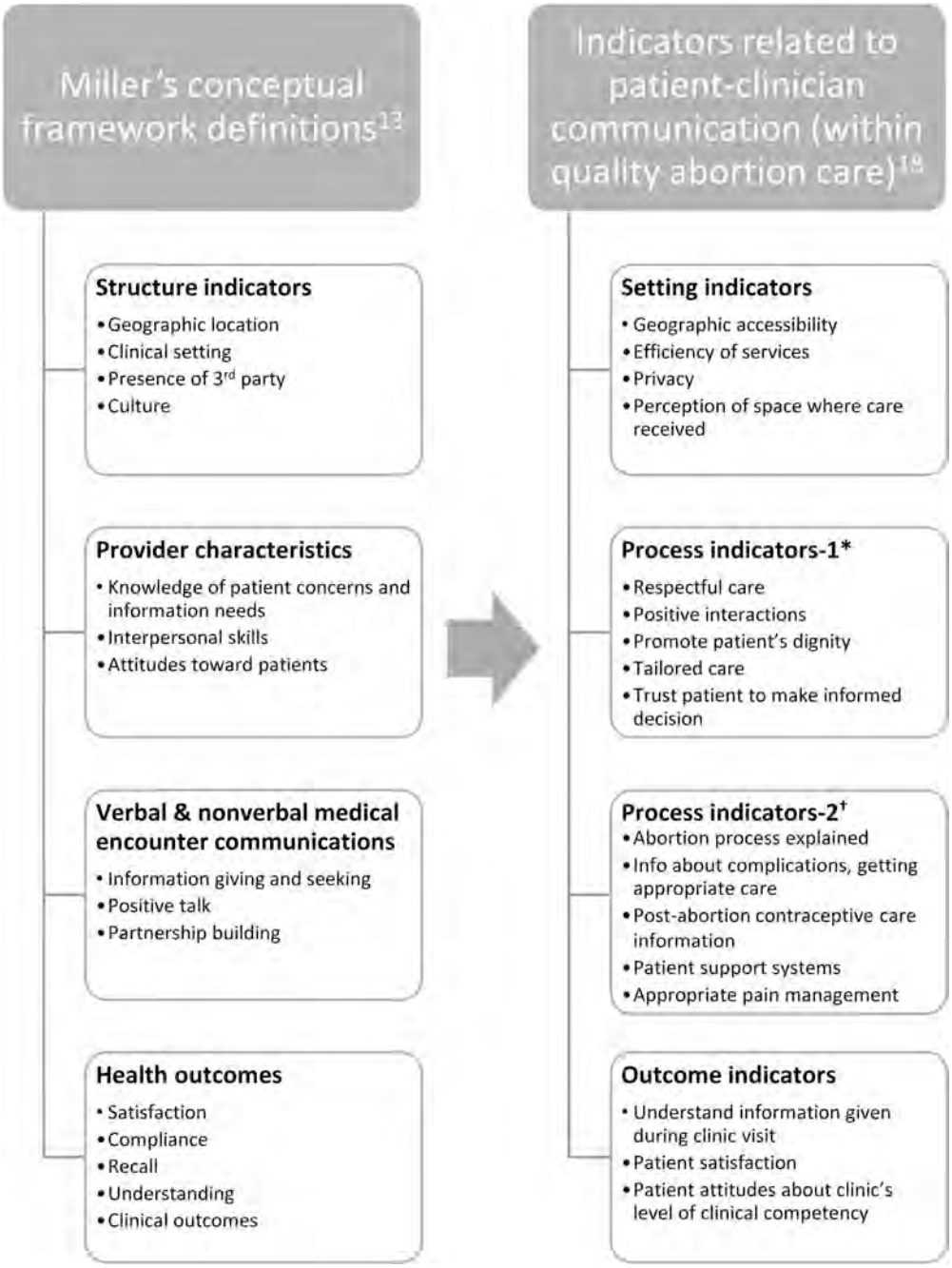

Fig. 1:

Adaptation of Miller's definitions to indicators related to patient–clinician communication within quality abortion care. *Client provider interactions, decision making. †Information provision, support, technical competence.

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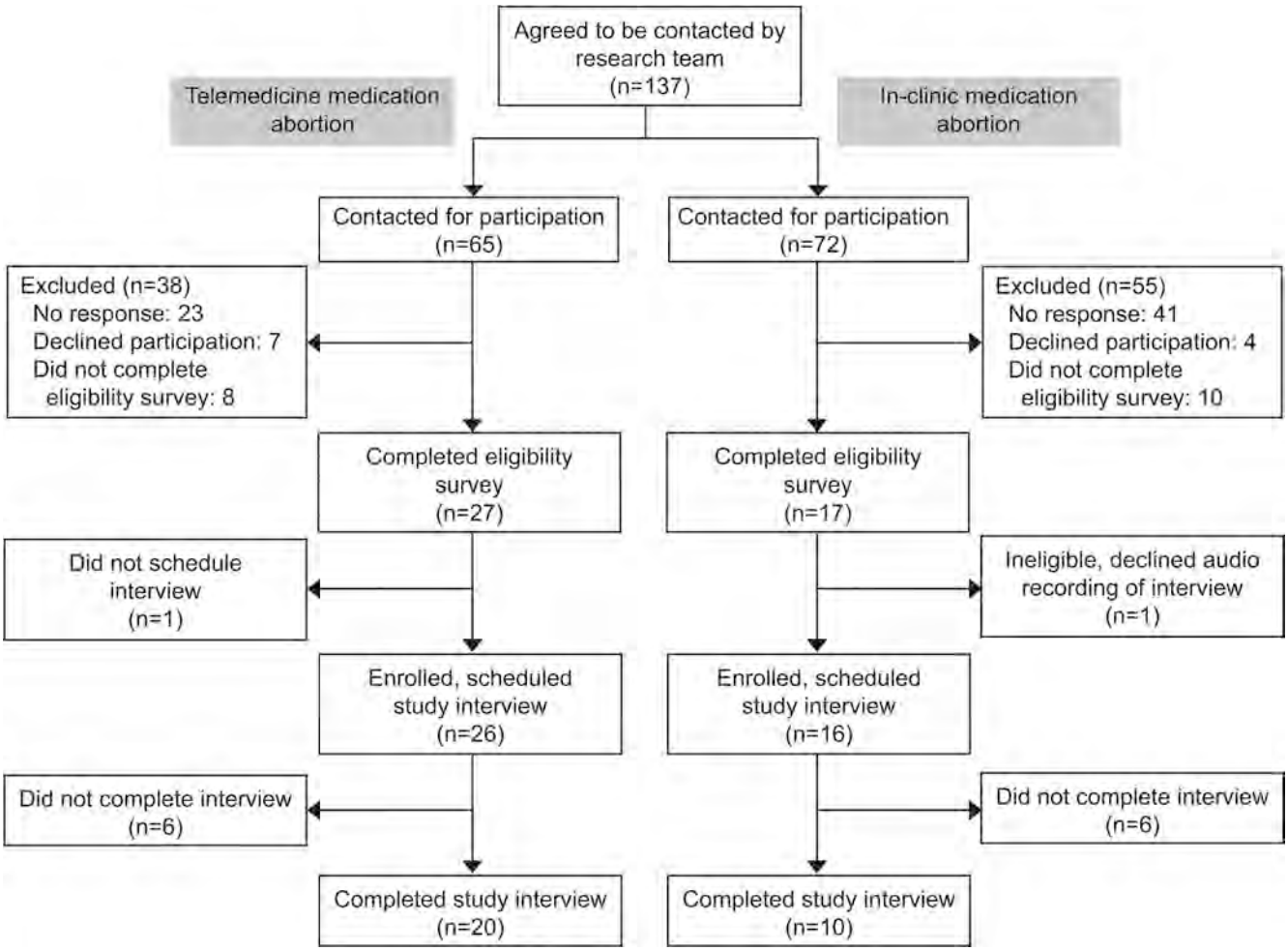

Fig. 2:
Study participant recruitment and enrollment flow diagram.

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Table 1:

Selected participant characteristics by medication abortion service (N=30)

Characteristic	Telemedicine (N=20)	In-clinic (N=10)
	Mean ±SD	**Mean ±SD**
Participant age (years)	31.0 ±5.7	27.0 ±5.9
Gestational age at time of service (days)	43.6 ±21.5	43.6 ±15.6
Self-reported prior abortion(s) *	**N (%)**	**N (%)**
0	10 (50.0)	7 (70.0)
1 or more	10 (50.0)	3 (30.0)
Self-reported race/ethnicity		
Declined to specify	3 (15.0)	2 (20.0)
Hispanic/Latino	5 (25.0)	1 (10.0)
Non-Hispanic/Latino		
Additional (unspecified) races and ethnicities	10 (50.0)	N/A
Asian	1 (5.0)	1 (10.0)
Black or African American	N/A	2 (20.0)
White	1 (5.0)	4 (40.0)
Area of residence		
Large metro area (1 million+ population)	7 (35.0)	6 (60.0)
Other (<1 million population)	13 (65.0)	4 (40.0)

* Includes medication and surgical abortions

N/A=No participants identified in this category

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Table 2:

Representative quotations, comparing telemedicine and in-clinic medication abortion care

Category	Factor	Telemedicine	In-clinic
Domain 1: Service geographic accessibility, efficiency of services, perception of space where care is received			
Setting	Geographic accessibility	"I wanted telehealth appointments because I live very rural. And I live on a farm and so access to services is really hard to get here and the community that my farm is near [a town that] is against all kinds of access to services like [abortion care]." (Participant 32, Telemedicine)	"Since I had to drive [more than 60 miles] to the clinic, [the in-clinic visit] …was like a whole day I spent doing that to take that first pill. Which if I had done it online and if I could take the pill at home, then I could have still gone about my day regularly and not wasted a day." (Participant 26, In-clinic)
Setting	Efficiency of services	"I liked the flexibility of doing things virtually, so I was able to just do it while I was at work. I didn't have to take time off because I [have to be at work during] the time that clinics are open." (Participant 08, Telemedicine)	"[While at the clinic I felt] like cattle herding, go in, get it done, go out and go to the next room. She didn't really say anything to me or walk me through anything, which I would have liked. But then [when you do get explained things], it felt redundant because you already get a big packet of paperwork while you're waiting… everyone is just reiterating the same thing, walking through the exact same thing. From Google I read it, I read it in the packet, I get told in the rooms and with the doctor, they tell me the same thing. So it kind of was redundant." (Participant 11, In-clinic) "Everybody was kind. Ultrasound tech was wonderful. And then I met the [clinician]. She was strained, I could see. She kept telling me, "I know it's you, I have not forgotten about you." And every time she passed by, she gave me some reassurance and very thorough, made sure I understood all the instructions. I just think it was just the waiting in between, that it could have been better." (Participant 09, In-clinic)
Setting	Privacy	"The doctor did tell me we were in a secure location, there wasn't anybody else around that had to deal with the appointment or anything. So I felt completely comfortable continuing on with the appointment via telemedicine." (Participant 15, Telemedicine)	"In the waiting room and there were 12 other women…And I was in that waiting room, I think for about half an hour. And then someone else came and brought me into an office type room. So there was the main meeting room, the ultrasound room, the second waiting room, and now I'm in an office room." (Participant 10, In-clinic)
Setting	Perception of space where care received	"I took the call on my lunch break from work… I was comfortable at a friend's apartment using her room…It was ideal for me…If it was in person, I would've been more emotional. I'm glad that I was in a safe place that if I needed anything, my friends were there…I felt very secure…Also I could be close to home versus traveling across the state to have this appointment…I would've had to get time off work. I didn't want to get in trouble with work. A video call made it way better." (Participant 03, Telemedicine)	"[The clinic space could have had] a more human touch to it. Like, hey, maybe there is like a vending machine or just something to distract yourself a little bit. Like they had a TV, but it wasn't on and it's just you get kind of antsy waiting there of course…just maybe a little cozier or something to put you at ease a bit more." (Participant 30, In-clinic) "The building was kind of set back away from the road. And there were two ladies with signs, right by the sidewalk, by the road. So I was in my car and I was just turning. But yeah, I saw a couple of protestors as I was leaving." (Participant 40, In-clinic)
Domain 2: Client-clinician interactions, decision making			
Client-clinician interactions	Respectful care	"[For the clinician] time seemed like it wasn't a concern. It wasn't like, 'Oh, I only have 15 minutes. Do you have any other concerns?' It was more making sure I felt comfortable, giving me that reassurance, going over the procedure, asking me if I had any questions." (Participant, 22, Telemedicine)	"I felt more heard than I ever have by any [clinician] ever prior talking to [Clinician Name] about birth control options....She gave me exactly what I asked for, which was a three month trial. And said I could come back for the rest of the year if I decide I like it." (Participant 37, In-clinic)
Client-clinician interactions	Positive interactions, promote an atmosphere of trust	"…I felt really comfortable with the doctor. He introduced himself, asked me about myself, told me about the process that he was going to go through…He was really knowledgeable, but also intentionally answered my questions in an accessible way. His whole demeanor was really	"She gave me time to ask questions and was reassuring that [abortion is a] pretty common thing, and it's not super scary…Her demeanor was supportive and she humored me with whatever I had to say. She behaved like a friendly mother… She gave you space and was not being overly scientific. I don't

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Category	Factor	Telemedicine	In-clinic
		calm and personable…He wasn't trying to hurry me along to get to his next appointment. And whenever I'd ask a question, he'd wait a second, he'd say something positive to indicate he had heard my question, and then he would think for a second and then he would answer thoughtfully." (Participant 08, Telemedicine)	mind that in any other kind of medical interaction, but I think [abortion] needs a little bit more air to breathe and a little bit more human touch." (Participant 30, In-clinic) "… when I was with the doctor, she was making sure, 'Are you comfortable with this? Are you understanding this?' Not just speaking at me, she was definitely checking in repeatedly, 'Are you getting this? Is this what you want?' So that was nice." (Participant 11, In-clinic)
Client-clinician interactions	Promote patient's dignity	"…hearing from another woman [the clinician] that they understand why I am thinking about this option [was important], 'I totally understand why you're feeling [an abortion] might be necessary, you have a 3 ½ month old baby,'…she was very relaxed, knowledgeable, and she communicated really well, so it helped make my decision." (Participant 35, Telemedicine)	"[The clinician] had a social worker feel to her…we were both seated and [she had good] eye contact…she let me vent…I think every woman that makes it there might have some emotional baggage, so just being able to listen to that." (Participant 9, In-clinic)
Client-clinician interactions	Tailored care	"… I'd already [had a medical abortion] once before, so I knew what I was doing....but I [still] needed more information because ..from the time that I took the first pill to when I take the second dose, the timeframe had changed. That was confusing to me… but I was rest assured because I knew I was getting [printed] information with the medication." (Participant 42, Telemedicine)	"The [clinician] got me in and out. She was like, 'I know you've been here all day…I can go through everything. Or, since you've said you've [had an abortion] before, you can tell me if you don't need me to go through this or if you want me to go through it again.' I told her I honestly just want to leave. So [she honored that]. She just sped through the things that she absolutely needed to tell me." (Participant 23, In-clinic)
Decision-making	Interactions absent of bias or coercion, trusting patient to make informed decision	"[The clinician] started off the call by saying, 'This is a no judgment zone. We just want to make sure it's your decision and you're not being influenced by anybody. And as long as it's what's best for you, then that would be the right decision.'…That gave me the reassurance that I need to know that I'm making the best decision…it's a huge weight lifted off my shoulders." (Participant 22, Telemedicine)	"She asked me how I'm doing, and if anyone pressuring me to come and do it..she reassured me....she asked, 'Why are you here?' And I told her, 'It's just not the right timing. I have a life to build. I can always have kids later'…I appreciated that a lot." (Participant 27, In-clinic) "[The clinician] definitely asked when I was going to take the second [set of] pills, just so that she could have note of it and if I had a day that would be best. Since I did have work on the weekend, I wanted to take it as soon as possible so I could be back to kind of normal as soon as possible…I kind of had my mind made up already, so when she asked I kind of had my answers ready that I knew, regardless of if she had any opinion on it." (Participant 11, In-clinic)
Domain 3: Clinician information provision, assessing support system, technical competence			
Information provision	Explanation of abortion process	"She was very thorough with the health information…the information was actually quite overwhelming…there was a really long list of different symptoms that may arise from the pill, the whole process of taking the pill… Even if I were to go to the clinic, there is not really any way around that." (Participant 04, Telemedicine) "[The clinician] told me, 'This is how often you will be needing to change your padding.' And I asked, 'What's a lot? Because I have a heavy period…And then he asked me to describe my level of flow. And he said, 'No, it would be a lot heavier than that…'He was really specific in when I should be concerned and when I shouldn't be concerned. And the description that he gave was really accurate to my experience." (Participant 08, Telemedicine)	"…[the clinician] talked through the abortion pill procedure…about what would happen in my body, things to expect before going ahead…I took the first one, and we talked through when to take the next one, and again, what to expect. She was really thorough.... I appreciated that she read the materials with me, instead of handing me some things to read later. I have a copy so that I could look back on it, but really explaining what things mean, taking time to make sure that I understand what's going to happen." (Participant 37, In-clinic) "[The clinician] highlighted specific things, the big takeaways from the [written instructions], so that was nice." (Participant 11, In-clinic) "[The clinician] reminded me, you're going to want to take it easy and you're going to expect the bleeding, and the size of the blood clots, how long I could be bleeding for…There was certainly a lot of bleeding, but I was prepared for that…he also told me that I would feel like I kind of like flu like symptoms, so I knew I was going to feel crummy…" (Participant 41, In-clinic)
Information provision	Information about possible complications	"[The clinician] did tell me that they have 24-hour telephone support, so if I had any concerns or needed anything…that made me feel more	"[The clinic staff] let me know that there was going to be a 24-hour service line, I could call if I needed any help or if I had any questions or if I was worried

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Category	Factor	Telemedicine	In-clinic
	and how to obtain appropriate care	comfortable, and it made me feel a lot better about their organization, just knowing that they have people that care enough to be on call 24 hours a day in case you would need something. Because it's something you don't want to just call like a friend or a regular doctor to ask about because a lot of people have varying opinions on abortion." (Participant 16, Telemedicine) "I definitely felt if there were more serious medical problems, then I could reach out to the clinic, but no [I did not need to call them], all of the symptoms that she said would happen, happened, and I was prepared for that…" (Participant 04, Telemedicine)	about something." (Participant 12, In-clinic) "[It was particularly helpful they said] to call them if there's any excessive bleeding over the four to six hour period…. there's also a 24-hour support line, if something is out of the ordinary or if there's excessive bleeding, I felt comfortable that I could call them and ask any questions." (Participant 26, In-clinic)
Information provision	Post-abortion contraceptive care information	"[The clinician] told me that she would send to the pharmacy Plan B just in case I do need it for the future…Not only did she care about the right now, she was trying to make sure I was good for future." (Participant 22, Telemedicine)	"[The clinician] gave me some plan Bs, which was really helpful." (Participant 27, In-clinic)
Support	Patient support systems	"[The clinician] asked if I had a support system and she was very concerned about who was going to be my care person. Which I thought was cool because it wasn't brought up to me in my first two visits at [an outside clinic]. And I thought looking back that was something that would've been extremely important… I had a lot of blood loss with my first [medication abortion] and it scared me to death and I didn't have anybody for helping me… [at this clinic], you have to have a care person. And I think that's absolutely how it should be." (Participant 07, Telemedicine)	"[The clinician] did say to have a support person, have someone to take care for your child [during the 4–5 hours of pain when passing the pregnancy]" (Participant 09, In-clinic).
Technical competence	Appropriate pain management	"I think what really helped is the tip that [the clinician] gave for while that process [of passing the pregnancy] was happening, to have a heating pad for the discomfort, because that helped more than anything. I didn't want to feel nauseous of having more pain medicine, so using the heat pad really, really eased everything." (Participant 02, Telemedicine) "The only thing that I would complain about is pain. I mean, [the clinician] had Naproxen sent to me, but …Naproxen…just wasn't what I needed because of how bad the pain was. And like me crying on the toilet because I'm in so much pain and basically screaming, yelling out because of the pain, it shouldn't be that bad." (Participant 29, Telemedicine).	"They gave me a tracking form to track my symptoms and track when I took the medication, so that was nice. Really easy process. I do remember there was one scary part on one of the forms that I filled out. It said that this might be the most pain that you've ever experienced in your whole life… I've birthed two children…it wasn't really painful at all." (Participant 40, In-clinic) "It was horrible pain, and Naproxen didn't do anything. I also took Tylenol…[The clinician] told us we could use a hot water bag…But the amount of cramping and the bleeding, it's just really hard to manage at home…" (Participant 09, In-clinic).
Domain 4: Outcome indicators: Patient knowledge and attitudes			
Client knowledge	Understand information given during clinic visit	"… Another nice thing is they send you a brochure with the medication. It was a quick, easy reference to answer common questions. I'm like, 'Oh, is this normal when I was taking it?' I could reference that pamphlet and that was super nice." (Participant 03, Telemedicine)	"[the clinical staff] gave me a lot of papers to read and I found those really, really good and all the kind of statistics and information and the things that could potentially go wrong. I thought that was really helpful and I felt comfortable because only recently I've heard at about the abortion pill." (Participant 26, In-clinic)
Client attitudes	Patient satisfaction	"I really felt cared for and even respected of how to take care of myself." (Participant 02, Telemedicine)	"[The clinician] was…easily the best doctor's appointment I have ever had. If I had to rank the experience, it would be a 10 out of 10 despite the wait." (Participant 37, In-clinic)
Client attitudes	Level of clinical competency	"I did end up bleeding a bunch and it was crazy. I was grateful that I was aware enough to say, '[The clinician] said to call this number on this paper.' [My husband called it and the nurse explained] to massage my stomach and it will help stop the bleeding and he did that and it worked." (Participant 25, Telemedicine)	"I didn't have anything happen [with the first pill], no cramping, no bleeding from that. 24 hours later almost exactly I dissolved the pills in my mouth. After the 30 minutes I swallowed them, and then probably 15 minutes later I threw everything up and I had to Google because I was like, 'Oh my god, did I just mess this whole thing up?' But I googled it and it basically was like, 'Yeah, it's fine as long as you

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Category	Factor	Telemedicine	In-clinic
			let it dissolve for 30 minutes.' So I was like, 'Well, hopefully that still works.' That was the only thing that I was like, 'They didn't tell me I could throw up then.'" (Participant 11, In-clinic) "Honestly the process seems kind of simple…. if it was super complicated, I'm sure [the clinician] probably could have dumbed it down, but you know, you just really put the pills in your mouth and let them sit there and whatever." (Participant 23, In-clinic)

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Early medical abortion using low-dose mifepristone followed by buccal misoprostol: a large Australian observational study

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Abstract

Objective: To describe the use of mifepristone in combination with buccal misoprostol in women undergoing an early medical abortion (EMA) in Australia.

Design, setting and participants: Retrospective, observational study of 13 345 EMAs (gestational age ⩽ 63 days) conducted at 15 Marie Stopes International Australia clinics between 1 September 2009 and 31 August 2011.

Intervention: Oral mifepristone 200 mg, administered at the clinic, followed 24–48 hours later by buccal misoprostol 800 μg, self-administered at home.

Main outcome measure: Failure rate (proportion of women with an incomplete abortion requiring surgical aspiration or a continuing pregnancy).

Results: Pregnancy termination follow-up information was available for 83.4% (11 155/13 376) of EMAs. From the patient demographic database, the EMA failure rate was 3.5% (465/13 345). Of these, most (382; 2.9% of total) were incomplete abortions requiring surgical aspiration, and 83 (0.6% of total) were continuing pregnancies. Haemorrhage (16; 0.1%) and known or suspected infection (25; 0.2%) were infrequent. One woman, who did not seek follow-up despite signs of infection, died from sepsis (< 0.01%). In 6755 EMAs with clinic follow-up from April 2010 to August 2011, 6381 women participated in a survey. Most reported medium or heavy bleeding and moderate or severe pain/cramps; most also reported that bleeding, pain/cramps and their overall experience were as expected or better than expected.

Conclusions: Mifepristone, with buccal misoprostol self-administered at home, for EMA up to 63 days of gestation had a low failure rate, was well accepted, and provided an effective treatment option with a favourable safety profile for women seeking an abortion in Australia.

The antiprogesterone mifepristone combined with a prostaglandin analogue (misoprostol or gemeprost) is effective for terminating early pregnancy and has a favourable safety profile.[1] Early medical abortion (EMA) regimens using 200 mg oral mifepristone and misoprostol have been endorsed by the Royal College of Obstetricians and Gynaecologists (RCOG) as an effective and appropriate method of terminating early pregnancy.[2] Randomised controlled trials have shown that mifepristone 200 mg followed 24–48 hours later by misoprostol is as effective as surgical abortion in gestations up to 63 days, with complete abortion generally occurring in 93%–98% of cases, incomplete abortion in 1.1%–4.2%, and ongoing pregnancy in 0.2%–2.7%.[3-10]

Since its first registration in France in 1988, mifepristone has been registered in around 50 countries and is on the World Health Organization list of essential medicines.[11] Mifepristone is currently an unapproved medicine in Australia, but can be accessed under the Authorised Prescriber provisions of the *Therapeutic Goods Act 1989*.[12] Results for Authorised Prescriber use of mifepristone in Australia[12-14] have been similar to those reported for other countries.[1]

The not-for-profit, non-governmental organisation Marie Stopes International Australia (MSIA) started Authorised Prescriber use of mifepristone–buccal misoprostol for EMA in Australia in 2009. This article describes outcomes from the use of this regimen in 13 345 EMAs.

Methods

Study information

This retrospective multicentre observational study was conducted at 15 MSIA clinics in New South Wales, Victoria, Queensland, Western Australia and the Australian Capital Territory. Women undergoing a medical abortion between 1 September 2009 and 31 August 2011 were retrospectively identified and data were collected from their patient records. The study was conducted in accordance with the Declaration of Helsinki. All women provided written informed consent for treatment. The Authorised Prescriber protocol and, retrospectively, publication of the data were approved by the Queensland Clinical Trials Network Human Research Ethics Committee. The study was retrospectively registered in the Australian New Zealand Clinical Trials Registry (ACTRN12611001051932).

Eligibility criteria

Women eligible for EMA had gestations of up to 63 days, as confirmed by ultrasound, and met the relevant state or territory's legal requirements for pregnancy termination.

Exclusion criteria included known or suspected ectopic pregnancy; concomitant administration of anticoagulants or corticosteroids; adrenal failure, inherited porphyria or haemorrhagic disorder; allergy to mifepristone and/or misoprostol; intrauterine device in situ; and pelvic infection. Unless they declined, women were screened for *Chlamydia trachomatis* and, based on a risk assessment, screened for other sexually transmitted infections. Women were not excluded based on their proximity to emergency medical care.

Treatment regimen

The mifepristone–buccal misoprostol regimen selected was based on the peer-reviewed literature, extensive experience of Marie Stopes International with mifepristone in the United Kingdom, and MSIA's 2-year experience using methotrexate–buccal misoprostol for medical abortion to 49 days of gestation. Mifepristone 200 mg (Linepharma) was administered orally at the clinic, followed 24–48 hours later by buccal misoprostol 800 μg (Pfizer), self-administered at home. Buccal administration involved placing four 200 μg tablets between

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the cheek and gum for at least 30 minutes; any undissolved residue was then swallowed. If women had no bleeding within 24 hours of misoprostol administration, they were instructed to contact the clinic and return, preferably within the next 24 hours, for a second dose of misoprostol 800 µg. Women were informed of the signs and symptoms of possible complications (including infection) and what to do if complications occurred. Women were strongly encouraged to have a support person present throughout the process and to attend a mandatory clinic visit about 2 weeks after their initial treatment to confirm pregnancy termination and exclude complications. All women had access to an MSIA-funded, Melbourne-based, 24-hour after-care, nurse telephone service; women with issues of concern were referred to an MSIA clinic or their local medical services. Prophylactic antibiotics were not routinely prescribed except for women considered at high risk of infection. Oral analgesics (paracetamol with codeine or ibuprofen with or without codeine) were recommended. Rhesus status was determined and rhesus D-negative women were administered rhesus D immunoglobulin (250 IU) at the time of mifepristone administration.

Assessments

Information on EMA outcomes and complications was collected, including incomplete abortion requiring surgical aspiration; ongoing pregnancy; bleeding; and infection. Pregnancy termination was confirmed using a combination of ultrasound, urine pregnancy test, serum β-human chorionic gonadotropin levels, patient history, and symptoms. At the follow-up visit, women were asked to complete a seven-item questionnaire on pain, bleeding and their overall experience; however, not all women completed the questionnaire or all questions. Questionnaire responses from April 2010 to August 2011 were analysed (the questionnaire was expanded in April 2010; data before this date were excluded).

Data collection and analysis

Patient demographic, follow-up and complications data were collected in three separate databases, with slight variances in the total numbers of EMAs. Patient disposition was summarised using frequency counts for the number of women undergoing an EMA, the number of EMAs conducted, and the proportion of women with a follow-up visit. Demographic variables were summarised using descriptive statistics, including mean, standard deviation and range for continuous variables, and frequencies and percentages for categorical variables. The number and type of complications were summarised using frequency counts and proportions. The failure rate was defined as the proportion of women with a treatment outcome of incomplete abortion requiring surgical aspiration or of continuing pregnancy. Statistical analyses were conducted using TIBCO Spotfire S+, version 8.2 (TIBCO Software Inc).

Results

Demographics

Between 1 September 2009 and 31 August 2011, 13 345 EMAs were conducted at 15 MSIA clinics using the mifepristone–buccal misoprostol regimen (Box 1). Of the 12 968 women who had an EMA, 362 women (2.8%) had more than one EMA (Box 1). The mean age of the women was 28.4 years (SD, 6.8 years) (Box 1) and the mean length of gestation was 6.3 weeks (SD, 0.9 weeks) (Box 2).

Follow-up

For most EMAs (11 155/13 376, 83.4%; Box 3), follow-up information was obtained, primarily via a clinic visit, to confirm pregnancy termination. During the study, an extra 31 EMAs were recorded in the follow-up database (13 376) than in the patient demographics database (13 345; 0.2% variance). This discrepancy may be related to duplication of patient records in the follow-up database and carryover of follow-up records from a previously used treatment protocol for EMA.

Complications and failure rate

The overall complication rate was low (519/13 345, 3.9%; Box 4). The EMA failure rate was 3.5% (465). Incomplete abortion requiring surgical aspiration occurred in 382 (2.9%) cases and continuing pregnancy in 83 (0.6%) cases. There were 16 cases of haemorrhage (0.1%). There were four cases (0.03%) of known and 21 cases (0.2%) of suspected infection, including one death from sepsis (< 0.01%). This woman suffered fever and flu-like symptoms about 6 days after taking mifepristone, but unfortunately did not seek medical advice, despite urging from family members. She died 9 days after taking mifepristone. Group A streptococcus (*Streptococcus pyogenes*) was identified from a vaginal swab and blood culture.

1 Demographic data for women undergoing early medical abortion (EMA) with mifepristone–buccal misoprostol

Characteristic	
Age, years	
Mean (SD)	28.4 (6.75)
Range	14–49
Total no. of EMAs	13 345
No. of women undergoing an EMA	12 968
No. of EMAs per woman	
1	12 606 (97.21%)
2	348 (2.68%)
3	13 (0.10%)
4	1 (< 0.01%)
No. of EMAs per age category*	
14 years	8 (0.06%)
15–19 years	931 (6.98%)
20–24 years	3546 (26.57%)
25–29 years	3559 (26.67%)
30–34 years	2543 (19.06%)
35–39 years	1797 (13.47%)
40–44 years	855 (6.41%)
45–49 years	105 (0.79%)

* Data missing for one woman. ◆

2 Length of gestation for women undergoing early medical abortion (EMA) with mifepristone–buccal misoprostol (*n* = 13 345)

Gestation	No. of EMAs*
Length, weeks	
Mean (SD)	6.3 (0.93)
Range	5–9
Gestation category	
5 weeks	2713 (20.33%)
6 weeks	5042 (37.78%)
7 weeks	4100 (30.72%)
8 weeks	1441 (10.80%)
9 weeks	49 (0.37%)

* Figures represent number of EMAs, except those relating to length of gestation. ◆

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3 Follow-up contact for women undergoing early medical abortion (EMA) with mifepristone–buccal misoprostol

	No. of EMAs	Follow-up contact	No follow-up contact
Total	13 376*	11 155 (83.40%)†	2221 (16.60%)
State/territory			
ACT	629	541 (86.01%)	88 (13.99%)
NSW	5178	4536 (87.60%)	642 (12.40%)
Qld	2887	2441 (84.55%)	446 (15.45%)
Vic	2911	2154 (74.00%)	757 (26.00%)
WA	1771	1483 (83.74%)	288 (16.26%)

ACT = Australian Capital Territory. NSW = New South Wales. Qld = Queensland. Vic = Victoria. WA = Western Australia. * During the study, an extra 31 EMAs were recorded in the follow-up database (13 376) than in the patient demographics database (13 345; 0.2% variance). This discrepancy may be related to duplication of patient records in the follow-up database and carryover of follow-up records from a previously used treatment protocol for EMA. † Follow-up contact was made via a clinic visit or a telephone call. The use of different databases for recording those who had any follow-up (11 155/13 376; clinic or phone) and those who specifically had a clinic visit (8955/13 345) precludes a precise breakdown of the type of follow-up contact (clinic or phone). As 8955 women were known to have a clinic-based follow-up, about 2175 women may have had a phone-based follow-up (ie, assuming 83.4% of 13 345 patients had any type of follow-up). ◆

Feedback on the EMA method

From April 2010 to August 2011, 10 093 EMAs were conducted. In 6755 of these EMAs, women attended follow-up and were asked to complete a seven-item questionnaire; if a woman had more than one EMA, she was asked to fill out a questionnaire for each EMA. Responses were available from 6381 women. Almost all of the women reported medium or heavy bleeding (5914/6330, 93.4%) and the majority reported moderate or severe pain/cramps (5001/6381, 78.4%) (Box 5, A and B). Most women said the bleeding (5226/6233, 83.8%), pain/cramps (4829/6340, 76.2%), and overall experience (5660/6265, 90.3%) were as expected or better than expected (Box 5, C–E). Most women reported that they would choose the EMA method again (4939/6335, 78.0%) and would recommend it to a friend (4770/5196, 91.8%) (Box 5, F and G).

4 Reported complications for women undergoing early medical abortion (EMA) with mifepristone–buccal misoprostol

	No. of complications*
Total no. of EMAs	13 345
Complications†	519 (3.89%)
Type of complication†	
Incomplete abortion requiring surgical aspiration	382 (2.86%)
Continuing pregnancy‡	83 (0.62%)
Haemorrhage with transfusion	11 (0.08%)
Haemorrhage without transfusion	5 (0.04%)
Suspected infection	21 (0.16%)
Known infection§	4 (0.03%)
Pain requiring hospital treatment	5 (0.04%)
Surgical procedure chosen before misoprostol administration	2 (0.01%)
Drug reaction to misoprostol	2 (0.01%)
Death§	1 (< 0.01%)
Other (not specified)	3 (0.02%)

* Figures represent number of complications, except that relating to total number of EMAs. † Proportion of complications calculated based on the total number of EMAs (13 345), not the number of EMAs with follow-up data (11 155); the number and type of complications could not be calculated for EMAs without follow-up data. ‡ 82 of the 83 women had surgical intervention; one woman chose to continue the pregnancy and delivered a healthy baby. § One woman died from sepsis as a result of group A Streptococcal (*Streptococcus pyogenes*) infection. ◆

Discussion

This is the first large-scale Australian study of mifepristone for EMA up to 63 days of gestation. Clinic-administered mifepristone (200 mg) in combination with home-administered buccal misoprostol (800 µg) was associated with a low failure rate, low rates of haemorrhage and infection, and was well tolerated.

The low failure rate (3.5%) with mifepristone in our study was similar to that reported for mifepristone in randomised controlled trials (failure rates, 2%–7%)[3-10] and in other Australian Authorised Prescriber Schemes (failure rates, 2.9%–5.6%).[13,14] Notably, the rate of surgical intervention for incomplete abortion declined from 4.3% during the first 3-month period of our study to 1.6%–2.6% during subsequent 3-month periods. We propose that as clinic staff gained experience with the EMA method, they felt more comfortable with expectant management rather than proceeding directly to surgical intervention.

In our study, there were four cases of known infection reported (0.03%), including one death from sepsis. Infection following medical termination of pregnancy is reported to occur in 0.02%–0.92% of cases.[15,16] Death resulting from infection and fatal toxic shock after medical abortion with mifepristone is a known, but very rare, risk (1.1/100 000).[15] Although the RCOG[2] recommends universal prophylactic antibiotics effective against *C. trachomatis* and anaerobes to reduce the risk of infection after medical abortion, the WHO[17] does not. At MSIA, all women are screened for *C. trachomatis*, unless they decline, and for other STIs based on a risk assessment. MSIA has upgraded its warnings to women regarding serious infections and also now provides an opt-in SMS service that reminds women 3–5 days after their visit about the after-care phone number and signs and symptoms of complications.

The regimen we used is similar to those recommended by the WHO[17] and the RCOG,[2] with buccal administration of misoprostol. Vaginal misoprostol has been associated with deaths from toxic shock syndrome in the United States[18] and some women may prefer buccal, rather than vaginal, administration. In addition, oral misoprostol is not sufficiently effective beyond 49 days of gestation.[1,2,17] Randomised controlled trials have shown mifepristone with buccal misoprostol to have efficacy similar to or greater than mifepristone with vaginal[7] or oral[19] misoprostol for terminating pregnancies up to 56 and 63 days, respectively. Our study provides further support for using 200 mg of mifepristone, which is lower than the 600 mg dose approved in the US and Europe.[1] Randomised controlled trials directly comparing the two mifepristone doses have shown similar efficacy for the 200 mg and 600 mg doses.[3,6] A Cochrane meta-analysis also found no difference in failure rates between the 200 mg and 600 mg doses.[20]

In our study, all women were informed of the need for mandatory follow-up to confirm pregnancy termination; contact with most women was achieved. Those who did not attend the clinic were telephoned and, if telephone contact was not possible, a registered letter was sent (the letter included a pregnancy test kit to facilitate home-testing). Despite these efforts, follow-up information was

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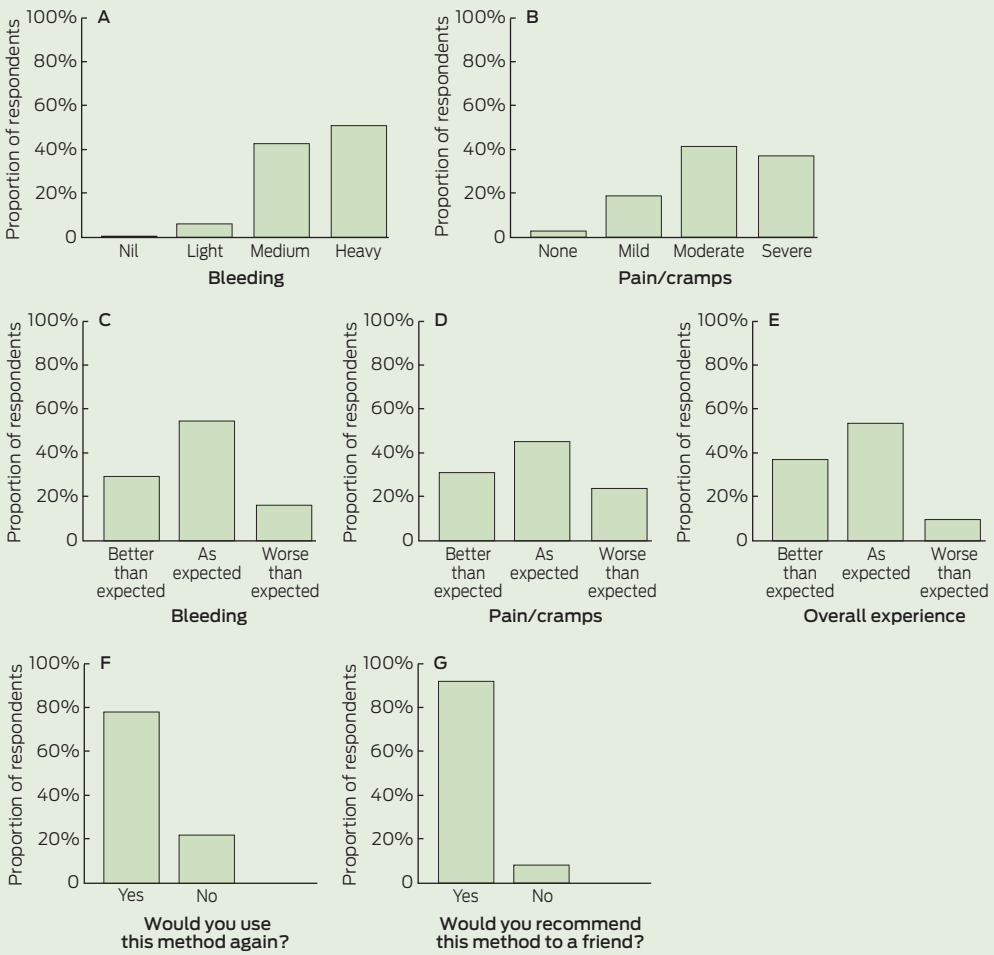
missing for around 17% of women. The loss to follow-up in our real-world setting of mifepristone use was higher than that observed in rigorous clinical trial settings (1.7%–8.6%).[3-5,8,9,21] As might be expected in clinical practice, not all patients may return for follow-up, even if instructed to attend a follow-up visit to assess treatment outcome. Given the emotional issues surrounding abortion, women who felt the abortion was complete and had no physical complications may have been reluctant to return to the clinic. While this is of concern, a recent study using early telephone follow-up after medical abortion to determine the need for further evaluation found that women who initially had not required evaluation returned to the clinic of their own accord if they experienced problems, such as bleeding or continuing pregnancy.[21] This finding suggests that women who experience adverse effects or feel that the abortion is not complete are likely to seek appropriate medical care. Indeed, in our study, about one-third of women did call the MSIA after-care service about issues such as pain or bleeding. While many women required reassurance only, some callers were referred to the clinic or a hospital for further assessment. In addition, it is possible that some women received follow-up care elsewhere. Not all women with complications, however, will decide to seek follow-up care and, in very rare cases (eg, one out of 13 345 cases in our study), this can have serious consequences. Understandably, such cases can raise concerns about the safety of home-based versus clinic-based administration of misoprostol. Although misoprostol could be administered in a clinic under medical supervision, home-based administration of misoprostol has been associated with a low complication rate, is preferred by women, and is common practice in France and the US.[1,22] Further, clinic-based administration of misoprostol would not necessarily enhance outcomes as medical abortion complications can occur hours or days after misoprostol is administered.

Overall, there was a high level of satisfaction with the mifepristone–buccal misoprostol regimen used, with most women who completed the study questionnaire reporting the bleeding, pain/cramps, and overall experience to be as they had expected or better than expected. Satisfaction with the EMA method used in our study was similar to that reported in other studies.[1,23,24] Notably, there has been a significant uptake of medical abortion in our clinics, with about a third of women requesting an abortion up to 63 days of gestation opting for the medical method (data not shown).

Our mifepristone–buccal misoprostol EMA method could be used outside a hospital setting. The diagnosis and initiation of treatment (mifepristone) can be conducted in a clinic and the second part of the treatment (misoprostol) can be carried out by the woman at home, with 24-hour access to after-care services to manage any issues. This arrangement, along with the 24–48-hour window for misoprostol administration, allows the abortion process to take place in the privacy of the woman's home and at the time of her choosing, factors known to be of importance to women undergoing an abortion.[1,23,24] The clinic- and home-based nature of the mifepristone–buccal misoprostol regimen makes it feasible for use in regional centres of Australia. These centres may have smaller hospitals than urban areas, but have the facilities and staff to manage spontaneous miscarriage.[24] The MSIA clinics are located in major metropolitan areas and women are provided with discharge letters. Any woman contacting the after-care service can be referred back to the MSIA clinic or to her local doctor or, if necessary, a nearby accident and emergency facility. In clinical

5 Results of patient survey on the early medical abortion method, April 2010 – August 2011



Women were asked (i) to describe the severity of their bleeding (A; *n* = 6330) and pain/cramps (B; *n* = 6381); (ii) whether the bleeding (C; *n* = 6233), pain/cramps (D; *n* = 6340), and overall experience (E; *n* = 6265) were better than expected, as expected, or worse than expected; (iii) whether they would choose the method again (F; *n* = 6335); and (iv) whether they would recommend the method to a friend (G; *n* = 5196). ◆

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practice, proximity to emergency services should be evaluated when considering the use of the mifepristone–buccal misoprostol regimen. The potential need for access to appropriate 24-hour emergency help could limit the use of this regimen in more remote areas of Australia.

The observational nature of our study allowed assessment of the mifepristone–buccal misoprostol regimen in a real-world setting. However, as discussed, one of the study limitations was the relatively high rate of loss to follow-up. As a result, it was not possible to accurately determine the complete abortion rate; instead the known failure rate was reported. In addition, the use of multiple databases for data collection led to some small discrepancies in the datasets used for the analyses (eg, different total numbers of EMAs), because of differences in how the data were collected.

In conclusion, our Australian study of 13 345 EMAs has shown that mifepristone followed by buccal misoprostol has a low failure rate, including a low ongoing pregnancy rate. The regimen, which involved self-administration of misoprostol and completion of the abortion process at home, had a favourable safety profile and was well accepted by the women in this study. While the potential risk of serious infection should be kept in mind and monitored, these results indicate that the mifepristone–buccal misoprostol regimen is an effective option for Australian women seeking an abortion up to 63 days of gestation.

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Medical termination of pregnancy at 63 to 83 days gestation

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Objective To assess the efficacy of a medical regimen for the termination of pregnancy within the gestational age range of 63 to 83 days.

Design Prospective observational study.

Setting Gynaecology department within a district general hospital.

Population Women attending the pregnancy advisory clinic between June 1996 and December 1997.

Methods The medical regimen used was mifepristone 200 mg orally followed after 36 to 48 h by misoprostol 800 μg administered vaginally.

Main outcome measures The success rate of the medical termination of pregnancy regimen, where success was defined as achieving complete abortion without the need for secondary intervention by either surgical or repeat medical means.

Results Primary medical termination of pregnancy was chosen by 253 (80·8%) of the 313 women and was successful in 239 (94·5%). Repeat medical treatment achieved completion of the abortion in a further three women (1·2%) and surgical evacuation of the uterus was required in 10 (4·0%). One woman declined further intervention after failed medical treatment but subsequently miscarried.

Conclusions The combination of mifepristone and misoprostol is effective for the termination of pregnancy for gestations of 63 to 83 days.

INTRODUCTION

The efficacy and acceptability of medical termination of first trimester pregnancies up to 63 days of gestation have been established[1]. Various medical regimens have been used, but those with the most favourable results have involved the sequential administration of mifepristone and a prostaglandin. Comparative trials have shown that a reduction in the oral dose of mifepristone from 600 mg to 200 mg does not affect the efficacy[2,3]. In the United Kingdom the most commonly used prostaglandin preparations are gemeprost and misoprostol. Misoprostol is much cheaper and does not require special storage facilities. The results of trials in very early first trimester and second trimester termination of pregnancy have shown that misoprostol is as effective as gemeprost[4–6]. Misoprostol is absorbed by the oral route but vaginal administration is associated with fewer side effects and improved efficacy[7,8].

Over 47% of the 154,315 terminations performed in England and Wales in 1995 were carried out at gestations of between 9 and 12 weeks[9]. Within the gestational age range of 63 to 83 days there has been little research into the efficacy of medical termination of pregnancy and the standard management is surgical.

At South Cleveland Hospital, before June 1996, the choice of surgical or medical termination of pregnancy using the combination of mifepristone and misoprostol was offered only to women with a pregnancy of less than 63 days. Medical termination of pregnancy was also used at gestations of 84 days or more. For women undergoing termination at gestations of 63 to 83 days, the only treatment offered was surgical. The aim of the present study was to assess the efficacy of extending the early first trimester medical termination management to those with gestations of 63 to 83 days.

METHODS

Women requesting termination of pregnancy attended the clinic in the gynaecology department and all the cases reported fulfilled the criteria of the 1967 Abortion Act. All women underwent a transvaginal ultrasound scan to confirm the gestational age. From June 1996, women with gestations of 63 to 83 days who had no medical contra-indications to the mifepristone–misoprostol regimen were offered termination by vacuum aspiration or medical treatment. They were informed

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that the success rate for the medical treatment at this gestation was not known and that if it failed they could proceed with the surgical treatment. Written consent for medical treatment was obtained.

Oral mifepristone 200 mg was administered either on the same day as the clinic visit or within the following two days, depending on the availability of the allocated beds in the gynaecology ward. The woman was allowed home half an hour after mifepristone administration, with an appointment to return for admission to the gynaecology ward after a further 36 to 48 h. She was advised that in some cases abortion may occur at home following the mifepristone.

After admission, misoprostol 800 μg was administered vaginally. All loss was assessed by staff for the presence of products of conception. If none were passed within eight hours of misoprostol administration, a speculum examination was performed and any products of conception in the vagina or cervix were removed. Unless there were complications, women were discharged home on the same day.

Women who had not responded to the medical treatment within 24 hours of misoprostol administration were offered surgical termination of pregnancy. If they had had some bleeding but had not passed definite products of conception they were offered, as an alternative to directly proceeding with a surgical termination, a repeat transvaginal ultrasound scan and review at the clinic the following week. Women who had passed products of conception consistent with a complete abortion had follow up at six weeks arranged with their general practitioner. No formal hospital follow up appointment was given. The women were advised to report to the hospital if there was an increase in the bleeding, if the bleeding had not subsided over the following 10 days, or if they developed pain or any other problem. When products of conception had been passed after the medical treatment but there was doubt about the completeness of the abortion, a follow up transvaginal ultrasound scan and clinic review were arranged for approximately 10 days later.

At the time of the initial clinic visit, the women were given a treatment information leaflet which included a telephone number and named members of staff to contact if there were any concerns or complications. They also had direct access to the clinic or gynaecology ward during the medical treatment and for six weeks after the termination.

All women undergoing termination of pregnancy received a 10 day course of oral doxycycline. Rhesus negative women received anti-D at the time of the abortion. Future contraceptive plans were established at the time of the initial assessment in the clinic.

The data were collected prospectively. Fisher's exact test and Armitage's χ^2 test for trend[10] were used for statistical analysis.

RESULTS

From June 1996 until December 1997, 313 women underwent a termination of pregnancy at 63 to 83 days of gestation. Of these, 253 (80·8%) chose medical treatment and 60 (19·2%) opted for primary surgical termination of pregnancy. The age range for those undergoing medical termination was 14 to 42 years with a median of 22 years. Of the 253 women, 151 (59·7%), were nulliparous.

Successful medical management was defined as complete abortion without the need for secondary intervention either by further prostaglandin administration or surgical evacuation of the uterus. The medical management was successful in 239 (94·5%) of the 253 cases. Table 1 shows the success rates for the various gestations within the 63 to 83 day range. There was no obvious trend between gestational age and success rate and Armitage's χ^2 test for trend proved insignificant (P = 0·44).

The outcomes for women undergoing medical management are illustrated in Fig. 1. In four cases (1·6%) complete abortion followed the administration of mifepristone alone. All four women were nulliparous and the gestational ages were 63, 64, 69 and 81 days.

Of the 235 women with successful medical termination after receiving misoprostol, no definite products of conception were seen by staff in four cases. In those cases where definite products of conception were identified and the time to achieve abortion after misoprostol administration was recorded, the range was from 70 to 690 minutes with a median of 290 minutes (Fig. 2).

In total there were 14 failures (5·5%) in the medically managed group. When there had been no response to medical treatment 24 hours after misoprostol administration, the women were offered surgical termination. Three women, however, requested continuation of medical management and after repeat prostaglandin therapy all three proceeded to complete abortion.

After medical management ultrasound scans were performed in 30 (11·9%) cases. Only two of these resulted from referrals with suspected complications. In one there was increased bleeding on the second day at home and in the other case slight bleeding persisted for three weeks. In both cases no treatment was required

Table 1. Success rates for medical termination of pregnancy at varying gestations.

Gestation (days)	Group size (n)	Successful (n)	Success rate (%)
63–69	127	120	94·5
70–76	75	73	97·3
77–83	51	46	90·2

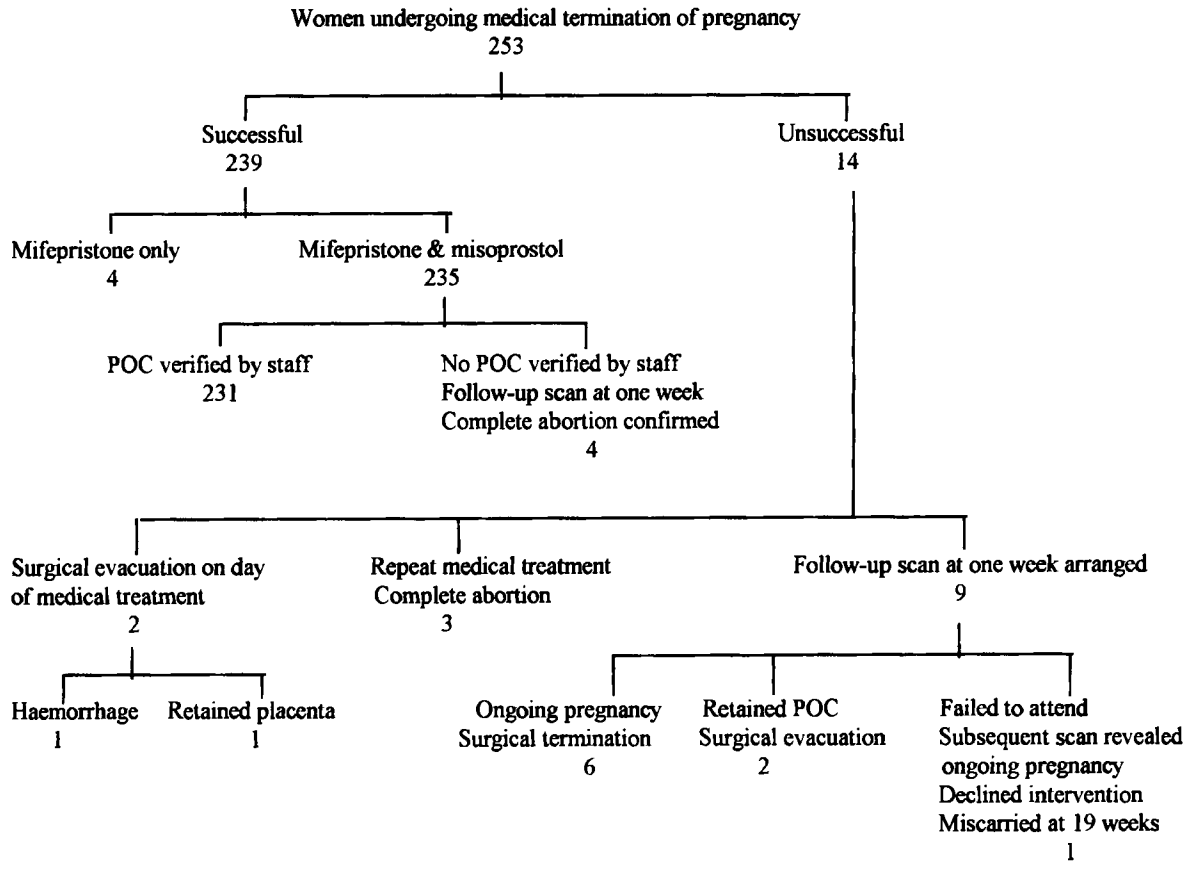

Fig. 1. Outcomes of medical management (POC = products of conception).

and the scans did not show signs of retained products of conception. In three cases a scan was organised to confirm complete abortion before inserting an intrauterine contraceptive device. The remainder of the scans were performed either because no definite products of conception had been seen or to assess the completeness of the abortion, and the details of the outcomes have already been outlined.

No analgesia was requested by 181 (71·5%) of the 253 women undergoing medical management. Nulliparous and multiparous women did not differ in this respect ($P = 1$). Oral analgesia only (Co-proxamol) was required by 63 women (24·9%). Nine women (3·6%) required intramuscular opioid analgesia. There was no statistical difference ($P = 0·32$) between the opioid analgesia requirements of the nulliparous women (4·6%) and the multiparous women (2·0%). There was a statistically significant trend ($P = 0·039$, Armitage's χ^2 test for trend) for increasing analgesic requirements with increasing gestational age, with some form of analgesia being required for 22·0% of women with gestations of 63 to 69 days, 34·7% at 70 to 76 days and 35·3% at 77 to 83 days.

Gastrointestinal side effects, mainly nausea and vomiting, were reported by 10 women (4·0%), of whom eight required anti-emetic treatment. Heavy bleeding was reported by seven (2·8%). In four women there was a brisk loss of short duration at the time of the abortion, requiring intramuscular ergometrine administration. In a fifth woman a moderate loss was reported at home. There were no clinically significant alterations in the haemoglobin concentrations in this group. There was clinically significant blood loss in two women (0·8%). In one there was heavy bleeding at the time of abortion,

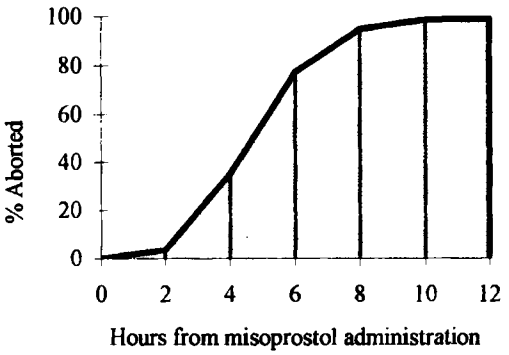

Fig. 2. Time to achieve abortion following misoprostol administration.

resulting in a fall in the haemoglobin concentration by 2 g/dL. The bleeding promptly resolved and oral iron therapy was the only treatment required. In the other woman surgical evacuation of the uterus and transfusion of two units of blood were required. There was one reported case of post-abortion pyrexia. Of the 253 women who commenced medical termination of pregnancy only six (2·4%) required overnight stay in the hospital.

DISCUSSION

The success rate of 94·5% reported in this study is similar to other studies for gestations of less than 63 days[1,2,4,7]. This is in contrast to the reported decline in efficacy with increasing gestation observed by Spitz *et al.*[11], although in that study the misoprostol was at a lower dose and administered orally. We did not demonstrate a trend between efficacy and gestation, although our study does not have the power to pick up a slight trend.

Repeat misoprostol administration has been shown to increase the abortion rate of a medical management regimen[12]. Ashok *et al.*[13] have recently published the results of 120 cases of medical termination of pregnancy at 9 to 13 weeks of gestation using vaginal misoprostol 800 μg followed by repeat misoprostol 400 μg three hourly on two occasions as required, and they reported a success rate of 95%. In our study the repeat administration of misoprostol 800 μg improved the complete abortion rate with medical management to 95·7%.

The uptake of medical termination of pregnancy was remarkably high in our study given that the women were aware that the success rate for such treatment at 63 to 83 days of gestation was not known and may be low. It is, however, consistent with the chosen method of termination by the women seen in this unit at gestations of less than 63 days. In 1994 Cameron *et al.*[14] reported on the progressive rise in uptake of medical termination of pregnancy. The fact that the woman has a choice is important. A woman who undergoes termination of pregnancy by the method of her choice is more likely to be satisfied with the treatment[15].

A comparative study of blood loss in medical and surgical termination of early first trimester pregnancies reported a statistically, but not clinically, significant increased blood loss in the medically managed group[16]. Rodger *et al.*[17] reported a median blood loss of 74 mL during early first trimester medical termination of pregnancy and a positive correlation between increasing gestation and haemorrhage. In our study, however, the transfusion rate was only 0·4%, which is similar to the 0·7% reported for gestations of less than 63 days[1].

The low rate of gastrointestinal side effects in this study possibly reflects the fact that the women were not asked to record any side effects. Most of the gastrointestinal side effects associated with medical regimens are mild. Our recorded rate more accurately reflects the more severe side effects which were reported by the women requiring anti-emetic or anti-diarrhoeal agents.

Reported analgesic requirements for early medical termination of pregnancy vary greatly between centres, ranging from 12·5%[12] to 68%[11]. The trend for increasing analgesic requirement with increasing gestational age in this study supports the previously reported association between pain and gestation at time of abortion[18].

The risk of developing post-abortion infective complications can be significantly reduced by the administration of prophylactic antibiotics at the time of the pregnancy termination[19]. A prophylactic antibiotic regimen was used in this study, but a preferred regimen would have included metronidazole in addition to the doxycycline[20]. In this study there was only one recorded case of post-abortion infection requiring antibiotic treatment. The majority of women, however, were not seen for review at the hospital and therefore the number treated for post-abortion infection by their general practitioner is not known. Medical termination of pregnancy in the early first trimester is associated with a lower rate of infection, as assessed clinically, compared with surgical treatment[18].

CONCLUSION

Sequential oral mifepristone and vaginal misoprostol are an effective medical regimen for the termination of pregnancy at 63 to 83 days and offer an alternative to conventional surgical management.

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Review article

Alternatives to ultrasound for follow-up after medication abortion: a systematic review

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Abstract

Background: Requiring a follow-up visit with ultrasound evaluation to confirm completion after medication abortion can be a barrier to providing the service.

Study Design: The PubMed (including MEDLINE), Cochrane Central Register of Controlled Trials and POPLINE databases were systematically searched in October and November 2009 for studies related to alternative follow-up modalities after first-trimester medication abortion to diagnose ongoing pregnancy or retained gestational sac. We calculated the sensitivity, specificity, positive predictive value and negative predictive value compared with ultrasound or clinician's exam. We also calculated the proportion of cases in each study with a positive screening test.

Results: Our search identified eight articles. The most promising modalities included serum human chorionic gonadotropin measurements, standardized assessment of women's symptoms combined with low-sensitivity urine pregnancy testing and telephone consultation. These follow-up modalities had sensitivities ≥90%, negative predictive values ≥99% and proportions of "screen-positives" ≤33%.

Conclusions: Alternatives to routine in-person follow-up visits after medication abortion are accurate at diagnosing ongoing pregnancy. Additional research is needed to demonstrate the accuracy, acceptability and feasibility of alternative follow-up modalities in practice, particularly of home-based urine testing combined with self-assessment and/or clinician-assisted assessment.

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Keywords: Abortion; Induced; Aftercare; Female; Follow-up studies; Humans; Pregnancy; Pregnancy trimester; First

1. Introduction

Routine follow-up visits after medication abortion are recommended or required by most medication abortion protocols, primarily to diagnose ongoing pregnancies [1–6]. While ongoing pregnancy is relatively rare following early medication abortion, occurring in approximately 0.4%–3% of women with the mifepristone–misoprostol regimen [7–9] and in 5% with the misoprostol-alone regimen [10], several studies have shown that the incidence of ongoing pregnancy increases with increasing gestational age [7,9,11,12].

Ongoing pregnancy is typically identified during a follow-up visit via ultrasound or clinician's exam, and although pelvic ultrasonography is not required by the FDA-approved mifepristone label [13], many US facilities employ it to detect ongoing pregnancy [14]. Routine use of ultrasound adds considerable costs to medication abortion provision, and it may not be widely available in low-resource settings [15]. Furthermore, attending follow-up visits incurs additional expenses to women, including travel costs, lost wages and childcare costs [16]. The number of abortion providers, particularly in rural areas and certain states, has declined in the United States [17–19], resulting in some women traveling farther to obtain care and further compounding the difficulties and costs of attending a follow-up visit. The health system itself is also impacted when clinics have no-shows and cancelations, for which they are not reimbursed [16]. Due to these factors, there is growing interest to consider alternative ways to identify ongoing pregnancy following medication abortion.

This systematic review examined the evidence regarding alternative modalities of follow-up that do not require ultrasound evaluation. We focused on the accuracy of these alternative modalities in detecting ongoing pregnancy

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or retained gestational sac compared with the gold standard of ultrasound (or clinician's exam if ultrasound was not performed).

2. Methods

2.1. Sources

Investigators systematically searched the PubMed (including MEDLINE), Cochrane Central Register of Controlled Trials and POPLINE databases in October and November 2009 to identify studies evaluating alternative modalities of follow-up after first-trimester abortion using the following search terms: ("Abortion, Induced" [Majr] OR "Abortion, Therapeutic" [Majr]) AND ("Office Visits" [Mesh] OR "Outcome Assessment (Health Care)" [Mesh] OR "Postoperative Care" [Mesh] OR "Aftercare" [Mesh] OR "Ambulatory Care" [Mesh] OR "return visit" OR "aftercare" OR "follow-up visit" OR "post-operative care") NOT ("Pregnancy Trimester, Second" [Mesh] OR "second trimester"). We reviewed articles that had at least the abstract in English. The bibliographies of relevant articles were reviewed to identify other pertinent publications, and we also contacted prominent researchers and colleagues to identify articles that were in press.

2.2. Study selection

We reviewed titles and abstracts to identify studies related to follow-up after first-trimester abortion. We included prospective cohort studies, diagnostic test evaluation studies, clinical trials and pilot studies that examined modalities of follow-up that are an alternative to ultrasound for diagnosing ongoing pregnancy after medication abortion. While ongoing pregnancy is the primary outcome of interest, we also included studies that examined follow-up modalities to diagnose retained gestational sacs after medication abortion if ongoing pregnancy was not specifically identified. We decided to use ongoing pregnancy and retained gestational sac as the outcomes of interest because they can be objectively diagnosed with ultrasound, as opposed to other complications of medication abortion, such as incomplete abortion, that are clinical diagnoses. We assessed study quality primarily by focusing on whether the reader of the alternative modality was blinded to the result of the reference test (usually ultrasound) and whether the alternative modality involved a standardized assessment. We excluded studies related to second-trimester abortion, unsafe abortion, medication abortion regimens, service delivery, legal analysis and abortion beliefs or attitudes.

In order to compare alternative follow-up protocols, we calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for diagnosing ongoing pregnancy or retained gestational sac, along with 95% confidence intervals (CIs) for these measures [20], compared with the gold standard of ultrasound [5] or clinician's exam. We also calculated the proportion of all cases in the study with a positive screening test. This measure is useful to compare the proportion of clients using the follow-up modality that would be referred for further evaluation (such as ultrasound). The three measures that we focused on were sensitivity (the proportion of women with ongoing pregnancy or retained gestational sac who were correctly identified by the modality), NPV (the proportion of women with negative test results who were correctly diagnosed) and the proportion with a positive screen. We contacted the authors to confirm our calculations and in one case reviewed the actual study data. Of note, in some articles, the accuracy measures were reported for diagnosing successful expulsion rather than ongoing pregnancy. Because ongoing pregnancy is the potentially concerning outcome, we recalculated accuracy measures for diagnosing ongoing pregnancy or retained gestational sac whenever possible.

We included participants who presented for unscheduled visits before going through the follow-up modality or algorithm being studied as "screen-positives" since these women end up receiving additional evaluation from the perspective of the clinic system. Any ongoing pregnancies or other complications among these self-referred women are also accurately detected. Therefore, our measures of accuracy relate more to how the modality performs in the context of a service, rather than the accuracy of the modality alone.

We did not conduct meta-analyses due to heterogeneity across studies with respect to the follow-up modalities studied and the outcomes measured.

3. Results

The literature search identified 393 articles. Among these, we identified eight studies that compared two or more follow-up modalities [12,15,21–26], including women's self-assessment, clinicians' assessment, serum human chorionic gonadotropin (hCG) measurements, urine pregnancy testing (UPT) and combinations of the above.

3.1. Women's self-assessment

Our review identified two studies that examined women's self-assessment for diagnosing ongoing pregnancy or retained gestational sac compared with ultrasound or physician's exam [12,24]. We identified a third study that examined women's self-assessment for diagnosing incomplete abortion [27], but it was excluded from our analysis due to the vagueness in definition of the outcome.

The first study was conducted in 1994–1995 among 2121 US women pregnant up to 63 days' gestation who were administered mifepristone 600 mg orally and misoprostol 400 mcg orally 48 h later [12]. At follow-up (Day 15), 1980 women were asked if they felt expulsion had occurred. Women's self-assessment correctly predicted 95 of the 111 ongoing pregnancies that were confirmed by the clinician

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Table 1
Accuracy of women's self-assessment to detect ongoing pregnancy or retained gestational sac after medication abortion

Study	*n*	No. of ongoing pregnancies	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Screen-positive
Harper et al. [12]	1980	111	85.6% (77.3%–91.3%)	19.2% (17.4%–21.0%)	5.9% (4.8%–7.2%)	95.7% (93.0%–97.5%)	81.1%
Creinin et al. [24]	50	27[a]	51.9% (32.4%–70.8%)	65.2% (42.8%–82.8%)	63.6% (40.8%–82%)	53.6% (34.2%–72%)	44.0%

[a] Reported retained gestational sac rather than ongoing pregnancy.

(via pelvic exam or ultrasound). Among women who thought expulsion had occurred, 4% were judged to have ongoing pregnancies by clinicians, and these women were concentrated at gestational ages ≥50 days [12]. This study had 86% sensitivity to detect ongoing pregnancy (95% CI 77%–91%) and 96% NPV (95% CI 93%–98%), and 81% of women screened positive and would therefore be referred for additional follow-up, such as ultrasound (Table 1).

The second study examined 50 women's assessments of complete abortion after administering methotrexate intramuscularly and misoprostol vaginally up to 56 days' gestation [24]. On Day 9, women were asked if they felt they had passed the pregnancy. Women's self-assessment correctly predicted 14 of the 27 retained gestational sacs that were confirmed by ultrasound [24]. This study had a lower percentage of women who screened positive: 44%; however, the sensitivity was 52% (95% CI 32%–71%) and the NPV was 54% (95% CI 34%–72%) (Table 1).

3.2. Clinical assessment

Our review identified three studies that compared clinical assessment of ongoing pregnancy or retained gestational sac with ultrasound [15,23,26]. Two of these studies compared both clinical assessment and women's self-assessment of ongoing pregnancy with ultrasound [15,26], and one study compared clinical assessment alone with ultrasound [23].

In the first study, conducted in 2002–2003, 931 US women pregnant up to 63 days' gestation were administered mifepristone 200 mg orally and misoprostol 800 mcg vaginally 6–8 or 24 h later [15]. Six to 8 days after the mifepristone treatment, after reviewing the subjects' diary and discussing the events that followed after taking misoprostol, clinicians asked the women if they felt they had passed the pregnancy. The clinicians could also ask for additional information to aid with their evaluation. The clinicians made a non-standardized assessment of completion based on this history and performed an ultrasound to determine if the gestational sac was still present. Women's and clinicians' assessment correctly predicted 8 of the 16 retained gestational sacs that were confirmed by ultrasound [15]. This study had 50% sensitivity (95% CI 26%–75%) and 99% NPV (95% CI 98%–99.6%), and 6% of women screened positive (Table 2).

In the second study conducted in 2008, 139 women up to 63 days' gestation in the United States were administered mifepristone 200 mg orally and misoprostol 800 mcg vaginally or buccally according to client preference [26]. Seven days after taking mifepristone, 133 women were contacted by a clinician via telephone and asked a standardized set of questions for the clinician to assess for expulsion. If either the woman or clinician believed she had not passed the pregnancy (*n*=8), she was asked to return for a follow-up ultrasound within 7 days; if both clinician and woman believed she had passed the pregnancy (*n*=125), the woman was told to use high-sensitivity (HS) UPT on Day 30. One woman was not contacted for UPT, and 3 women who had positive or inconclusive urine pregnancy results did not return for follow-up — their pregnancy status was therefore unknown, and they were excluded from our analysis. An ultrasound was performed for the 26 women with positive or inconclusive urine pregnancy results who came in for a clinic visit. All of the four ongoing pregnancies were identified via the protocol — one was identified during an unscheduled office visit prior to the first phone call, two were identified based on the women's and clinicians' assessments during the phone call and the remaining one was identified during an unscheduled interim visit after the

Table 2
Accuracy of clinicians' assessment to detect ongoing pregnancy or retained gestational sac after medication abortion

Study	Modality	*n*	No. of ongoing pregnancies	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Screen-positive
Rossi et al. [15]	Women and clinicians	931	16[a]	50.0% (25.5%–74.5%)	95.3% (93.7%–96.5%)	15.7% (7.5%–29.1%)	99.1% (98.1%–99.6%)	5.5%
Perriera et al. [26]	Women and clinicians	135	4	100.0% (39.6%–100%)	86.3% (78.9%–91.4%)	18.2% (6.0%–41.0%)	100.0% (95.9%–100%)	16.3%
Pymar et al. [23]	Clinicians only	40	3[a]	33.3% (1.8%–87.5%)	94.6% (80.5%–99.1%)	33.3% (1.8%–87.5%)	94.6% (80.5%–99.1%)	7.5%

[a] Reported retained gestational sac rather than ongoing pregnancy.

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Table 3
Accuracy of serum hCG measurements to detect ongoing pregnancy after medication abortion

Study	*n*	No. of ongoing pregnancies	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Screen-positive
Fiala et al. [21]	217	2	100.0% (19.7%–100%)	98.1% (95.0%–99.4%)	33.3% (6.0%–75.9%)	100.0% (97.8%–100%)	2.8%

call [26]. This study had 100% sensitivity (95% CI 40%–100%) and 100% NPV (95% CI 96%–100%), and 16% of women screened positive (Table 2).

In the study that evaluated the ability of the clinician alone to predict ongoing pregnancy, 40 women up to 49 days' gestation were administered mifepristone 200 mg orally and misoprostol 800 mcg vaginally 6–8 h later [23]. Twenty-four hours after taking misoprostol, women were questioned about the side effects that occurred following the mifepristone/misoprostol. Three women had retained gestational sacs, and the clinician correctly predicted one [23]. This study had 33% sensitivity (95% CI 2%–88%) and 95% NPV (95% CI 81%–99%), and 8% of women screened positive (Table 2).

3.3. Serum hCG measurement

Several studies have shown that serial serum hCG measurements are accurate markers of ongoing pregnancy after medication abortion [28–31]. Our review identified three studies that compared a regimen of hCG follow-up with ultrasound or some other means of determining completion [21,32,33]. While all of these studies demonstrated that hCG testing was feasible in their respective settings, only one had cases of ongoing pregnancy that allowed for accuracy calculations [21]. In this study, conducted in 1999, 217 women pregnant up to 49 days' gestation in Austria were administered mifepristone 600 mg orally, followed 48 h later by misoprostol 400 mcg orally, which was repeated 3 h later if no bleeding occurred. Transvaginal ultrasound was performed, and serum hCG was collected on the day of mifepristone administration and again on Days 6–18. A positive test was defined as a ratio of post-treatment hCG to pre-treatment hCG of 0.2 or higher (or a decline of less than 80%). Both ongoing pregnancies identified by ultrasound were identified by hCG measurement. In fact, in both cases, hCG levels increased [21]. This study had 100% sensitivity (95% CI 20%–100%) and 100% NPV (95% CI 98%–100%), and 3% of women screened positive (Table 3).

3.4. UPT

Our review identified three studies that compared UPT with ultrasound [22,25,26]. The first was conducted in 2002–2003 among 1080 US women pregnant up to 63 days' gestation who were administered mifepristone 200 mg followed by misoprostol 800 mcg vaginally 6–8 or 24 h later [22]. At 1 week and 2 weeks after taking mifepristone, women underwent low-sensitivity (LS) and HS UPT, with transvaginal ultrasonography as the reference standard to detect the true absence or presence of a gestational sac. At the 1-week visit, ultrasound diagnosed a retained gestational sac in 14 women. None of the LS tests and two of the HS tests produced false-negative results. At the 2-week visit, 6 women with retained gestational sacs were detected by ultrasound. One of the LS tests and two of the HS tests were falsely negative [22]. At Week 1, the LS test had 100% sensitivity (95% CI 73%–100%) and 100% NPV (95% CI 96%–100%), and 87% of women screened positive; the HS test had 86% sensitivity (95% CI 56%–98%) and 96% NPV (95% CI 86%–99%), and 93% of women screened positive. At Week 2, the LS test had 83% sensitivity (95% CI 37%–99%) and 99.6% NPV (95% CI 97%–99.9%), and 62% of women screened positive; the HS test had 67% sensitivity (95% CI 24%–94%) and 99% NPV (95% CI 96%–99.8%), and 66% of women screened positive (Table 4).

The largest study of alternative follow-up modalities after medication abortion, conducted in 2005–2007, prospectively evaluated five algorithms, all of which included a clinic-based LS UPT plus clinicians' and/or women's assessment compared with ultrasound [25]. For the study, 3103 US women pregnant up to 63 days' gestation were given mifepristone 200 mg followed 6–72 h later by misoprostol 800 mcg orally, buccally or vaginally. Participants maintained a symptom diary that recorded whether they observed the expulsion of the pregnancy and whether they experienced heavy bleeding, pain or cramps. At a follow-up visit 7–14 days after mifepristone, women indicated on a questionnaire whether they still felt pregnant or had any symptoms of pregnancy. Clinicians reviewed the symptom diary at the follow-up visit, and at some of the sites they performed a physical exam. Clinicians then made a final assessment about whether the abortion was complete based on the woman's symptoms and exam. A urine specimen was obtained for an LS pregnancy test, which was performed by a laboratory technician. A clinician then performed a vaginal ultrasound.

Four algorithms that relied on clients' self-assessment plus the LS UPT (each included additional and less stringent self-assessment criteria) were evaluated, and a fifth algorithm added the clinicians' assessment. For the purposes of the analysis presented here, we included 49 women who presented for an unscheduled visit prior to the follow-up visit, which we interpret as a "screen-positive" self-assessment, although they technically presented for a visit before going through the algorithm. Twenty-two ongoing pregnancies were observed in this study; 20 of them were detected by algorithms 1 and 2, 21 by algorithm 3 and all

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Table 4
Accuracy of UPT to detect ongoing pregnancy or retained gestational sac after medication abortion

Study	Modality	*n*	No. of ongoing pregnancies	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Screen-positive
Godfrey et al. [22]	LS UPT, 1 week	826	14[a]	100.0% (73.2%–100%)	13.3% (11.1%–15.9%)	1.9% (1.1%–3.3%)	100.0% (95.7%–100%)	86.9%
	HS UPT, 1 week	821	14[a]	85.7% (56.2%–97.5%)	6.6% (5%–8.6%)	1.6% (.9%–2.8%)	96.4% (86.4%–99.4%)	93.3%
	LS UPT, 2 weeks	609	6[a]	83.3% (36.5%–99.1%)	38.6% (34.8%–42.7%)	1.3% (.5%–3.3%)	99.6% (97.3%–99.9%)	61.6%
	HS UPT, 2 weeks	606	6[a]	66.7% (24.1%–94%)	33.5% (29.8%–37.5%)	1.0% (.3%–2.7%)	99.0% (96.1%–99.8%)	65.5%
Clark et al. [25]	Algorithm 1: UPT with most stringent self-assessment	3103	22	90.9% (69.3%–98.4%)	67.6% (65.9%–69.2%)	2.0% (1.2%–3.1%)	99.9% (99.6%–100%)	32.8%
	Algorithm 4: UPT with least stringent self-assessment	3103	22	100.0% (81.5%–100%)	35.7% (34.0%–37.4%)	1.1% (0.7%–1.7%)	100.0% (99.6%–100%)	64.6%
	Algorithm 5: UPT with least stringent self-assessment plus clinician assessment	2847	22	100.0% (81.5%–100%)	65.0% (63.2%–66.8%)	2.2% (1.4%–3.3%)	100.0% (99.7%–100%)	35.5%

[a] Reported retained gestational sac rather than ongoing pregnancy.

were detected by algorithms 4 and 5 [25]. The most stringent self-assessment plus LS test algorithm (algorithm 1) had 91% sensitivity (95% CI 69%–98%) and 100% NPV (95% CI 99.6%–100%), and 33% of women screened positive; the least stringent self-assessment plus LS test algorithm (algorithm 4) had 100% sensitivity (95% CI 82%–100%) and 100% NPV (95% CI 99.7%–100%), and 65% of women screened positive. The fifth algorithm with the clinicians' assessment had 100% sensitivity (95% CI 82%–100%) and 100% NPV (95% CI 99.7%–100%), and 36% of women screened positive (details of algorithms 1, 4 and 5 are presented in Table 4).

In the study by Perriera et al. [26] described above, women performed an HS UPT at home on Day 30 (see details of study in Section 3.2). There were no ongoing pregnancies identified by urine testing alone (all were identified prior to performing the urine test), so it was not possible to calculate accuracy measures for the urine testing component of the algorithm [26].

4. Discussion

Our review identified eight studies that evaluated follow-up modalities that could be used instead of ultrasound to detect ongoing pregnancy or retained gestational sac after medication abortion. However, the fact that the outcomes of interest after the mifepristone regimen are so rare makes it difficult to evaluate protocols that aim to detect them. Several of the studies had fewer than 10 cases of ongoing pregnancy or retained gestational sac [21–23,26]. While this highlights the safety and efficacy of medication abortion, for this analysis, it resulted in large CIs for the sensitivity and PPV measures, which make interpretation of the findings difficult. It is also important to note that PPV is dependent on the prevalence of ongoing pregnancy in the population studied, and it is therefore not surprising that the study using the methotrexate regimen [24] had a higher PPV for women's self-assessment than the study using the mifepristone regimen [12].

Additional limitations of this review include the fact that the outcome of interest was not consistently defined in the studies, varying between ongoing pregnancy and retained gestational sac. The disparate nature of the follow-up modalities studied and the outcomes measured precluded any meta-analysis of the results. In addition, only one of the studies [25] explicitly mentioned that the readers of the index test and reference standard were blinded to the results of the other test.

Despite these limitations, we are able to draw some conclusions about alternative follow-up modalities after first-trimester medication abortion. In general, the self-assessments and clinicians' assessments that were standardized and that used detailed questions or criteria were more accurate than non-standardized, single-question modalities. The two women's self-assessment studies were based on

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single-question, non-standardized criteria, and both resulted in sensitivities <90% [12,24]. The non-standardized clinicians' assessments [15,23] also had low sensitivities, each ≤50%, and were less accurate than the modality employing standardized clinicians' assessment [26].

The most promising follow-up modalities include serum hCG measurements [21], LS UPT combined with a standardized assessment of women's symptoms [25], and standardized telephone consultation (perhaps followed by HS UPT) [26]. These follow-up modalities had sensitivities ≥90% and NPVs ≥99%, and they resulted in a proportion of "screen-positives" ≤33%.

Measuring serum hCG levels is a promising alternative to ultrasound for follow-up because of its high accuracy [21] and because it may be more accessible than ultrasound; however, it still incurs high costs. Including before-and-after hCG tests can add between $100 and $200 to the overall cost of medication abortion [34]. Nonetheless, hCG testing does not necessarily require a visit with the clinician and can simplify follow-up for some women. For example, women who live in a rural area could have their blood drawn at a nearby laboratory. It also allows providers to offer the method even if they do not have access to ultrasound. Furthermore, it is likely that ectopic pregnancies can be detected with this protocol because, although they can produce low hCG levels, they would be unlikely to have a decline in hCG level to 20% or less by the follow-up visit [32].

Another promising follow-up modality is UPT performed later than 1 week after abortion, combined with self-assessment or clinicians' assessment. UPT alone after 1 week had relatively high sensitivities; however, it resulted in a large proportion of women screening positive [22], and therefore a large number of women would be referred for additional follow-up. The study by Clark et al. [25], however, showed that adding a standardized assessment resulted in a lower proportion of screen-positives, while maintaining high sensitivity and NPV. The CIs of these measures were also narrow due to the study's large size. Algorithm 5 of the Clark et al. study, which included women's self-assessment, an LS UPT and clinical assessment, was highly sensitive with a high NPV, and only 36% would be referred for additional evaluation by ultrasound, making it a promising modality in settings where an in-person visit is feasible but access to ultrasound is limited. The low PPVs of this and many of the other modalities are a reflection of how rare ongoing pregnancy is, and the proportion with a positive screen is a more useful measure to compare the modalities.

It is important to note that as more elements of the self-assessment were added to the algorithms in the Clark et al. study, the proportion of women with a positive screen increased [25]. With algorithm 1, only 33% of women would be referred for further evaluation, while with algorithm 4, which included additional and less stringent self-assessment criteria, 65% would be referred for additional follow-up. Taking into account the 95% CIs, however, no significant difference in sensitivity was observed between the two algorithms. While the study suggests that LS UPT combined with a few discrete questions could be an accurate way to perform follow-up without ultrasound, the urine test that was used was performed by a laboratory technician and was not designed for home use. Additional research is needed on the use of home-based LS UPT after medication abortion documenting outcomes that are comparable with the current standard of care.

Although its small sample size is a significant limitation, the study by Perriera et al. [26] of telephone follow-up with standardized questions is also promising both because of the modality's high sensitivity to detect ongoing pregnancy and high NPV and the relatively low proportion of women with a positive screen. In practice, this means that only 16% of all medication abortion clients would be referred (or self-refer) for an in-person clinic visit. Although telephone follow-up may not be feasible in all settings, the findings of Perriera et al. suggest that the limited questions that were asked of participants could also be used in a clinic to triage those who need ultrasound or other follow-up evaluations [26]. More research on this algorithm is needed with a larger sample size.

Alternative follow-up modalities are particularly useful in settings where access to ultrasound may be limited. They do not prevent women who choose to attend a routine follow-up visit from doing so; they can, however, allow for greater options for those women who may find these visits to be a burden or expensive. Additional research with adequate sample sizes is needed to demonstrate the accuracy and feasibility of home-based urine testing combined with self-assessment and/or clinician-assisted assessment. More studies in low-resource settings of alternative follow-up, either at home or in a clinic without the use of ultrasound, are also required. It is critical that these studies clearly define the outcome of interest, such as ongoing pregnancy, and follow recommended guidelines for reporting studies of diagnostic accuracy, including blinding the readers of the index and reference tests [35]. The elements of any clinical assessment should also be standardized in order to be able to replicate the follow-up protocol in other settings.

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Effectiveness and Acceptability of Medical Abortion Provided Through Telemedicine

Daniel Grossman, MD, Kate Grindlay, MSPH, Todd Buchacker, RN, Kathleen Lane, and Kelly Blanchard, MSc

OBJECTIVE: To estimate the effectiveness and acceptability of telemedicine provision of early medical abortion compared with provision with a face-to-face physician visit at a Planned Parenthood affiliate in Iowa.

METHODS: Between November 2008 and October 2009, we conducted a prospective cohort study of women obtaining medical abortion by telemedicine or face-to-face physician visits. We collected clinical data, and women completed a self-administered questionnaire at follow-up. We also compared the prevalence of reportable adverse events between the two service delivery models among all patients seen between July 2008 and October 2009.

RESULTS: Of 578 enrolled participants, follow-up data were obtained for 223 telemedicine patients and 226 face-to-face patients. The proportion with a successful abortion was 99% for telemedicine patients (95% confidence interval [CI] 96–100%) and 97% for face-to-face patients (95% CI 94–99%). Ninety-one percent of all participants were very satisfied with their abortion, although in multivariable analysis, telemedicine patients had a higher odds of saying they would recommend the service to a friend compared with face-to-face patients (odds ratio, 1.72; 95% CI 1.26–2.34). Twenty-five percent of telemedicine patients said they would have preferred being in the same room with the doctor. Younger age, less education, and nulliparity were significantly associated with preferring face-to-face communication. There was no significant difference in the prevalence of adverse events reported during the study period among telemedicine patients (n=1,172) (1.3%; 95% CI 0.8–2.1%) compared with face-to-face patients (n=2,384) (1.3%; 95% CI 0.9–1.8%) (82% power to detect difference of 1.3%).

CONCLUSION: Provision of medical abortion through telemedicine is effective and acceptability is high among women who choose this model.

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LEVEL OF EVIDENCE: II

Mifepristone was approved by the U.S. Food and Drug Administration in September 2000. Early medical abortion using mifepristone with misoprostol is effective and highly acceptable to U.S. women with some preferring it over vacuum aspiration.[1–3] Medical abortion is not a surgical procedure and can be offered by nonspecialist clinicians,[4] a fact that led some to believe that its availability would improve access to abortion services in the United States. However, a recent analysis found that almost all medical abortion-only providers were located within 50 miles of a large-volume surgical abortion provider.[5]

In approximately 15 states, certified nurse–midwives, physician assistants, and nurse practitioners are permitted to provide medical abortion.[6] In the remaining states, laws that limit provision of abortion to physicians have been applied (or assumed to apply) to medical abortion as well.

Telemedicine, the delivery of health care services at a distance using information and communication technology, has been used in many fields of medicine to improve access to services. For example, telemedicine has been used to provide specialist consultation to primary care services and to deliver rural outpa-

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tient care, generally with patient outcomes that are comparable to in-person treatment.[7] In 2008, Planned Parenthood of the Heartland, a clinic network located in Iowa that provided 74% of all abortions in the state that year,[8] had 17 clinic sites. Three of these clinics had an on-site physician, whereas an additional three sites intermittently offered abortion care when a physician traveled to the clinic; the remaining 11 clinics did not provide abortions. In June 2008, Planned Parenthood of the Heartland launched a program to provide medical abortion using telemedicine at clinic sites not staffed by a physician to improve access to early abortion and reduce physician travel to outlying clinics. The objective of this study was to estimate the effectiveness and acceptability of the telemedicine provision model compared with the standard practice of a face-to-face visit with a physician.

MATERIALS AND METHODS

Between November 2008 and October 2009, women seeking medical abortion at six Planned Parenthood of the Heartland clinics in Iowa were invited to participate in the study. At four sites, medical abortion was offered only through telemedicine; at one site it was offered only with a face-to-face physician visit; and at one site both models were offered, depending on physician availability. Women seeking abortion at Planned Parenthood of the Heartland called a central call center, which gave them information about the nearest clinic and soonest appointment and informed them whether the service would be provided by telemedicine or not, and women selected the appointment they preferred. In the areas served by the telemedicine clinics, there was no other abortion clinic closer than the closest physician-staffed Planned Parenthood clinic. Once at the clinic, women who chose medical abortion and were eligible for the method (including being pregnant at 63 days gestation or less and not having other standard contraindications[9]), were 18 years old or older, able to speak English, and able to give informed consent were eligible to participate in the study.

Clinical information was collected at the participants' first clinic visit, including demographic information and gestational age according to ultrasonography. Participants were given the standard medical abortion regimen at the clinics: 200 mg mifepristone administered orally followed 24–48 hours later by 800 μg misoprostol administered buccally at home.[10] All women had ultrasonography performed by a trained technician, received information about medical abortion, and underwent standard informed consent for the abortion. A physical examination was not routinely done, consistent with the standard of care.[9] For face-to-face visit patients, one of two physicians reviewed the patient's medical history and ultrasonographic images and had a brief discussion with the patient. If the patient was eligible for a medical abortion, the physician handed her the mifepristone and misoprostol tablets, observed her swallow the mifepristone, and gave her final instructions. For those who received services through telemedicine, clinic staff uploaded the patient's medical history and ultrasonographic image to a secure server for the physician to review. One of the same two physicians then had a discussion with the patient using video teleconference equipment that was linked through a dedicated Multiprotocol Label Switching data connection. If the patient was eligible for medical abortion, the physician entered a password into her computer that remotely unlocked a drawer in front of the patient containing the mifepristone and misoprostol tablets. The physician observed her swallow the mifepristone and gave her final instructions through the video teleconference.

Women were scheduled for a follow-up visit within 2 weeks after receiving mifepristone. Pelvic ultrasonography was performed at follow-up to confirm completion of the abortion. If the abortion was incomplete, women were given the option of expectant management, additional misoprostol, or vacuum aspiration; ongoing pregnancies were treated with vacuum aspiration. If a telemedicine patient required a nonemergent vacuum aspiration, she was scheduled at a physician-staffed clinic for the procedure. If the abortion was not complete at the time of this visit, another visit was scheduled. Clinical information was collected at each follow-up visit, including the ultrasonographic result, any medications given, and whether a vacuum aspiration was performed. Effectiveness of medical abortion was defined as the proportion of women with a complete abortion not requiring a surgical procedure, including vacuum aspiration.

Once the abortion was complete, participants were asked to fill out a self-administered questionnaire focusing on their experience with the abortion service, including satisfaction with the service they received. If participants did not return for follow-up, they were contacted at least three times by phone and once by mail to schedule either an in-person follow-up visit or a telephone interview to complete the questionnaire. Information on adverse events was collected from participants at each follow-up visit or

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during the telephone interview, and medical records from other facilities were reviewed when relevant.

All statistical analyses were performed using STATA 10.1. χ^2 analyses and *t* tests were used to compare study participants to all medical abortion patients aged 18 years or older seen during the study period to assess potential selection bias and to compare demographic, clinical, and acceptability information between telemedicine and face-to-face study participants. All analyses among cohort participants were conducted among women with complete follow-up information.

Univariable and multivariable analyses were conducted to identify potential associations between service delivery model (telemedicine compared with face-to-face) and the primary effectiveness and acceptability outcomes. To account for the possibility that a patient's experience might vary by the clinic she attended, clinic site was introduced into the multivariable model as a random effect, and the standard error was adjusted with a modified-sandwich estimator using STATA's vce (cluster clustervar) option for cluster-correlated data.[11,12] Automated forward selection was used to build the multivariable models with the entry level set at $P<.20$. Demographic and clinical covariates with univariable significance of $P<.20$ not entered during forward selection were next added to the model in order of ascending univariable *P* value and were included in the final model if their inclusion changed the predictor variable's effect estimate by 10% or more. Gestational age was forced into the multivariable model assessing effectiveness because of evidence that the prevalence of ongoing pregnancy after medical abortion increases with increasing gestational age.[1] Covariates were added using these rules up to the maximum number of allowable covariates in a multivariable model based on the rule: number of events/10.[13]

Sample size was based on the acceptability outcome of overall satisfaction, because we anticipated that effectiveness would be comparable between groups. We also anticipated that acceptability of the telemedicine service would be high but might be somewhat lower than the standard provision model. Assuming 90% of women in the standard provision group reported being satisfied or very satisfied with their experience,[10] a sample of 219 in each group was needed to detect a difference in acceptability among telemedicine patients of 10% or more (two-sided $\alpha=0.05$, power=80%). Recruitment was continued until the desired sample of participants with follow-up data was obtained.

Because of the relatively small sample size of the cohort study, we also analyzed deidentified data on all adverse events after medical abortion reported to the Planned Parenthood Federation of America and Danco Laboratories by Planned Parenthood of the Heartland between July 1, 2008 (shortly after telemedicine was initiated) and October 31, 2009 (shortly after cohort recruitment ended). Planned Parenthood affiliates are required to report the following adverse events: ongoing pregnancy, emergency room treatment, hospitalization, transfusion, unrecognized ectopic pregnancy, allergic reaction, infection requiring intravenous treatment, and death. We calculated the prevalence, 95% confidence intervals (CIs), and χ^2 analyses of any adverse event, ongoing pregnancy, or blood transfusion, comparing telemedicine with face-to-face patients during this period. We also conducted a multivariable analysis of any adverse event comparing telemedicine with face-to-face patients during this period adjusting for possible confounders.

All cohort study participants gave informed consent to participate in the study. They received a $10 gift card for completing the questionnaire. The study was approved by Allendale institutional review board.

RESULTS

The study flow diagram is shown in Figure 1. Fifty-six percent of patients aged 18 years or older seen during the study period were enrolled into the study. Reasons for nonparticipation were not collected, although study staff noted that fewer patients were enrolled on busy clinic days, possibly because staff did not have time to thoroughly explain the study. After excluding seven patients, 578 women were included in the cohort study. Among the 281 telemedicine patients, 205 (73%) had an in-person and 18 (6%) had a phone follow-up interview; 58 (21%) were lost to follow-up. Among the 297 face-to-face patients, 196 (66%) had an in-person and 30 (10%) had a phone follow-up interview; 71 (24%) were lost to follow-up. The proportion of patients that attended an in-person visit was not significantly different between the two groups ($P=.07$).

Age, marital status, and race were similar between cohort study participants and all patients receiving medical abortion aged 18 years or older seen during the study period. A lower proportion of study participants were Latina (4% compared with 7%, $P=.008$) and had a maximum completed education of 12 years or less (52% compared with 58%, $P=.03$). Table 1 shows the enrollment demographic and clinical information for cohort study participants with follow-up data. Among study participants, telemedicine and face-to-face patients were similar in terms of age, marital status, race, ethnicity, parity, and gesta-

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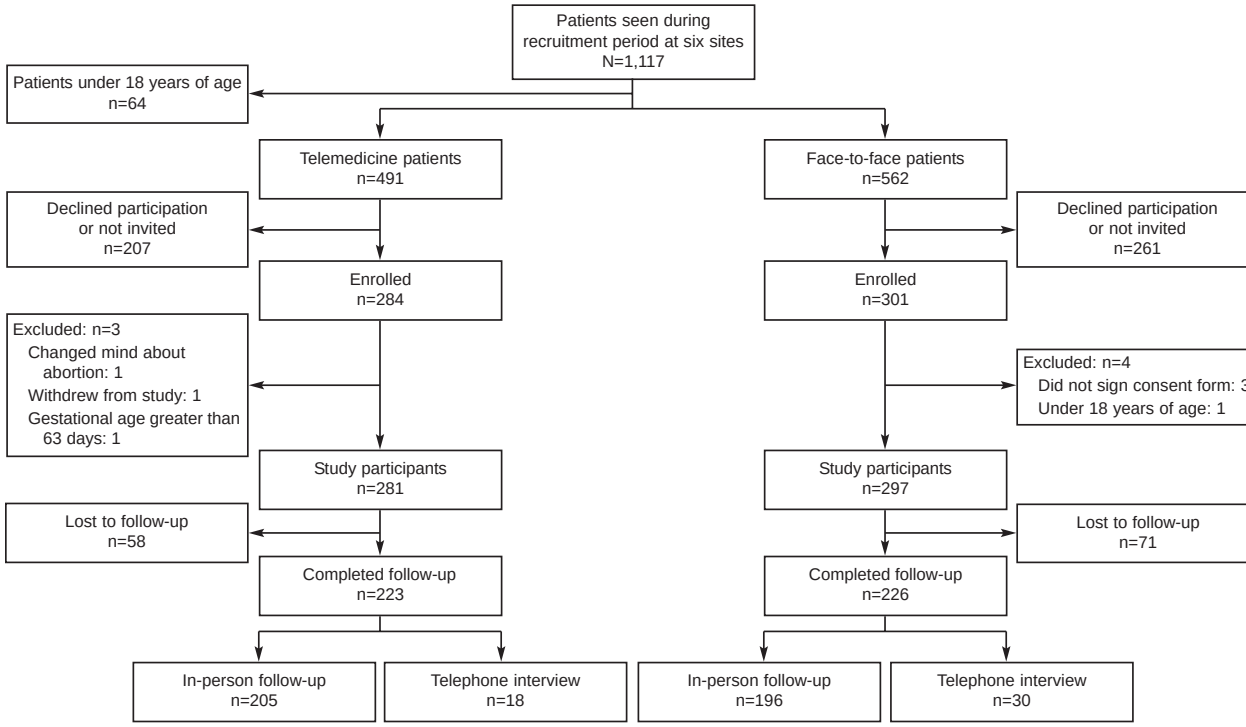

Fig. 1. Flow of patients through the study.
Grossman. Telemedicine Provision of Medical Abortion. Obstet Gynecol 2011.

tional age. Compared with telemedicine participants, more face-to-face participants had a maximum completed education of 12 years or less (58% compared with 46%, *P*=.01) and reported a prior abortion (38% compared with 26%, *P*=.006).

Follow-up information was obtained a median of 15 days after enrollment for those with in-person visits and 27 days after enrollment for those who had phone interviews. At follow-up, eight women (three telemedicine and five face-to-face patients) were given an additional dose of misoprostol and scheduled for a second follow-up visit.

Contraceptive uptake postabortion was slightly higher among participants with a face-to-face visit. Eighty-eight percent (n=199) of face-to-face participants and 80% (n=179) of telemedicine participants were given or had started a contraceptive method by the time of the follow-up visit or phone interview (*P*=.02). Use of specific contraceptive methods was not significantly different between the cohorts, except more face-to-face participants were given condoms (21% compared with 6%, *P*<.001) or had an intrauterine device inserted (23% compared with 12%, *P*=.005) at the follow-up visit.

Two of the 223 telemedicine patients underwent vacuum aspiration for ongoing pregnancy (n=1) or incomplete abortion (n=1), and one woman elected to continue an ongoing pregnancy for a total effectiveness of 98.7% (95% CI 96.1–99.5%). Six of the 226 face-to-face patients underwent vacuum aspiration and one underwent dilation and curettage for ongoing pregnancy (n=2) or incomplete abortion (n=5) for a total effectiveness of 96.9% (95% CI 93.7–98.5%). The odds of successful abortion with telemedicine compared with face-to-face provision was not significantly different in the multivariable model, which adjusted for within-cluster correlation and gestational age (odds ratio [OR] 2.34, 95% CI 0.84–6.55).

There were no deaths or hospitalizations among the cohort study participants. Adverse events, including emergency room visits and visits to other clinics, occurred among 2.5% of participants and were not statistically different between groups (*P*=.78). One telemedicine participant received a blood transfusion in an emergency room. The telemedicine participant who decided to continue with an ongoing pregnancy reported her child was normal at 7 months of age.

Table 2 shows the prevalence of adverse events among all patients undergoing medical abortion from July 1, 2008, to October 31, 2009. A total of 46 adverse events were reported (1.3% of 3,556 medical abortions). No deaths were reported. There was no

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Table 1. Characteristics of Cohort Study Participants

	Telemedicine Cohort (n=223)	Face-to-Face Cohort (n=226)	*P*
Age (y)			.65
18–25	137 (61)	130 (58)	
26–35	71 (32)	77 (34)	
36–45	15 (7)	19 (8)	
Median	23	24	
Mean	24.9	25.7	.11
Marital status			.72
Single	163 (74)	164 (73)	
Married or partnered	35 (16)	42 (19)	
Divorced, widowed, or separated	22 (10)	20 (9)	
Latina or Hispanic	5 (2)	12 (5)	.09
Race			.85
White	179 (82)	182 (85)	
African American	28 (13)	22 (10)	
Asian American	5 (2)	4 (2)	
Other*	6 (3)	6 (3)	
Highest grade completed 12 y or less	102 (46)	130 (58)	.01
Median	13	12	
Mean	13.5	13.1	.01
Parous	112 (50)	133 (59)	.07
Mean	1.01	1.09	.49
Prior abortion	58 (26)	86 (38)	.006
Gestational age (d)			.79
49 or less	141 (63)	142 (63)	
50–56	53 (24)	50 (22)	
57–63	29 (13)	34 (15)	
Median	46	46	
Mean	46.7	47.1	.58

Data are n (%) unless otherwise specified.
* Other race includes women who reported more than one race and women who reported their race as Native American or Alaska Native.

significant difference in the prevalence of any adverse event, ongoing pregnancy, or blood transfusion between women who received services through telemedicine compared with face-to-face provision. With a one-sided α of 0.05, this sample size had 82% power to detect an increase in the prevalence of any adverse event from 1.3% among face-to-face patients to 2.6% among telemedicine patients. The odds of any adverse event among telemedicine compared with face-to-face patients was not significantly different in the multivariable model, which adjusted for within-cluster correlation, marital status, Latina ethnicity, and race (OR 0.96, 95% CI 0.48–1.91).

Table 2. Adverse Events Among All Medical Abortion Patients, July 1, 2008, Through October 31, 2009

	Telemedicine (n=1,172)	Face-to-Face (n=2,384)	*P*
Any adverse event	1.3 (0.8–2.1)	1.3 (0.9–1.8)	.96
Ongoing pregnancy	0.9 (0.5–1.7)	1.0 (0.6–1.4)	.94
Blood transfusion	0.3 (0.1–0.9)	0.1 (0.04–0.4)	.23

Data are % (95% confidence interval) unless otherwise specified.

Table 3 shows information on acceptability of abortion services. Overall satisfaction was very high among participants, although more telemedicine patients (94%) reported being very satisfied compared with face-to-face patients (88%), which was significantly different in the univariable analysis (P=.03). However, when adjusted for within-cluster correlation (no additional covariates met the multivariable model inclusion criteria), this difference was no longer significant (OR 2.10, 95% CI 0.75–5.92).

More telemedicine patients (90%) said they would recommend the medical abortion service to a friend in a similar situation than face-to-face patients (83%, P=.04). In the multivariable model, which adjusted for within-cluster correlation, age, education, and prior abortion, telemedicine patients had greater odds of saying they would recommend the service compared with face-to-face patients (OR 1.72, 95% CI 1.26–2.34).

Patients in both groups reported liking similar aspects of the service, including the staff (58%), information received (30%), and the fact that they did not feel judged (11%). A minority of patients reported dislikes, and a significantly higher proportion of face-to-face patients (32%) complained about the waiting time in the clinic compared with telemedicine patients (7%, P<.001).

We asked women several questions about the factors that influenced their decision about what abortion method to have and which clinic to go to. Seventy-one percent of participants said they strongly wanted medical abortion when they were making their decision (no difference between cohorts), and 94% of participants said having the abortion as early as possible was very important to them (no difference between cohorts). However, 69% of telemedicine patients said having the abortion close to home was very important compared with 58% of face-to-face patients (P=.02).

Three fourths of patients reported being satisfied with the conversation with the doctor (the video teleconference for those receiving telemedicine services), and this did not differ between the two groups (P=.89). Among telemedicine patients, 99% said it was easy to see the doctor, and 99% said it was easy to hear the doctor; 89% said they felt comfortable asking the doctor questions during the video teleconference.

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Table 3. Acceptability of Abortion Services

	Telemedicine Cohort (n=214)	Face-to-Face Cohort (n=217)	*P*
Overall satisfaction			
Very satisfied	201 (94)	191 (88)	.03*
Somewhat satisfied	10 (5)	21 (10)	
Somewhat or very dissatisfied	1 (.5)	1 (.5)	
Not sure or no response	2 (1)	4 (2)	
Would recommend a medical abortion in this clinic to a friend	192 (90)	180 (83)	.04
What liked best (more than one response possible)			
Staff	128 (60)	123 (57)	.51
Information received	67 (31)	61 (28)	.47
Did not feel judged	20 (9)	27 (12)	.30
Other	18 (8)	20 (9)	.77
Felt comfortable	14 (7)	16 (7)	.74
Privacy and confidentiality	14 (7)	11 (5)	.51
Fast	11 (5)	11 (5)	.97
Nothing or no response	10 (5)	8 (4)	.61
What liked least (more than one response possible)			
Nothing or no response	148 (69)	110 (51)	<.001
Waiting time	16 (7)	70 (32)	<.001
Other†	50 (23)	37 (17)	.10
Information received			
Very helpful	195 (91)	202 (93)	.45‡
Somewhat or not helpful	16 (8)	13 (6)	
Not sure or no response	3 (1)	2 (1)	
Satisfaction with conversation with doctor			
Very satisfied	163 (76)	164 (76)	.89*
Somewhat satisfied	34 (16)	36 (17)	
Somewhat or very dissatisfied	11 (5)	6 (3)	
Not sure or no response	6 (3)	11 (5)	
Initial feelings about medical compared with surgical abortion			
Strongly wanted medical abortion	156 (73)	152 (70)	.51§
Leaning toward medical abortion	33 (15)	36 (17)	
Strongly wanted surgical abortion	2 (1)	2 (1)	
Leaning toward surgical abortion	2 (1)	5 (2)	
No strong feeling either way	19 (9)	19 (9)	
No response	2 (1)	3 (1)	
Feelings about importance of having abortion close to home			
Very important	147 (69)	126 (58)	.02‖
Somewhat important	38 (18)	50 (23)	
Not important	21 (10)	31 (14)	
Not sure or no response	8 (4)	10 (5)	
Feelings about importance of having an early abortion			
Very important	202 (94)	202 (93)	.58‖
Somewhat important	8 (4)	10 (5)	
Not important or not sure	4 (2)	5 (2)	
Easy to see doctor during telemedicine encounter			
Yes	211 (99)		
No	3 (1)		
Easy to hear doctor during telemedicine encounter			
Yes	212 (99)		
No	2 (1)		
Comfortable asking questions during telemedicine encounter			
Yes	190 (89)		
No	24 (11)		
Would prefer doctor in room instead of telemedicine			
Yes	53 (25)		
No	154 (73)		
No response	5 (2)		

Data are n (%) unless otherwise specified.
* *P* value for very satisfied compared with not very satisfied.
† Other includes: staff (nine), telemedicine (nine), not enough information received (eight), having abortion (seven), lack of privacy (seven), distance (six), partner could not attend visit (five), and general (36).
‡ *P* value for very helpful compared with not very helpful.
§ *P* value for strongly wanted medical abortion compared with other responses.
‖ *P* value for very important compared with not very important.

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One fourth of telemedicine patients said they would have preferred being in the same room with the doctor. Participants were allowed to write in comments about this response, which generally indicated that although they would have preferred to be in the same room, because that was not an option, they were satisfied with the video teleconference. These open responses are representative of some of the comments participants gave: "I am always generally more comfortable dealing with serious issues in person" and "It was rather irritating, but probably faster/more convenient. (I'm a face to face person)."

In multivariable analysis, the following covariates were associated with a preference for being in the same room with the physician: age 18–25 years (compared with 26 years or older; OR 1.58, 95% CI 1.20–2.09); education 12 years or less (compared with more than 12 years; OR 1.80, 95% CI 1.51–2.14); and nulliparous (compared with parous; OR 1.71, 95% CI 1.15–2.54).

DISCUSSION

We found that provision of medical abortion through telemedicine had comparable clinical outcomes to the face-to-face provision model with equivalent success rates and a low prevalence of adverse events. Both the high success rate and low prevalence of adverse events for the telemedicine service are similar to those reported for medical abortion in the literature.[1,10,14] Although contraceptive uptake was slightly higher among the face-to-face cohort, this was most likely the result of the limited number of providers trained to insert intrauterine devices at telemedicine sites.

Acceptability was high among both groups of women in this study, and these results were similar to other studies on medical abortion with buccal misoprostol.[10,15] We found one measure of acceptability–willingness to recommend the service to a friend–to be significantly higher among telemedicine patients, even after controlling for confounders. The fact that telemedicine patients reported high levels of satisfaction may be related to the convenience of receiving services closer to home or earlier in pregnancy, both of which were important for this group. Our results do not indicate that telemedicine patients were coerced to have a medical abortion despite this being the only method available at the clinics they accessed, because a high proportion reported strongly wanting medical abortion from the outset, and this did not differ from face-to-face patients. The fact that telemedicine patients had a restricted choice at the clinics they attended, if anything, might have biased them to have lower levels of satisfaction compared with face-to-face patients, who also had the option of aspiration abortion.

We found that 25% of telemedicine patients would have preferred a face-to-face visit with the physician, and this was more common among younger, less educated, and nulliparous women. Another study of clinic-based medical abortion found that older age was an independent predictor of a positive experience, whereas education level was not.[16] In our study, participants were told at the time they scheduled their appointment whether they would receive abortion services through telemedicine or not. It seems that some decided to have the abortion through telemedicine perhaps because the clinic was closer to their home or because they could get an appointment sooner, although ideally they would have preferred to be in the same room with the physician. This finding highlights the importance of informing women about what the telemedicine service involves so patients can weigh the options about which service they prefer.

This study has several limitations. Participants were not randomized and instead selected the treatment they received (telemedicine compared with a face-to-face visit), which might have introduced selection bias. However, because this was the first study of telemedicine provision of medical abortion, we felt it was important for women to be well informed of the two provision models and be allowed to choose which they preferred. In the future, a randomized controlled trial might be possible among women who have no real preference between the two models as has been done to compare medical and surgical abortion.[17,18] Overall, 56% of patients aged 18 years or older seen during the study period agreed to participate in the cohort study, and participants were somewhat more educated and less likely to be Latina than the general medical abortion clinic population. This might have introduced selection bias, although the acceptance rate likely affected both cohorts similarly. In addition, 22% of participants were lost to follow-up despite multiple attempts to contact them. Although this loss to follow-up is high, it is similar to proportions reported in the literature[19] and did not differ between cohorts. Finally, our results are specific to the provision models offered in this clinic system, and we cannot generalize our findings to other service delivery settings.

In states where physicians are required to perform medical abortion, the findings from this study indicate that telemedicine can be used to provide medical abortion in an effective and highly acceptable manner. Future research should evaluate whether

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telemedicine provision improves access to services for women in rural areas as well as whether there are cost savings associated with the model. Just as telemedicine has been used to extend the reach of physicians in other disciplines, this provision model has the potential to provide abortion services earlier in pregnancy and closer to a woman's home and to help overcome the barriers to abortion access in the United States.[20]

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Original Research Article

Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment ☆,☆☆

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ABSTRACT

Objective(s): To estimate the effectiveness, acceptability, and feasibility of medication abortion with mifepristone dispensed by a mail-order pharmacy after in-person clinical assessment.
Study Design: This is an interim analysis of an ongoing prospective cohort study conducted at five sites. Clinicians assessed patients in clinic and, if they were eligible for medication abortion and ≤ 63 days' gestation, electronically sent prescriptions for mifepristone 200 mg orally and misoprostol 800 mcg buccally to a mail-order pharmacy, which shipped medications for next-day delivery. Participants completed surveys three and 14 days after enrollment, and we abstracted medical chart data.
Results: Between January 2020 and April 2021 we enrolled 240 participants and obtained clinical outcome information for 227 (94.6%); 3 reported not taking either medication. Of those with abortion outcome information (N = 224), 216 (96.4%) completed day-3 and 212 (94.6%) day-14 surveys. Of the 224 that took medications, none reported taking past 70 days' gestation, and complete medication abortion occurred for 217 participants (96.9%, 95% CI 93.7%-98.7%). Most received medications within three days (82.1%, 95% CI 76.5%-86.9%). In the day-3 survey, 95.4% (95% CI 91.7%-97.8%) reported being very (88.4%) or somewhat (6.9%) satisfied with receiving medications by mail. In the day-14 survey, 89.6% (95% CI 84.7%-93.4%) said they would use the mail-order service again if needed. Eleven (4.9%, 95% CI 2.5%-8.6%) experienced adverse events; two were serious (one blood transfusion, one hospitalization), and none were related to mail-order pharmacy dispensing.
Conclusions: Medication abortion with mail-order pharmacy dispensing of mifepristone appears effective, feasible, and acceptable to patients.
Implications: The in-person dispensing requirement for mifepristone, codified in the drug's Risk Evaluation and Mitigation Strategy, should be removed.

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1. Introduction

For over 20 years, the U.S. Food and Drug Administration (FDA) has required that mifepristone (200 mg) used for medication abor-

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tion be dispensed only in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber; this restriction is codified in the drug's Risk Evaluation and Mitigation Strategy (REMS) [1]. During this time a considerable amount of data has been collected on the safety of pregnancy termination with mifepristone [2]. In addition, a recent study found that dispensing mifepristone at brick-and-mortar pharmacies after in-person assessment by a clinician was effective and acceptable to patients seeking abortion, with a low prevalence of adverse events (AEs) [3].

A growing proportion of U.S. patients obtain medications from mail-order pharmacies [4]. Mail-order pharmacy dispensing of mifepristone could further allow medication abortion patients to bypass geographical obstacles to the service and receive abortion care earlier in pregnancy [5–7]. Considering the declining number of abortion providers in the U.S. [8,9], it could also help increase the number of clinicians willing and able to provide medication abortion by enabling them to avoid cost and logistical challenges of stocking and dispensing mifepristone in their facilities, thereby improving access to care [10].

Under an Investigational New Drug Application (IND) from the FDA, we began a prospective cohort study of the acceptability, feasibility, and effectiveness of dispensing medications for abortion using a mail-order pharmacy following an in-person assessment for eligibility. In April 2021, the FDA announced it would suspend the in-person dispensing requirement for mifepristone during the COVID-19 public health emergency. We conducted this interim analysis at the midpoint of planned recruitment to provide additional information to the FDA as it considers the future of the mifepristone REMS after the emergency ends.

2. Material and Methods

From January 2020 to April 2021, we enrolled patients at five clinics in four states seeking medication abortion who consented to receive their medications from a mail-order pharmacy; two clinics had not previously provided abortion care. The Institutional Review Boards (IRBs) of the University of California San Francisco (UCSF), Albert Einstein College of Medicine, Kent Hospital, and Alameda Health System approved the study. Site investigators completed the mifepristone Prescriber Agreement Form. Clinicians evaluated patients in person for medical eligibility according to the mifepristone label after confirming interest in medication abortion. Patients were eligible for the study if they were aged 15 years or older, spoke English or Spanish, were willing to administer misoprostol buccally as mandated by the FDA, and had a gestational duration of $\leq$ 63 days (to reduce the chance that shipping delays might result in a participant taking mifepristone past 70 days' gestation). Clinicians at study sites determined gestational duration based on patients' history, confirmed by physical examination or ultrasound.

Those interested and eligible provided written informed consent. Patients signed the mifepristone Patient Agreement Form and received instructions on medication use. All participants were scheduled for clinical follow-up, which varied at sites and included: (1) in-person ultrasonography one to two weeks after mifepristone, (2) serum human chorionic gonadotropin (hCG) measurements on the day of enrollment and one to two weeks after mifepristone, or (3) a telephone call one week after mifepristone with a home urine pregnancy test four weeks after mifepristone, sometimes accompanied by a telehealth visit. If clinical follow-up did not occur, we relied on patients' self-report of abortion outcome in their survey responses, as done in prior research [3].

Treating clinicians electronically prescribed each participant mifepristone 200 mg and misoprostol 800 mcg, as well as analgesics, antibiotics, antiemetics, or contraceptives at their discretion. Clinicians instructed participants to take misoprostol buccally 24 to 48 hours after mifepristone. The mail-order pharmacy processed the prescriptions according to their standard "next-day delivery" workflow and shipped the medications to each participant's preferred address.

Three days later, we emailed participants a Qualtrics survey link to collect information about whether their medication package delivery time was "reasonable" or "too long," whether the package had been damaged or opened, and whether their confidentiality might have been compromised in any way. We also collected information on participants' sociodemographic characteristics, satisfaction with receiving the medications by mail, if and/or when they took or planned to take the medications, whether they thought they had "passed the pregnancy," and whether they had any new medical problems related to their abortion. We asked those who reported a prior medication abortion, "How would you compare your experience of getting the pills this time by mail compared with last time in the clinic?".

Two weeks later, we emailed participants a second survey, which included similar questions about taking the medications, medical problems for which they sought further care, clinic follow-up, and abortion completion. Participants who believed their abortion was complete were asked how they knew that, including whether they had an ultrasound, blood tests, a negative urine pregnancy test, a normal period, whether their pregnancy symptoms went away, or for some other reason (with an open response). We also asked about their overall medication abortion experience and whether they would recommend mail-order dispensing of mifepristone to a friend. We also asked, "If you were to have an undesired pregnancy in the future and chose to have a medication abortion, would you want to get the pills by mail again?".

Six or more weeks after enrollment, personnel from each participating site entered de-identified data about all visits or contact with the patient into an electronic REDCap form. We used these data abstracted from medical records, in combination with survey data, to identify abortion outcomes and AEs occurring within six weeks of enrollment, including any emergency department visits at least possibly related to the medication abortion. We considered serious AEs to be death, hospitalization, blood transfusion, or surgery, according to FDA criteria [11,12].

Participants received electronic gift cards at enrollment ($15) and after completing each survey ($25 each). The study paid for the medication abortion, including the cost of clinical visits, mifepristone, misoprostol, pharmacy dispensing fees, and shipping.

We evaluated the effectiveness of medication abortion as the proportion of participants who had a complete abortion with medications alone. We used data abstracted from clinic records for this outcome; if the patient did not have follow-up with the clinic, we used self-reported survey data to document abortion outcome, similar to prior research [3]. We evaluated safety as the proportion who had any AE that was at least possibly related to the medication abortion. For acceptability, we assessed the proportion of participants reporting in the day-14 survey they would use mail-order dispensing again if needed and the proportion reporting they were "satisfied" or "very satisfied" with the medication abortion. For feasibility, we measured the proportion who received packages within three days, reported the packages they received remained intact, and reported their confidentiality was maintained. We calculated binomial 95% confidence intervals for main outcomes in Stata 15 (College Station, TX).

The planned sample size for the ongoing study is a minimum of 440 participants. This will give us approximately 80% power to estimate acceptability of the care model and over 90% power to estimate effectiveness and demonstrate if these estimates are within a 5% non-inferiority margin of published estimates for facility-dispensed medication abortion. Prior research with patients ob-

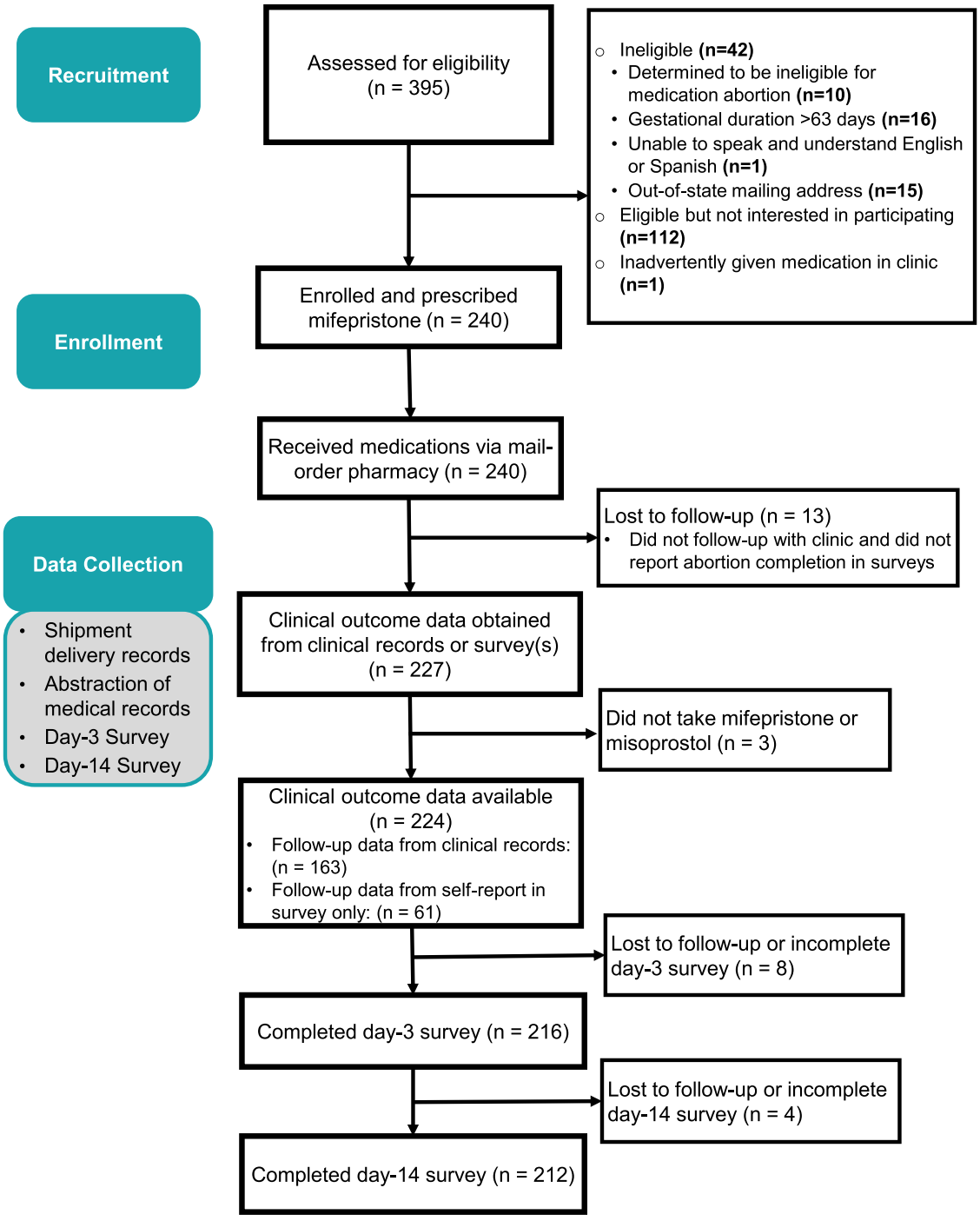

Fig. 1. Study flow of patients seeking medication abortion who were evaluated in person and then received mifepristone from a mail-order pharmacy in the U.S. in 2020 to 2021

taining medication abortion with in-person mifepristone dispensing has estimated the proportion who would use medication abortion again as 89.7% [13] and overall effectiveness as 97.4% [14].

3. Results

Clinic staff assessed 395 patients for eligibility and enrolled 240 participants; 155 were ineligible or declined to participate (Fig. 1). All enrolled participants received the study medications by mail. We obtained clinical outcomes for 227 participants (94.6%); 13 (5.4%) participants were lost to follow-up. Three participants reported not taking mifepristone or misoprostol; two returned the package, and one reported losing it. We excluded them from the analysis, leaving a final sample of 224 participants.

Table 1 shows the characteristics of study participants; of note, as of the time of this interim analysis, we had not recruited any minors. Table 2 shows the delivery time for the medication package; the details of when and how participants reported using the medications, including gestational duration on date of taking mifepristone, initial misoprostol dosage and route of administration, and interval between medications; and abortion outcome, including how abortion outcome was assessed. Overall, 217 of 224 participants (96.9%, 95% CI 93.7%-98.7%) had a complete abortion with medications alone, including eight (3.6%) who received

Table 1
Characteristics of study participants having medication abortion who received mifepristone from a mail-order pharmacy in the U.S. in 2020-21 ($N = 224$)*

Characteristic	N	%
Age (years)		
≤17	0	0.0
18-24	65	29.0
25-29	70	31.3
30-34	60	26.8
≥35	29	12.9
Median age in years (IQR)	28 (24-32)	
Race and ethnicity		
Non-Hispanic White	39	17.4
Non-Hispanic Black	134	59.8
Hispanic	24	10.7
Asian / Asian-American	4	1.8
Native Hawaiian or Other Pacific Islander	0	0.0
Alaska Native or Native American	0	0.0
Other† and multiracial	11	4.9
Missing	12	5.4
Education		
High school or less	80	35.7
Some college or professional school	68	30.4
College degree	26	11.6
Advanced degree	25	11.2
Missing	25	11.2
Parity		
Nulliparous	46	20.5
Parous	178	79.5
Previous abortion experience		
None	83	37.1
Previous medication abortion	82	36.6
Previous abortion procedure	56	25.0
Missing	3	1.3
Gestational duration at initial clinic visit (days)		
≤49	168	75.0
50-56	36	16.1
57-63	20	8.9

IQR, interquartile range.
* Among participants who took medications and had abortion outcome data available.
† Three participants selected "other" race and did not give additional information.

Table 2
Dosing details and clinical outcomes for study participants having medication abortion and receiving mifepristone from a mail-order pharmacy in the U.S. in 2020-21 ($N = 224$)*

	N	%
Medication delivery time (days from prescription to package delivery)		
≤3 days	184	82.1
4-7 days	39	17.4
>7 days	1	0.4
Gestational duration at date of taking mifepristone (days)		
≤49	134	59.8
50-56	50	22.3
57-63	28	12.5
64-70	11	4.9
Missing	1	0.4
Median gestational duration at mifepristone in days (IQR)	48 (43-54)	
Reported interval between mifepristone and misoprostol		
<24 hours	2	0.9
24-48 hours	220	98.2
Missing	2	0.9
Reported initial misoprostol dose		
800 mcg	216	96.4
Missing	8	3.6
Reported route of misoprostol administration		
Buccal	217	96.9
Vaginal	3	1.3
Missing	4	1.8
Abortion outcome		
Complete with medications only	217	96.9
Complete with repeat dose of misoprostol	8	3.6
Unsuccessful medication abortion	7	3.1
Incomplete abortion, underwent aspiration	2	0.9
Ongoing pregnancy†	5	2.2
Method of confirmation of abortion outcome among participants who followed up with study clinic	$N = 163$	
Clinical history and home urine pregnancy test (telephone visit)	78	47.9
Ultrasound	41	25.2
Clinical history alone (telephone visit)	37	22.7
Serial serum hCG testing	6	3.7
Negative urine pregnancy test (in clinic)	1	0.6
Method of confirmation of abortion outcome among participants who did not follow up with study clinic & indicated abortion completion in survey responses	$N = 61$	
Negative home urine pregnancy test	39	63.9
Reported the clinic said abortion was complete	3	4.9
Ultrasound at another facility	3	4.9
Reported abortion complete based on history alone‡	16	26.2
No more pregnancy symptoms	13	21.3
Normal period returned	2	3.3
Self-report - no reasons given	2	3.3

IQR, interquartile range
* Among participants who took medications and had abortion outcome data available.
† 4 participants underwent procedural abortion and 1 continued the pregnancy.
‡ Some participants reported more than one history-based response.

a second dose of misoprostol 800 mcg. Five participants (2.2%) had ongoing pregnancies, and two (0.9%) had incomplete abortions treated with uterine aspiration. One of the participants with an ongoing pregnancy elected to continue the pregnancy; we contacted her last at 31 weeks' gestation, and she reported her pregnancy was uncomplicated. No participant was found to have an ectopic pregnancy. We present outcomes by gestational duration in Supplemental Table 1.

Eleven participants (4.9%, 95% CI 2.5%-8.6%) had an AE that was determined by the site and principal investigators to be at least possibly related to the medication abortion; however, the investigators determined that none of these AEs would have been avoided by dispensing medications in person rather than with the mail-order pharmacy. All participants with an AE reported taking the medications at ≤ 70 days' gestation as instructed. Among those with an AE, 10 had an emergency department visit (one reported two visits for the same problem), and two had a possible serious AE (one received a blood transfusion, and one reported being hospitalized overnight but received no additional treatment).

Packages arrived within three days for 184 of 224 participants (82.1%, 95% CI 76.5%-86.9%); most reported packages were in good condition (97.2%, 95% CI 94.1%-98.9%) and that confidentiality was uncompromised (96.8%, 95% CI 93.4%-98.7%) (Tables 2 and 3). Of those who reported compromised confidentiality, three said someone found the medications, three reported other privacy concerns, and one reported that both someone found the medications and they had other privacy concerns. Medications were not affected in any cases where the package was reported damaged. All who reported the date they took mifepristone had a gestational duration of ≤ 70 days on that date.

For the day-3 survey, we excluded eight of 224 (3.6%) participants missing data on satisfaction with receiving medications by mail. In the survey, 206 (95.4%, 95% CI 91.7%-97.8%) reported being very (88.4%) or somewhat (6.9%) satisfied with receiving medications by mail. Among those who reported a prior medication abortion ($N = 78$), 89.7% reported their experience of getting the pills this time by mail was better (55.1%) or the same (34.6%) compared with last time in the clinic (Table 3).

Table 3
Acceptability and satisfaction at day-3 survey among study participants having medication abortion and receiving mifepristone from a mail-order pharmacy in the U.S. in 2020-21 ($N = 216$)*

	N	%
Acceptability of medication delivery time		
Reasonable	196	90.7
Too long	20	9.3
Condition of package		
Good condition (no evidence of tampering)	210	97.2
Damaged (opened, punctured, crushed, etc.)	5†	2.3
Missing data	1	0.5
Confidentiality maintained during delivery		
Yes	209	96.8
No, confidentiality was compromised	7	3.2
Adequate information received from clinic		
Yes	215	99.5
No, I would have liked more information	1	0.5
Satisfaction with receiving medications by mail		
Very satisfied	191	88.4
Somewhat satisfied	15	6.9
Neither satisfied nor dissatisfied	5	2.3
Somewhat dissatisfied	2	0.9
Very dissatisfied	3	1.4
Among those who had previous medication abortion, how they would compare experience of getting pills this time by mail compared with last time in clinic	$N = 78$	
This time was better	43	55.1
Same	27	34.6
Last time was better	3	3.8
Not sure	4	5.1
Missing	1	1.3

* Among participants who had abortion outcome data available and completed day-3 survey.
† Medications were not affected in any cases where package was damaged.

Table 4
Acceptability and satisfaction at day-14 survey among study participants having medication abortion and receiving mifepristone from a mail-order pharmacy in the U.S. in 2020-21 ($N = 212$)*

	N	%
Overall satisfaction with medication abortion		
Very satisfied	172	81.1
Somewhat satisfied	21	9.9
Neither satisfied nor dissatisfied	13	6.1
Somewhat dissatisfied	3	1.4
Very dissatisfied	3	1.4
Would recommend medication abortion to a friend		
Yes	193	91.0
No	5	2.4
Not sure	14	6.6
Would recommend mail-order dispensing to a friend		
Yes	200	94.3
No	1	0.5
Not sure	10	4.7
Missing	1	0.5
If had an undesired pregnancy in the future and chose to have a medication abortion, would want to get the pills by mail again		
Yes	190	89.6
No	9	4.2
Not sure	13	6.1

* Among participants who had abortion outcome data available and completed day-14 survey.

For the day-14 survey, we excluded 12 of 224 (5.4%) participants missing data on overall satisfaction with medication abortion. In this survey, 193 (91.0%, 95% CI 86.4%-94.5%) reported satisfaction with their overall medication abortion experience, and 190 (89.6%, 95% CI 84.7%-93.4%) said that they would use the mail-order service again if needed (Table 4). Most said they would recommend medication abortion (91.0%) and mail-order dispensing (94.3%) to a friend.

4. Discussion

Preliminary findings from this study suggest that medication abortion with mail-order pharmacy dispensing of mifepristone was effective, feasible, and acceptable to patients seeking early abortion. Outcomes were similar to those reported when mifepristone has been dispensed in a clinic [13-20], with few serious adverse events.

While most participants received their medications within three days, 18% experienced a longer wait. We conservatively restricted enrollment to participants at ≤ 63 days' gestation to account for potential delays in delivery; however, given evidence supporting mifepristone use up to 77 days' gestation [21], this was likely overly restrictive.

The study may have limited generalizability given that we recruited only in four states with few restrictions on abortion care. This model is not possible in the 19 states that require physicians to be in the same room with the patient when mifepristone is dispensed [22]. This interim analysis is also limited by the sample size. The full analysis will include at least four more sites, including in two new states, and up to 385 additional participants. A strength of the study is its low loss to follow-up.

We look forward to completing recruitment for the study in the coming year, which will provide more precise estimates of the effectiveness, acceptability, and feasibility of medication abortion with mail-order pharmacy dispensing of mifepristone. However, these interim results, together with studies of other care models that include mailing pills for medication abortion [23–26] and pharmacist dispensing at brick-and-mortar pharmacies [3], support the removal of the FDA's in-person dispensing requirement for mifepristone.

Clinical Trial Registration

Clinicaltrials.gov, NCT03913104.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.contraception.2021.09.008.

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OPEN

Original Research

Medication Abortion With Pharmacist Dispensing of Mifepristone

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OBJECTIVE: To estimate effectiveness and acceptability of medication abortion with mifepristone dispensed by pharmacists.

METHODS: We conducted a prospective cohort study at eight clinical sites and pharmacies in California and Washington State from July 2018 to March 2020. Pharmacists at participating pharmacies underwent a 1-hour training on medication abortion. We approached patients who had already been evaluated, counseled, and consented for medication abortion per standard of care. Patients interested in study participation gave consent, and the clinician electronically sent a prescription to the pharmacy for mifepristone 200 mg orally, followed 24–48 hours later by misoprostol 800 micrograms buccally. Participants were sent web-based surveys about their experience and outcomes on days 2 and 14 after enrollment and had routine follow-up with study sites. We extracted demographic and clinical data, including abortion outcome and adverse events, from medical records. We performed multivariable logistic regression to assess the association of pharmacy experience and other covariates with satisfaction.

RESULTS: We enrolled 266 participants and obtained clinical outcome information for 262 (98.5%), of whom two reported not taking either medication. Of the 260 participants with abortion outcome information, 252 (96.9%) and 237 (91.2%) completed day 2 and 14 surveys, respectively. Complete medication abortion (primary outcome) occurred for 243 participants (93.5%, 95% CI 89.7–96.1%). Four participants (1.5%, 95% CI 0.4–3.9%) had an adverse event, none of which was serious or related to pharmacist dispensing. In the day 2 survey, 91.3% (95% CI 87.1–94.4%) of participants reported satisfaction with the pharmacy experience. In the day 14 survey, 84.4% (95% CI 79.1–88.8%) reported satisfaction with the medication abortion experience. Those reporting being very satisfied with the pharmacy experience had higher odds of reporting overall satisfaction with medication abortion (adjusted odds ratio 2.96, 95% CI 1.38–6.32).

CONCLUSION: Pharmacist dispensing of mifepristone for medication abortion is effective and acceptable to patients, with a low prevalence of adverse events.

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Each author has confirmed compliance with the journal's requirements for authorship.

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Medication abortion with mifepristone and misoprostol is approved by the U.S. Food and Drug Administration (FDA) for use through 70 days of gestation. Extensive research has documented the safety and effectiveness of medication abortion, as well as high levels of patient satisfaction.[1] Since mifepristone's approval in 2000, the FDA has required that the drug only be dispensed in clinics, medical offices, or hospitals, a restriction that is codified in the mifepristone Risk Evaluation and Mitigation Strategy.[2] The FDA instituted these restrictions likely because of the limited experience with medication abortion in the United States in 2000. However, there is no evidence that in-person dispensing improves safety, and medications associated with more risks to the patient do not have similar restrictions.[3]

Twenty years later, such evidence is still lacking, and countries such as Australia and Canada have approved mifepristone without dispensing restrictions.[4,5] The mifepristone Risk Evaluation and Mitigation Strategy may be a barrier to access; a national survey of obstetrician–gynecologists found that the number who would provide medication abortion might double if this dispensing restriction were removed.[6] The American College of Obstetricians and Gynecologists advocates the removal of the mifepristone Risk Evaluation and Mitigation Strategy.[7]

Pharmacists dispense medications and controlled substances for all types of indications, including sensitive health issues such as sexually transmitted infections and erectile dysfunction. Currently, 12 states permit pharmacists to prescribe hormonal contraception[8]; a recent national survey found that 65% of all pharmacists were interested in such prescribing.[9]

We performed this study under an FDA Investigational New Drug application to document clinical outcomes with and the acceptability of medication abortion when mifepristone is prescribed by clinicians and dispensed by pharmacists. We also sought to identify factors associated with satisfaction with the pharmacist-dispensing model, as well as to explore whether satisfaction with the pharmacy experience was associated with overall satisfaction with medication abortion.

METHODS

We performed a multicenter prospective cohort study of patients undergoing medication abortion who agreed to obtain pharmacist-dispensed mifepristone. The Institutional Review Boards (IRBs) of the University of California San Francisco (UCSF), Kaiser Permanente Northern California, and the University of Washington approved the study, with reliance on the University of California San Francisco IRB granted by the IRBs of the University of California, Davis, and the University of California, San Diego.

From July 2018 through March 2020, we enrolled patients at eight study sites in California and Washington State, each of which was paired with a nearby pharmacy that agreed to dispense mifepristone. Each of the clinical sites provided medication abortion before the study with clinic dispensing of mifepristone; patients obtained other prescribed medications at pharmacies. Six of the eight clinics partnered with an affiliated pharmacy in the same or adjacent building (n=5) or 1.5 miles away (n=1). Two clinics partnered with independent pharmacies, one of which was located in an adjacent building, and the other was located 1.5 miles away. Study investigators trained participating pharmacists on medication abortion and mifepristone dispensing using a standardized 1-hour presentation at the beginning of the study and as needed when new participating pharmacists were hired. At all study pharmacies, leadership permitted pharmacists to participate in the study if interested, including undergoing training, and committed to having coverage during study recruitment times by a pharmacist who could dispense mifepristone. Of note, three chain pharmacies near potential clinic sites declined to participate. Each clinical site principal investigator completed the mifepristone Prescriber Agreement Form.

Clinicians included physicians, physician assistants, and nurse practitioners. Research staff provided study details, including study coverage of clinical costs (see below) to patients only after the clinician had completed all medically necessary requirements for medication abortion. All patients approached for the study had already been fully evaluated for medication abortion medical eligibility according to the FDA-approved mifepristone labeling and local standard of care, signed the mifepristone Patient Agreement Form and any clinic-specific consent form, and received mifepristone use and follow-up instructions. Clinical follow-up options were site-specific and included returning for an in-clinic ultrasonography examination approximately 1–2 weeks later, obtaining serum human chorionic gonadotropin measurements on the day of taking mifepristone and 1–2 weeks later, or performing telephone follow-up 1 week later with a home urine pregnancy test 4 weeks after mifepristone.

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Participants were eligible for the study if they spoke English or Spanish, were age 15 years or older (18 years or older at two study sites), had been fully evaluated and consented for medication abortion with a gestational age of 70 days or less confirmed by ultrasonography, and were willing to go to the study pharmacy to obtain mifepristone and to use misoprostol buccally per the FDA-approved mifepristone label. Participants also had to be willing and able to be contacted by email, telephone, or text message to complete survey data collection. Eligible and interested participants provided written study informed consent, including Health Insurance Portability and Accountability Act authorization to allow clinical data abstraction from their medical record.

A clinician then electronically prescribed mifepristone 200 mg and misoprostol 800 micrograms, along with analgesics, antibiotics, antiemetics, or contraceptives, as needed. The prescribing clinician instructed participants to use the mifepristone at an agreed-on time and take the misoprostol buccally 24–48 hours after swallowing the mifepristone, consistent with the FDA-approved labeling.[10] Participants went to the pharmacy to obtain the prescribed medications. A trained pharmacist dispensed the mifepristone and other prescribed medications, maintained a study log and provided brief counseling, unless declined by the patient.

On the day after enrollment, the University of California San Francisco study team emailed participants a link to a web-based survey (day 2 survey) in Qualtrics to collect sociodemographic information, including self-described race and ethnicity. Given the evidence of negative health care experiences during pregnancy among people of color due to racism,[11] we believed it was important to collect race and ethnicity information to explore associations with satisfaction outcomes. Participants also confirmed whether they obtained the medications at the pharmacy, and if and when they took or planned to take the medications. If they had taken the misoprostol, we asked the route of administration. If a participant obtained the medications and decided not to take them, we asked what they did or planned to do with the medications; if a participant reported they still had the medications, a survey prompt instructed them to return the medications to the pharmacy or the clinic. Participants were asked whether they thought the pregnancy had already been expelled and whether they had had a medical problem that required them to go to a hospital, emergency department, or doctor's office since starting the medication abortion, and, if so, we asked participants to provide details.

In addition, the day 2 survey assessed participant experiences obtaining mifepristone at the pharmacy with multiple choice questions as well as open-response fields for those who reported dissatisfaction to explain their responses. We asked whether the wait time at the pharmacy was "reasonable" or "too long." All participants were asked, "Did you feel that you got enough information from the pharmacist about how to use the medications?" with response options of "Yes," "No, I would have liked more information from the pharmacist," and "No, but I got all the information I needed from the doctor or nurse in clinic." We asked participants who reported having had a prior medication abortion, "How would you compare your experience of getting the abortion pill this time in the pharmacy compared with last time in the clinic?" with response options of "This time was better," "Last time was better," "They were both the same," or "Not sure."

Two weeks after enrollment, we sent participants an email link to the day 14 survey, which had similar questions about taking the medications, medical problems for which they sought care, follow-up with the clinic, use of additional misoprostol, and whether they thought the abortion was complete and reasons why they thought it was complete. If a participant reported being unsure whether the abortion was complete, a survey prompt instructed the participant to contact the clinical site and asked permission to follow-up with them again after the visit.

The day 14 survey also included questions about the patient's experience with the overall medication abortion experience and whether they would recommend medication abortion to a friend in a similar situation who decided to have an abortion. We also asked whether they would recommend that the friend "get the abortion pill at the pharmacy like you did." Finally, we asked, "If you have another medication abortion in the future, how would you feel about the way you get the service?" Responses options were "I would prefer to have medication abortion be available through many primary care providers and providers of women's health care (doctors and nurses) and I would like to pick up my abortion pill at the pharmacy," "I would prefer to have medication abortion available only in select clinics where the abortion pill can be given to me directly in clinic," "Either way is fine," or "Unsure." The day 14 survey also included open-response questions that allowed participants to elaborate on their responses.

Participants who did not complete the surveys were sent reminders by text, email, or phone, depending on their contact preferences. Those who had not

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yet completed the day 2 survey received a longer day 14 survey, including the day 2 survey items. The surveys remained open for 1 month.

Six or more weeks after participants enrolled, site investigators abstracted data from patient charts and entered the de-identified data into an electronic REDCap form. Abstracted data included demographics, clinical information from the initial visit, and information about any follow-up visits or contacts with the patient related to the medication abortion, including whether the abortion was complete, additional treatments given, and adverse events. Adverse events were also identified from the patient surveys. Adverse events were captured up to 6 weeks after participants were recruited into the study, and any ongoing adverse events were followed until resolution. Adverse events were defined as serious using the FDA criteria and included death, hospitalization, blood transfusion, and surgery.[12,13]

Study participants received a $25 electronic gift card for completing each survey. Participants that had to travel from the clinic to the pharmacy also received a small stipend to cover travel expenses. The study covered the cost of mifepristone, misoprostol, and pharmacy dispensing fees, as well as the cost of other medications and clinical care related to the medication abortion provided during the initial and follow-up visits at some sites, depending on whether the site was able to bill for the service in the usual fashion or not.

We aimed to recruit a minimum of 300 and up to 350 patients for this study, which we thought was feasible during the study period. With a sample size of 300, if the proportion of patients with a complete abortion is 95%, the 95% CI of that proportion is ±3.1%; with a sample of 350, the interval is ±2.7%.

We examined four outcomes related to clinical experience and satisfaction with the pharmacist-dispensing model. These included two clinical outcomes: 1) effectiveness of medication abortion (primary outcome) and 2) adverse events, as well as two patient satisfaction outcomes that we examined in multivariate mixed-effects logistic regression analyses: 3) satisfaction with the pharmacy experience at day 2 and 4) satisfaction with the overall medication abortion experience at day 14. Effectiveness of medication abortion was defined as the proportion of participants who had a complete abortion with medications alone and did not undergo vacuum aspiration. Given the accuracy of patient self-assessment of abortion completion,[14,15] we used self-reported survey data to document abortion outcome if the participant did not have follow-up contact with the clinic. Satisfaction outcomes were based on participants' ratings on a Likert scale. On the day 2 survey, we asked participants "Overall, how satisfied were you with your experience at the pharmacy when you got the abortion pill?" with response options "Very satisfied," "Somewhat satisfied, "Somewhat dissatisfied," and "Very dissatisfied." On the day 14 survey we asked, "Looking back on your experience overall, how satisfied were you with the abortion pill?" with the same response options. We dichotomized responses to the two questions by those who were very satisfied compared with all other responses. We calculated 95% CIs using the binomial method.

We performed multivariable mixed-effects logistic regression analyses to explore associations between participant and pregnancy characteristics and our two patient satisfaction outcomes (satisfaction with pharmacy experience and satisfaction with overall medication abortion experience). We used mixed-effects regression with random intercepts for recruitment site to account for clustering. Independent variables included the following demographic and pregnancy characteristics, selected a priori based on our hypotheses and previous literature[16]: age, race and ethnicity, highest completed level of education, relationship status, parity, gestational age in days at the initial clinic visit, and prior abortion experience (none, previous medication abortion, or previous procedural abortion only). We also adjusted for whether the participant reported receiving adequate information from the pharmacist about medication abortion and pharmacy wait time (reasonable or too long). We included a dichotomized measure of satisfaction with treatment by pharmacy staff as an independent variable in the analysis of satisfaction with the pharmacy experience outcome. To assess whether the pharmacy experience contributed to overall satisfaction with the medication abortion experience, we also included satisfaction with the pharmacy experience as an independent variable to model this outcome.

To account for missing covariate data, we conducted multiple imputation then deletion methods, using chained equations.[17] We excluded participants with missing outcome data after performing multiple imputation. All demographic variables and pharmacy experience responses were collected from patient surveys except gestational age at the clinic visit, which came from clinical charts. Missing survey data for age, race and ethnicity, and parity were obtained from patients' clinical chart data when available.

We conducted all analyses using Stata 15 and reported significance at $P<.05$. Open-ended survey responses were sorted by relevance to study intervention and organized under unifying themes.

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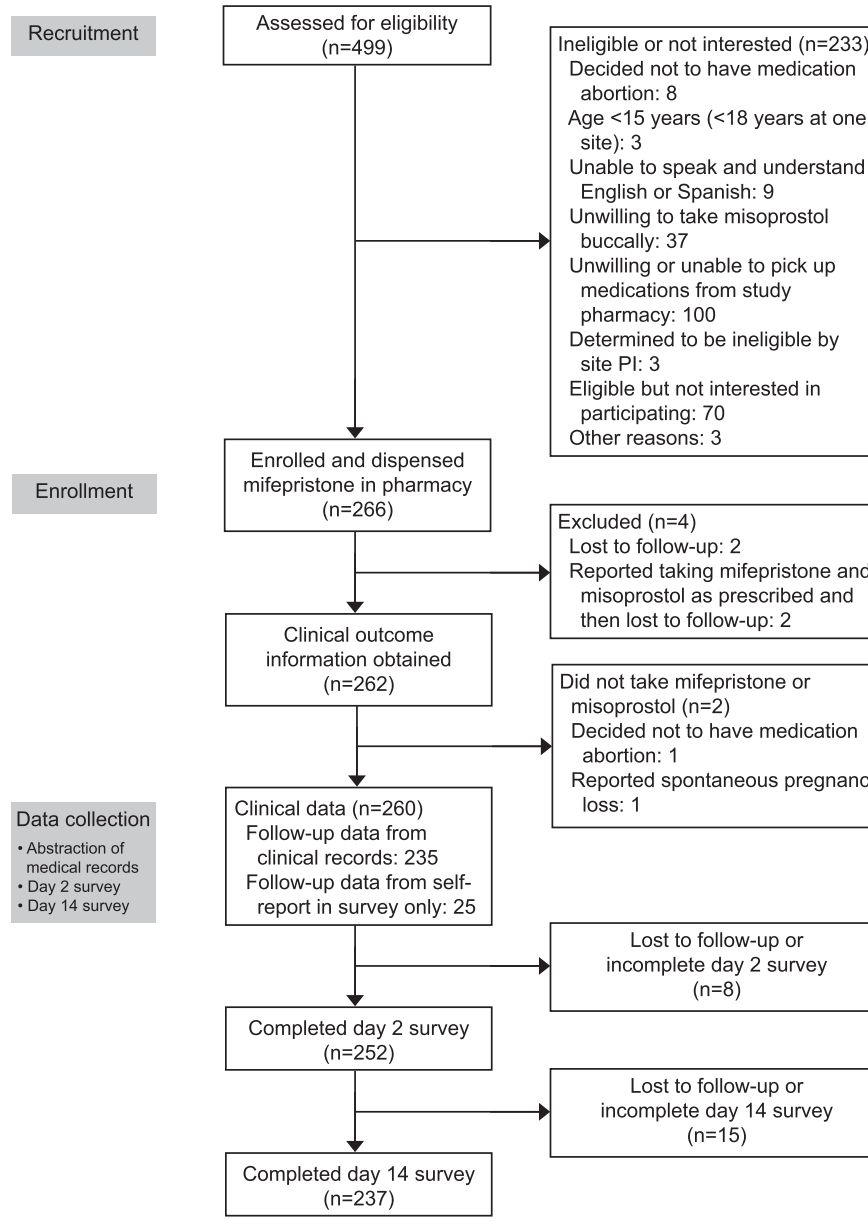

Fig. 1. Medication abortion study flow of patients who received mifepristone from pharmacists. PI, principal investigator.

Grossman. Pharmacist Dispensing of Mifepristone. Obstet Gynecol 2021.

RESULTS

Study recruitment began in July 2018 and was halted before reaching our desired sample size in March 2020 owing to the coronavirus disease 2019 (COVID-19) pandemic, which limited the ability to have research staff in clinical facilities and lengthen patient visits for the purposes of research consent. Research staff assessed 499 patients for eligibility, of whom 233 were ineligible (n=163) or declined to participate (n=70) (Fig. 1). We enrolled 266 participants, all of whom received the study medications from the pharmacy. The median number of participants recruited at the eight sites was 27 (range 8–74). Medication abortion and study outcome information was available for 262 participants (98.5%); the other four were lost to follow-up. In addition, one participant opted not to have a medication abortion and returned the medications to the study site, and one reported flushing the medications down the toilet after having a spontaneous pregnancy loss. The characteristics of the 260 participants (97.7%) who took the medications and have abortion outcome data are presented in Table 1. The median gestational age was 46 days at the time of initial clinic visit. Two hundred forty-six participants (94.6%) reported the date they took mifepristone; all had a gestational age of 70 days or less on that date.

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Table 1. Characteristics of Study Participants Having Medication Abortion and Receiving Mifepristone at a Pharmacy (n=260)

Characteristic	Value
Age (y)	28 (16–44)
16–20	22 (8.5)
21–24	45 (17.3)
25–29	78 (30.0)
30–34	69 (26.5)
35–44	46 (17.7)
Race and ethnicity	
Non-Hispanic White	99 (38.1)
Non-Hispanic Black	29 (11.2)
Hispanic	65 (25.0)
Asian or Pacific Islander	45 (17.3)
Alaska Native or Native American	2 (0.8)
Other* and mixed race and ethnicity	19 (7.3)
Missing	1 (0.4)
Education	
High school or less	39 (15.0)
Some college or professional school	93 (35.8)
College degree	90 (34.6)
Advanced degree	28 (10.8)
Missing	10 (3.8)
Relationship status	
Neither married nor in a relationship	84 (32.3)
Married	54 (20.8)
Committed relationship	110 (42.3)
Missing	12 (4.6)
Parity	
Nulliparous	171 (65.8)
Parous	89 (34.2)
History of abortion	
None	165 (63.5)
Previous medication abortion	48 (18.5)
Previous procedural abortion only	40 (15.4)
Missing	7 (2.7)
Gestational age at initial clinic visit (d)	46 (30–70)
49 or less	176 (67.7)
50–56	43 (16.5)
57–63	32 (12.3)
64–70	9 (3.5)

Data are median (range) or n (%).
* Four participants selected "other" race and did not give additional information.

Table 2. Acceptability and Satisfaction at Day 2 Survey Among Women Having Medication Abortion and Receiving Mifepristone at a Pharmacy (n=252)

	n (%)
Satisfaction with pharmacy experience	
Very satisfied	173 (68.7)
Somewhat satisfied	57 (22.6)
Somewhat dissatisfied	18 (7.1)
Very dissatisfied	4 (1.6)
Satisfaction with treatment by pharmacy staff	
Very satisfied	201 (79.8)
Somewhat satisfied	43 (17.1)
Somewhat dissatisfied	5 (2.0)
Very dissatisfied	3 (1.2)
Wait time at pharmacy	
Reasonable	200 (79.4)
Too long	51 (20.2)
Missing	1 (0.4)
Adequate information received from pharmacist	
No, I would have liked more information	4 (1.6)
No, but I got all the information I needed from the doctor or nurse	96 (38.1)
Yes	151 (59.9)
Missing	1 (0.4)
Current vs previous experience among those who had previous medication abortion (n=48)	
This time better	17 (35)
Last time better	1 (2)
Same	22 (46)
Not sure	8 (17)

We obtained abortion outcomes for most participants (n=235, 90.4%) based on completed clinical follow-up, with the remainder based on survey responses. Follow-up assessments are detailed in online Appendix 1, available online at http://links.lww.com/AOG/C227. Complete abortion occurred for 243 participants (93.5%, 95% CI 89.7–96.1%) with medication alone. Twenty-seven participants received a second dose of misoprostol, including 18 who ultimately had a complete abortion. Seventeen participants were diagnosed with incomplete abortion based on symptoms and ultrasonography findings, all of whom underwent vacuum aspiration. No participant had an ongoing pregnancy. Outcomes by gestational age are presented in Appendix 2, available online at http://links.lww.com/AOG/C227.

Four participants (1.5%, 95% CI 0.4–3.9%) had an adverse event possibly related to the abortion. Three participants went to an emergency department: one received intravenous fluids for dehydration, one reported heavy bleeding and was treated with pain medication, and one was diagnosed with pelvic inflammatory disease after an aspiration for incomplete abortion. None were hospitalized. In addition, one participant reported at a follow-up visit that she had transient pain and swelling in her cheeks after taking the misoprostol buccally, which had resolved and was thought to be a possible allergic reaction. After review by the site principal investigators, no adverse event was thought to be related to pharmacist dispensing. No participant reported a serious adverse event, and none were identified in chart abstraction.

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For survey data, we excluded 8 of 260 (3.1%) participants missing pharmacy satisfaction data and 23 of 260 (8.8%) participants missing overall medication abortion satisfaction data. Participants completed the day 2 survey a median of 2 days after enrollment (interquartile range 1–4 days) and completed the day 14 survey a median of 16 days after enrollment (interquartile range 14–21 days). Table 2 shows participants' satisfaction as reported in the day 2 survey (n=252). Among survey respondents, 91.3% (95% CI 87.1–94.4%) reported being very (68.7%) or somewhat (22.6%) satisfied with their experience at the pharmacy, and 96.8% (95% CI 93.8–98.6%) reported being very (79.8%) or somewhat (17.1%) satisfied with their treatment by pharmacy staff. Four-fifths (79.4%) of participants said the wait time in the pharmacy was reasonable.

Participants who were less than very satisfied with the pharmacy experience (n=76) or treatment by pharmacy staff (n=42) gave open-ended responses describing their dissatisfaction. Common themes cited included complaints about long wait times (n=38), confusion on the part of pharmacists or staff regarding dispensing (n=27), perceived negative pharmacist attitudes (n=10), inadequate pharmacist knowledge about the medications (n=8), initially not receiving all prescribed medications (n=8), and privacy not adequately maintained (n=4), among others. Some participants pointed to more than one factor that contributed to their dissatisfaction.

In the day 2 survey, most participants reported they received adequate information from the pharmacist (59.9%) or reported they did not receive enough information from the pharmacist but received all the information they needed from the clinician they had seen previously (38.1%). Only four participants (1.6%) reported that they would have liked more information about how to use the medications from the pharmacist.

Among the 48 participants who reported a prior medication abortion, most said the current experience was the same (n=22, 46%) or better (n=17, 35%) as receiving the medications in the clinic. Eight (17%) were unsure and one (2%) reported the experience as worse. In an open-response field, participants wrote they appreciated the ability to schedule when they would take the medications, which improved convenience and allowed them to have more control over when the abortion would take place. Although some participants saw this model of care as allowing more privacy and social support, a few thought the model was less private and felt less supported by the pharmacy staff compared with the clinic staff.

Table 3. Acceptability and Satisfaction at Day 14 Survey Among Women Having Medication Abortion and Receiving Mifepristone at a Pharmacy (n=237)

	n (%)
Overall satisfaction with medication abortion	
Very satisfied	155 (65.4)
Somewhat satisfied	45 (19.0)
Neither satisfied nor dissatisfied	23 (9.7)
Somewhat dissatisfied	12 (5.1)
Very dissatisfied	2 (0.8)
Would recommend medication abortion to friend	
Yes	161 (67.9)
No	14 (5.9)
Depends	53 (22.4)
Unsure	8 (3.4)
Missing	1 (0.4)
Would recommend pharmacy dispensing	
Yes	176 (74.3)
No	10 (4.2)
Depends	42 (17.7)
Unsure	9 (3.8)
Future model preference reported	
Prefer to have medication abortion available through primary care and pick up at pharmacy	147 (62.0)
Prefer to have medication abortion available only in select clinics where pill is given directly in clinic	13 (5.5)
Either way	68 (28.7)
Unsure	7 (3.0)
Missing	2 (0.8)

Table 3 shows measures of satisfaction collected from the 237 (91.2%) women who completed the day 14 survey. Overall, 84.4% (95% CI 79.1–88.8%) reported being very (65.4%) or somewhat (19.0%) satisfied with their medication abortion experience. The majority said they would recommend medication abortion (67.9%) and pharmacist dispensing (74.3%) to a friend in a similar situation. When asked how they would prefer to obtain medication abortion in the future, if needed, the majority (62.0%) said they would prefer to have medication abortion available through prescriptions from primary care clinics with medications dispensed in pharmacies. Only 5.5% said they would prefer to have the service only available in select clinics where the medications are dispensed directly to patients in clinic. About one quarter (28.7%) said either way was fine, and 3.0% were unsure.

Table 4 shows the results of multivariable mixed-effects logistic regression analyses exploring factors associated with patient satisfaction with the pharmacy and medication abortion experience. Those reporting

Table 4. Multivariable Adjusted Odds Ratios for Reporting Satisfaction With the Pharmacy Experience and Overall Abortion Experience Among Women Having Medication Abortion and Receiving Mifepristone at a Pharmacy

	Very Satisfied With Pharmacy Experience at Day 2 Survey (n=252)		Very Satisfied With Medication Abortion Experience Overall at Day 14 Survey (n=237)	
Participant Characteristics	aOR (95% CI)	%	aOR (95% CI)	%
Received adequate information from pharmacist				
No or No, but received the info from clinician	Ref	64.0	Ref	55.2
Received adequate info from the pharmacy	1.86 (0.82–4.26)	71.5	1.86 (0.99–3.51)	72.1
Wait time at pharmacy				
Reasonable wait time	Ref	81.0	Ref	68.5
Too long wait time	0.04* (0.01–0.13)	21.6	0.87 (0.37–2.09)	55.1
Satisfaction with treatment by pharmacy staff				
Dissatisfied or somewhat satisfied	Ref	21.6		
Very satisfied	16.79* (6.00–46.98)	80.6		
Satisfaction with the pharmacy experience				
Dissatisfied or somewhat satisfied			Ref	47.4
Very satisfied			2.96* (1.38–6.32)	73.9

aOR, adjusted odds ratio; Ref, referent group.
Mixed-effects logistic regression analyses controlled for age, race and ethnicity, education, relationship status, parity, gestational age at initial visit, and prior abortion experience and accounted for clustering by clinical site.
* $P<.05$.

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excessively long wait times had lower odds of satisfaction with pharmacy dispensing (adjusted odds ratio [aOR] 0.04, 95% CI 0.01–0.13), and those who reported being very satisfied with the treatment by pharmacy staff had higher odds of satisfaction with pharmacy dispensing (aOR 16.79, 95% CI 6.00–46.98). Those who reported that they were very satisfied with the pharmacy experience had higher odds of being very satisfied with their medication abortion overall compared with those who were somewhat satisfied or dissatisfied with the pharmacy experience (aOR 2.96, 95% CI 1.38–6.32).

DISCUSSION

In this study, medication abortion provision with pharmacist dispensing of mifepristone was effective and acceptable to patients. Among participants with follow-up data, 93% had a complete abortion, and none had an ongoing pregnancy. These outcome proportions are similar to those reported in the literature when the medications are dispensed by a clinician.[18,19] Few patients (1.5%) had adverse events, and none were related to pharmacist dispensing.

We also found that the vast majority of patients were satisfied with the model of care, and overall satisfaction was similar to other studies of medication abortion with clinician-dispensed mifepristone, which have found that 87–88% were satisfied with the method.[19,20] Satisfaction with the pharmacy and treatment by pharmacy staff, reported on the day 2 survey, were somewhat higher than overall satisfaction with medication abortion reported later. This is not surprising given that overall method satisfaction is correlated with symptoms and outcomes of the medication abortion,[21] which might not yet have been apparent by the day 2 survey. The vast majority reported they received adequate information–either from the clinician or pharmacist–and more than 90% indicated their support for pharmacist dispensing of mifepristone in the future.

Although satisfaction with this model was high, the open-ended responses point to areas for improvement that could be addressed through additional training of pharmacists and pharmacy staff. The finding that elements of the pharmacy experience, such as wait time and treatment by the pharmacy staff, were associated with satisfaction with the pharmacy experience, which in turn was associated with overall abortion satisfaction, is similar to research on other pharmacy services.[22]

It is a reassuring finding that one-third of participants who had had a prior medication abortion reported that the current experience of getting the medications at the pharmacy was better. The open-ended responses suggest that patients appreciated the convenience of being able to schedule when to take the medications. Since the FDA approved updated labeling for mifepristone in 2016, patients are no

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longer required to take the pill in the facility after it is dispensed,[10] although some state laws still require this. It is also notable that two participants did not proceed with the medication abortion after completing their clinic visit and filling the prescription. Other studies that allow patients to take the mifepristone at home after receiving it in the clinic or that mail the medications patients have also reported that a very small number of patients choose not to proceed with the abortion.[23,24]

One concern that has been raised with allowing clinicians to issue prescriptions for mifepristone is that some pharmacists may refuse to fill the prescription, limiting the feasibility of this model.[25] In our study, the participating pharmacies were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. As a result, all participants were able to fill their prescriptions when they went to the pharmacy. We also collected survey and interview data with the pharmacists at the study pharmacies to evaluate their perceptions of the model, which will be reported separately. Although we did not have challenges with individual pharmacists refusing to dispense mifepristone, we did have difficulty obtaining study approval at chain pharmacies. If the dispensing requirement for mifepristone is eliminated, some pharmacies may refuse to stock the medication, as has been reported for ulipristal acetate emergency contraception,[26] highlighting a potential role for mail-order pharmacies once the Risk Evaluation and Mitigation Strategy is removed.

This study has several strengths, including low loss to follow-up and standardized pharmacist training. It also has several limitations. We had to stop recruitment early because of the COVID-19 pandemic, reaching 89% of our planned minimum sample size. However, the effect of the reduced sample size on the precision of our estimates was small. The sample size is similar to the only other published report on providing medication abortion in the United States without in-clinic dispensing (n=190 with abortion outcome data).[24] In addition, our findings may have limited generalizability given that no chain pharmacy participated; patient experiences at chain pharmacies theoretically may be different. Finally, satisfaction with the pharmacy experience may increase over an extended time as pharmacy staff become more accustomed to dispensing mifepristone.

This study, together with another report of a direct-to-patient telemedicine service in which patients received the medications by mail,[24] demonstrate that medication abortion may be offered with a high level of effectiveness and satisfaction and low prevalence of adverse events without requiring mifepristone to be dispensed in the clinic or medical office. These data further support eliminating the dispensing requirement for mifepristone and allowing pharmacies to dispense the medication.

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Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *No.*

What data in particular will be shared? *No data beyond what is presented in the manuscript will be shared.*

What other documents will be available? *Study protocol and data collection forms will be available.*

When will data be available (start and end dates)? *Study documents will be available from the date of publication for a period of 5 years.*

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *Individuals interested in obtaining study documents should email the corresponding author.*

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LIFE AND FAMILY INITIATIVE

Frequently Asked Questions About the Largest Study on Chemical Abortion

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Ryan T. Anderson, President, Ethics and Public Policy Center

MAY 7, 2025

The report we released last week is the largest-known study of the abortion pill, based on analysis of data from an all-payer insurance claims database that includes 865,727 prescribed mifepristone abortions from 2017 to 2023. We found that 10.93 percent of women experience sepsis, infection, hemorrhaging, or another serious adverse event within 45 days following a mifepristone abortion. This means that the real-world rate of serious adverse events following mifepristone abortions is at least 22 times as high as the summary figure of "less than 0.5 percent" in clinical trials reported on the drug label.

Some have raised questions about our data and methodology. We address some of those below. And will be updating this document with additional questions and answers and clarifications as needed.

1. How did you confirm solely from ICD-10 codes that the hospitalization or ER visits were related to the abortion? Isn't it possible that a person who had a medical abortion could end up at the ER within 45 days for something completely unrelated, such as a car accident or broken bone?

The emergency room visits included in the report are only those related to the chemical abortion, based on the diagnosis and procedure codes in the insurance records, and are counted only if treatment for a serious complication related to the chemical abortion took place. Thus, if a woman took the chemical abortion pill and then got into a car accident or broke a bone, that did not count. Likewise, if a woman took the chemical abortion pill and had mild cramping related to the chemical abortion, that also did not count. Only an ER visit when the woman was treated for a serious adverse event related to the chemical abortion was counted.

This led us to exclude 72% of emergency room visits that took place within 45 days of abortion from our analysis because they were either not serious enough or were unrelated to the chemical abortion. That is, 98,483 ER visits that occurred within 45 days of the chemical abortion involved diagnoses not clearly related to the chemical abortion or not medically serious, such as COVID-19 exposure, nicotine dependence, asthma, and anxiety disorder.

Moreover, our findings are consistent with existing FDA information: in the serious adverse event section, the Mifeprex label reports abortion-related ER visits of up to 4.6%, and this study identified a nearly identical rate of 4.7%.

The reason we reported on ER visits is because the FDA does so on the drug label for mifepristone.

2. What if one woman experienced multiple serious adverse events? Aren't you inflating the percentage of women who experience a serious adverse event?

Our reported 10.93% rate of serious adverse events means that women experienced at least one serious adverse event in 10.93% of pregnancies for which a mifepristone abortion was prescribed. We ensured that each pregnancy was counted only once, even if a woman experienced multiple serious adverse events within the same category or across different categories. 10.93% is simply the ratio of the sum of women who experienced one or more serious adverse events associated with the prescribed mifepristone abortion of a given pregnancy to the total number of pregnancies for which a mifepristone abortion was prescribed. It is not, as some have erroneously suggested, a rate of how many serious adverse events women experienced, on average, per pregnancy aborted with mifepristone.

3. Why have you included ectopic pregnancy as an adverse event associated with medical abortion? The pill can't cause a pregnancy to move from the uterus, so why include that as a condition that resulted from taking the medication?

We do not claim or suggest that mifepristone causes ectopic pregnancies. The warning on the first page of the FDA-approved drug label requires that ectopic pregnancy be ruled out as a condition prior to using mifepristone, precisely because the use of mifepristone by a woman with an ectopic pregnancy poses extraordinary, heightened risk to her health. As noted on page 5 of our report, only events occurring within 45 days *following* the abortion are included. The study reports 3,062 cases of ectopic pregnancy. These are cases in which a woman was diagnosed with this condition only after she had already taken mifepristone. This failure to properly diagnose the ectopic pregnancy before the abortion attempt placed each of these women's life at risk.

This reinforces why, at minimum, the safety protocols requiring an in-person doctor visit should be restored to protect women's health. Without a doctor visit, how can the FDA expect women with ectopic pregnancies to follow the FDA requirement that ectopic pregnancies be ruled out prior to a chemical abortion and thereby avoid the extreme risk of a chemical abortion for them? This data clearly shows that in over 3,000 cases in our data alone, the FDA, the manufacturer, and the prescriber of mifepristone failed these women who had pre-existing ectopic pregnancies and did not know it.

4. Could you be including miscarriage care as if it were an abortion? After all, isn't it accurate that you included patients who were only prescribed mifepristone and not also given misoprostol? Since the protocol for medical abortion is to take both medications, is it possible that your data includes some patients who were given mifepristone for other conditions, including miscarriage?

No, we were very careful to exclude miscarriage care in our report by requiring any mifepristone only prescription was accompanied by a Z332 code (encounter for elective termination of pregnancy) or Z640 (problems related to unwanted pregnancy).

5. Didn't you simply label everything a serious adverse event? How did you define it and then code for it?

We based our analysis on the official FDA definition of a serious adverse event and then identified treatment and diagnosis codes that matched that definition. For an event to be counted in our serious adverse event rate, it had to meet three criteria:

1. It aligned with the FDA's definition of a serious adverse event—for example, it was life-threatening, required hospitalization, or led to surgical intervention.
2. It occurred within 45 days of the medication abortion.
3. It was reasonably related to the abortion, as previously described.

The events we included covered hospitalizations for hemorrhage, sepsis, blood transfusions, surgical procedures after failed abortions, and complications from confirmed ectopic pregnancies. We limited our analysis to severe (Grade 3) and life-threatening (Grade 4) events as defined by the NIH's Common Terminology Criteria for Adverse Events (CTCAE). We were not yet able to include Grade 5 events (deaths).

Critics imply that the FDA definition of serious adverse event is simply whatever the FDA chose to count on the drug label. However, the drug label does not contain a definition of "serious adverse event," only an incomplete yet overlapping list of categories (three diagnoses, one treatment, and two places of service) *with* reported data, followed by a list of post-marketing categories *without* reported data (which includes "ruptured ectopic pregnancy"). We cited and followed the official FDA definition of the term (linked above); to then say that we use "a broader definition of 'serious adverse event' than the FDA" is highly misleading.

6. Can you explain what "other abortion-specific complications" includes in the paper's serious adverse events by category section? It accounts for around half of the serious adverse event rate but I don't see any more specifics about those 49,169 "other abortion-specific complications."

Other abortion-specific complications include problems like damage to the woman's internal organs from the abortion, fetal tissue remaining inside the woman's uterus after the abortion, kidney failure, as well as life-threatening mental health diagnoses occurring after the abortion.

These are overwhelmingly DRG 770 (Abortion with D&C, Aspiration Curettage, or Hysterotomy) and DRG 769 (Postpartum and Post Abortion Diagnoses with Operating Room Procedure) codes that were determined to be severe or life-threatening following CTCAE version 5. Furthermore, we limited mental health codes to only those that met the criteria for life-threatening in order to not overestimate that category. There were just a few diagnosis codes (representing a small share of the cases) that met our inclusion criteria, namely R45850 (Homicidal ideations) and R45851 (Suicidal ideations). Many women who were counted in the other categories in Figure 1 of our report also experienced an event that fell within this category.

7. Why wasn't this paper peer-reviewed?

The point is not peer review, but replicability. We have made our study fully replicable for anyone who wants to analyze the insurance claims data. The replicability crisis, well-documented in the press and denied by no responsible person, is the evidence that peer review guarantees little.

We stand behind our analysis of healthcare claims data which is why we are asking the FDA to conduct its own review of this data. Real world data in which money changed hands based on the treatment of patients and coding by doctors brings a higher level of confidence. The dataset is available for purchase and our methodology is public. This study is fully replicable, and we encourage others to replicate it.

The peer-review process is broken. It is terribly biased against conservatives, especially social conservatives, particularly pro-lifers. The paper would have been leaked, so as to prepare hostile responses, if it were ever published to begin with. Given the extensive pro-abortion bias in the peer-review process, there are, effectively, no opportunities to publish peer-reviewed analysis that offer major substantive critiques of the abortion pill or abortion.

8. Why should we trust insurance claims data?

Insurance claims data is a cornerstone of public health and safety monitoring. The FDA, CDC, NIH, CMS, and countless peer-reviewed journals rely on it precisely because it reflects real-world outcomes across massive populations. For example:

- The **FDA Sentinel Initiative** uses claims and electronic health record data to monitor post-market safety of medical products.
- The **CDC's Vaccine Safety Datalink (VSD)** uses claims data from millions of individuals to monitor vaccine safety.
- The **Centers for Medicare & Medicaid Services (CMS)** conduct quality assessments and cost analyses through large-scale claims-based research.

Peer-reviewed journals such as *JAMA*, *The New England Journal of Medicine*, and *Health Affairs* regularly publish studies based on administrative claims.

It is especially vital for medications like mifepristone, where:

- Controlled trials have small samples, carefully recruited healthy patients, physician oversight, and limited follow-up.
- Post-marketing surveillance (e.g., FAERS) is passive and incomplete.
- Reporting requirements were loosened in 2016, obscuring complications.

Our analysis examines hundreds of thousands of real-world chemical abortion events—across settings, payors, and demographics—and identifies follow-up care patterns at scale. This is real-world data, in real-world clinical settings, in which real money changed hands from public and private payors as a result of real serious harm faced by real women. These women, and hundreds of thousands like them, were seriously harmed, not carefully protected in idealized clinical studies.

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The Abortion Pill Harms Women: Insurance Data Reveals One in Ten Patients Experiences a Serious Adverse Event

Jamie Bryan Hall, Director of Data Analysis, Ethics and Public Policy Center
Ryan T. Anderson, President, Ethics and Public Policy Center

April 28, 2025

Summary

- This largest-known study of the abortion pill is based on analysis of data from an all-payer insurance claims database that includes 865,727 prescribed mifepristone abortions from 2017 to 2023.
- 10.93 percent of women experience sepsis, infection, hemorrhaging, or another serious adverse event within 45 days following a mifepristone abortion.
- The real-world rate of serious adverse events following mifepristone abortions is at least 22 times as high as the summary figure of "less than 0.5 percent" in clinical trials reported on the drug label.
- The FDA should immediately reinstate its earlier, stronger patient safety protocols to ensure physician responsibility for women who take mifepristone under their care, as well as mandate full reporting of its side effects.
- The FDA should further investigate the harm mifepristone causes to women and, based on objective safety criteria, reconsider its approval altogether.

Danco Laboratories markets Mifeprex as "the safe and effective abortion pill," but our research shows that mifepristone abortion, as currently practiced in the U.S., is not safe and effective.[1] The manufacturer and the FDA rely on the results of 10 clinical trials with a total of 30,966 participants, less than 0.5 percent of whom reportedly experienced serious adverse reactions. In contrast, we analyzed real-world insurance claims data for 865,727 prescribed mifepristone abortions, broadly representative of women who obtain mifepristone abortions in the U.S. today, and we find a serious adverse event rate of 10.93 percent—at least 22 times as high as the summary figure reported on the drug label. In light of this research, we urge the FDA to reinstate earlier, stronger patient safety protocols and reconsider its approval of mifepristone altogether. Women deserve better than the abortion pill.

Our Key Findings

10.93 percent of women experience sepsis, infection, hemorrhaging, or another serious or life-threatening adverse event within 45 days following a mifepristone abortion, far greater than the summary figure of "less than 0.5 percent" in clinical trials reported on the drug label. *Figure 1, next page.*

[1] Danco Laboratories, "The Safe and Effective Abortion Pill | Mifeprix (mifepristone)," https://www.earlyoptionpill.com (accessed April 14, 2025)

Figure 1

Serious Adverse Events by Category

	Number with adverse events	Serious adverse event rate
Sepsis	824	0.10%
Infection	11,707	1.34%
Transfusion	1,257	0.15%
Hemorrhage	28,658	3.31%
Hospitalization (related to the abortion)	5,699	0.66%
ER visit (related to the abortion)	40,960	4.73%
Ectopic pregnancy	3,062	0.35%
Other life-threatening adverse events (cardiac, pulmonary, thrombosis, anaphylaxis, surgery)	1,956	0.22%
Repeated (surgical) abortion	24,563	2.84%
Other abortion-specific complications	49,169	5.68%
Overall	94,605	10.93%

Note: The overall serious adverse event rate of 10.93% is adjusted for the fact that some women suffer from adverse events in multiple categories.

Simply stated, mifepristone, as used in real-world conditions, is not "safe and effective."

Our real-world post-market observational study of mifepristone is, to our knowledge, the most comprehensive study of chemical abortion safety ever conducted in the U.S.:

- We identify and include 865,727 prescribed mifepristone abortions, 28 times as many as were included in all FDA-cited clinical trials combined.
- Our dataset is more recent, no earlier than 2017, while the FDA approval of mifepristone relies entirely on data from more than a decade ago.
- The women in our dataset are broadly representative of the women who obtain mifepristone abortions in the U.S.; they are not a prescreened group of generally healthy women recruited into various clinical trials conducted at different times around the world.
- The women in our dataset receive (or fail to receive) pre- and post-abortion healthcare of the real-world quality that prevails in the U.S. today, not the carefully controlled regimen of care that ordinarily prevails in a clinical trial.

Policy Implications

The FDA should reinstate the original patient safety protocols that were required when mifepristone was first approved. Doing so will likely reduce the harms to women and permit better monitoring to determine whether this drug should remain on the market:

- Prescribing mifepristone and misoprostol for the termination of pregnancy should require at least three in-person office visits by the patient—as originally required by the FDA.
- Mifepristone should be prescribed only by physicians—as originally required by the FDA—who have read and understood the prescribing information.
- Mifepristone should be administered only in a clinic, medical office, or hospital, by or under the supervision of a physician, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies—all of which was originally required by the FDA.
- Physicians must be able to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Healthcare providers should be required once again to report to the FDA (and manufacturers of mifepristone) all serious adverse events resulting from the use of mifepristone.
- Mifepristone should only be prescribed to a woman who is confirmed by a physician to be in the first seven weeks of pregnancy—as originally required by the FDA.

Background on FDA Approval and Regulation of Mifepristone

Mifepristone was developed by the French pharmaceutical company Roussel Uclaf S.A. and brought to the United States at the urging of President Clinton and after Congressional pressure. The FDA approved it under a little-used approval process for "certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments."[2] Thus, to grant approval in this manner, the FDA had to consider an unwanted pregnancy a "serious or life-threatening illness" and find that mifepristone was more effective than surgical abortion in treating it. The FDA's decision cites minimal data: clinical trials with only 859 participants in the U.S. and 1,800 in France.[3]

The original FDA-approved drug label for Mifeprex (the brand name of mifepristone) from September 2000 indicated use of the drug for "the medical termination of intrauterine pregnancy through 49 days' pregnancy."[4] It required several modest safeguards for women's health:

> Treatment with Mifeprex and misoprostol for the termination of pregnancy requires three office visits by the patient. Mifeprex should be prescribed only by physicians who have read and understood the prescribing information. Mifeprex may be administered only in a clinic, medical office, or hospital, by or under the supervision of a physician, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies. Physicians must also be able to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.[5]

During the Obama and Biden administrations, the FDA chipped away at these initial safeguards, risking women's health in order to increase access to abortion. Under the current Risk Evaluation and Mitigation Strategy (REMS) in effect since 2023:

1. a mifepristone abortion now requires as a little as one telehealth visit with any approved healthcare provider (not necessarily a physician),
2. a woman may self-administer drugs obtained from a mail-order pharmacy, and
3. the prescriber need not report any adverse events unless he or she knows that a patient has died. *Figure 2.*

Figure 2

Weakening FDA Safeguards for Mifepristone

	2000 Clinton Initial Approval	2016 Obama REMS Changes	2023 Biden REMS Changes
Required number of in-person visits	3	1	0
Maximum gestational age (LMP)	7 weeks	10 weeks	10 weeks
Drugs prescribed only by physician	✓	✗	✗
Drugs dispensed only in office	✓	✓	✗
Drugs taken only in office	✓	✗	✗
Required in-office follow-up	✓	✗	✗
Required reporting of adverse events	✓	✗	✗

2 Alliance for Hippocratic Medicine v. FDA, Complaint, https://adflegal.org/wp-content/uploads/2022/11/Alliance-for-Hippocratic-Medicine-v-FDA-2022-11-18-Complaint.pdf
3 Mifeprex (mifepristone) drug label, September 2000, page 3, https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.pdf
4 Mifeprex (mifepristone) drug label, September 2000, page 6, https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.pdf
5 Mifeprex (mifepristone) drug label, September 2000, page 14, https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.pdf

The current FDA-approved drug label refers to the results of 10 clinical trials with a total of 30,966 participants, less than 0.5 percent of whom reportedly experienced serious adverse reactions.[6] But these figures are based entirely on data from trials taking place more than a decade ago.

The Increasing Market Share of Chemical Abortion

Increased access to chemical abortion has coincided with a rapid increase in its prevalence. Chemical abortions—the vast majority of which are performed using a combination of mifepristone and misoprostol—now account for roughly two-thirds of all abortions in the United States. *Figure 3.*

In fact, Danco Laboratories boasts that more than 5 million U.S. women have used its abortion pill since it was approved in 2000.[7] Thus, it has become increasingly important to understand the risks and harms to women from chemical abortion in general and from mifepristone in particular.

How We Identified Mifepristone Abortions

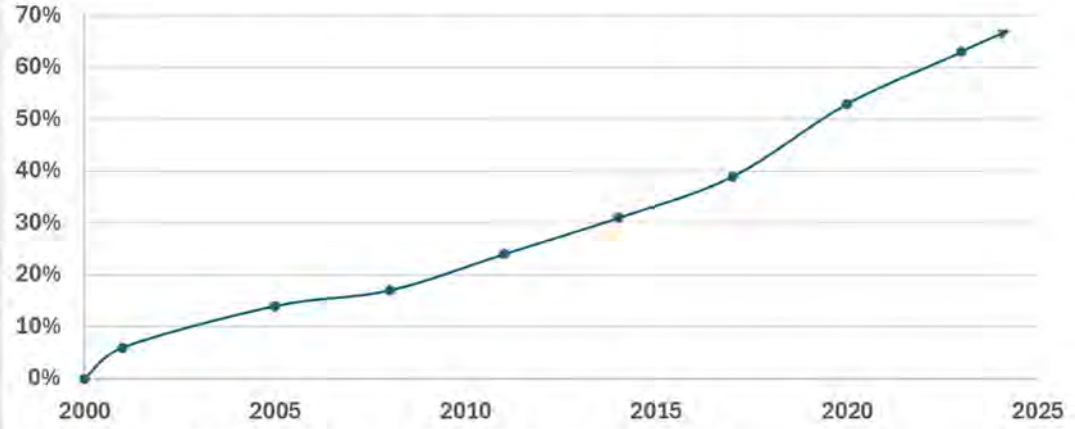
In our data, a mifepristone abortion was identified in one of three ways:

1. procedure code S0199: medically induced abortion by oral ingestion of medication including all associated services and supplies,
2. a prescription for mifepristone (with or without misoprostol within the next 3 days), or
3. a diagnosis code for elective termination or unwanted pregnancy, along with other billing coding consistent with manufacturer instructions for reimbursement for a mifepristone abortion for a given state and insurer combination.[8]

Following this method, we identified a total of 865,727 mifepristone abortions prescribed for a total of 692,873 women from 2017 to 2023. This includes 566,446 women, each of whom had one such abortion, and 126,427 women with multiple such abortions.

Figure 3

Chemical abortion has increased rapidly since approval in 2000 and now accounts for approximately two-thirds of all abortions.



Source: Guttmacher Abortion Provider Census and Monthly Abortion Provision Study, via https://www.guttmacher.org/2024/03/medication-abortion-accounted-63-all-us-abortions-2023-increase-53-2020

6 Page 7 of the drug label states, "Serious adverse reactions were reported in <0.5% of women. Information from the U.S. and non-U.S. studies is presented in Table 2." Table 2 on page 8 indicates that some categories of serious adverse reactions were observed at higher rates in some trials, but this is never discussed in the text, leaving only the previous statement with which to interpret the table. See Mifeprex (mifepristone) drug label, January 2023, https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s026lbl.pdf

7 Danco Laboratories, "The Safe and Effective Abortion Pill | Mifeprex (mifepristone)," https://www.earlyoptionpill.com (accessed April 14, 2025)

8 Danco Laboratories, "Mifeprex State Payer Policies," https://www.earlyoptionpill.com/how-do-i-get-mifeprex/state-payer-policies (accessed April 14, 2025)

How We Identified Serious Adverse Events

We followed the official FDA definition of "serious adverse event."[9] To do so, we identified relevant ICD-10 diagnosis codes and CPT/HCPCS procedure codes for adverse events from multiple sources:

- CDC Severe Maternal Morbidity (SMM) indicators,[10]
- CMS Diagnosis-Related Group (DRG) 770 and 769 codes,[11]
- FDA Adverse Events Reporting System (FAERS) reports (interpreted and translated into diagnosis and procedure codes by the doctors on our team),[12] and
- a small number of (mostly gynecological) codes suggested by our doctors.

These codes were then graded by a team of physicians using the the NIH Common Terminology Criteria for Adverse Events (CTCAE version 5), which categorizes adverse events by severity on a 5-point scale.[13] We included CTCAE Grade 3 (severe) and Grade 4 (life-threatening). We did not include Grade 1 (mild) or Grade 2 (moderate). (Grade 5 is death, which would count as a serious adverse event under the FDA definition but could not necessarily be observed in the insurance claims data. We hope to show the rate of death in a subsequent report.)

For reporting, we have grouped the relevant diagnosis and procedure codes as follows:

1. The mifepristone label divides serious adverse events into six categories identified in the clinical trials: sepsis, infection, transfusion, hemorrhage, hospitalization, and emergency room visit. Only those hospitalizations and emergency room visits with abortion-related diagnosis and procedure codes are included in our analysis.
2. FAERS received reports of various events that our doctors judge to be life-threatening and have grouped into broad categories: ectopic pregnancy, surgery, cardiac, pulmonary, thrombosis, and anaphylaxis.
3. Repeated (surgical) abortion procedures are considered serious adverse events.
4. Other abortion complications include codes specifically related to an abortion or miscarriage, as well as life-threatening mental health diagnoses, etc.

We consider only serious adverse events that occurred within 45 days following the abortion. This is conservative, as some adverse events may present later (and studies relied on by the FDA used a timeframe as long as 72 days). Additionally, the likelihood of a subsequent pregnancy within this timeframe is negligible, which ensures that adverse events are related to the abortion rather than to a subsequent pregnancy.

Our Data

Our team has purchased access to a commercially available all-payer health insurance claims database including de-identified data for all U.S. patients during the years 2017 to 2023. It includes information on hospital and office visits, diagnoses, procedures, and prescriptions processed through private health insurance, Medicaid, Medicare, TRICARE, and the Department of Veterans Affairs (VA). The data excludes transactions for which the insurer is also the provider (as is the case with some HMOs and much VA care), as well as cash pay transactions (which are disproportionately common for abortion). This dataset provides longitudinal tracking of medical diagnoses, procedures, and prescriptions for each patient and is widely used in academic and regulatory research.

9 FDA, "What is a Serious Adverse Event?," https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event
10 CDC, "Identifying Severe Maternal Morbidity (SMM)," https://www.cdc.gov/maternal-infant-health/php/severe-maternal-morbidity/icd.html
11 CMS, "ICD-10-CM/PCS MS-DRG v37.0 Definitions Manual," https://www.cms.gov/icd10m/version37-fullcode-cms/fullcode_cms/P0287.html
12 FDA, "FDA Adverse Events Reporting System (FAERS) Public Dashboard," https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f-7f1c25ee/sheet/33a0f68e-845c-48e2-bc81-8141c6aaf772/state/analysis
13 NIH, "Common Terminology Criteria for Adverse Events (CTCAE)," https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Our Research Project Team

Our research project was conducted and validated by a team of data scientists, analysts, and engineers, with assistance from our clinical team of board-certified obstetricians and gynecologists. Members have a history of academic research and peer-reviewed publication.

Conclusion

Our research shows unequivocally that mifepristone abortion, as currently practiced in the U.S., is considerably more dangerous to women than is represented on the FDA-approved drug label. The FDA should immediately reinstate its earlier, stronger patient safety protocols to ensure physician responsibility for women who take mifepristone under their care, as well as mandate full reporting of its side effects. The FDA should further investigate the harm this drug causes to women and, based on objective safety criteria, reconsider its approval altogether. Women deserve better than the abortion pill.

This paper is the first in a series investigating women's health and abortion using real-world data.

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The Abortion Pill Harms Women: Insurance Data Reveals Repeated Abortion Attempts Due to High Failure Rate

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Ryan T. Anderson, President, Ethics and Public Policy Center

MAY 12, 2025

Summary

- The real-world failure rate of mifepristone abortion—at least 5.26 percent, or about one in 19 cases—is double the failure rate from the U.S. clinical trials and roughly two-thirds higher than the combined failure rate from all clinical trials reported on the FDA-approved drug label.
- Combined with our prior finding that 10.93 percent of women experience a serious adverse event and adjusting to avoid double-counting, we find that 13.51 percent of women—roughly one in seven—experience at least one serious adverse event or repeated abortion attempt within 45 days of first attempting a mifepristone abortion.
- This largest-known study of the abortion pill is based on analysis of data from an all-payer insurance claims database that includes 865,727 prescribed mifepristone abortions from 2017 to 2023.
- The FDA should immediately reinstate its earlier, stronger patient safety protocols to ensure physician responsibility for women who take mifepristone under their care, as well as mandate full reporting of its side effects.
- The FDA should further investigate the harm this drug causes to women and, based on objective safety and effectiveness criteria, reconsider its approval altogether.

Danco Laboratories markets Mifeprex as "the safe and effective abortion pill," but our research shows that mifepristone abortion, as currently practiced in the U.S., is not safe or effective.[1] The manufacturer and the FDA rely on the results of clinical trials in which less than 0.5 percent of participants reportedly experienced serious adverse reactions and all but 2.6-3.8 percent obtained a complete abortion by taking mifepristone plus misoprostol.[2] In contrast, we analyzed real-world insurance claims data for 865,727 prescribed mifepristone abortions, broadly representative of women who obtain mifepristone abortions in the U.S. today, and we find a serious adverse event rate of 10.93 percent and a failure rate of at least 5.26 percent. In light of this research, we urge the FDA to reinstate earlier, stronger patient safety protocols and reconsider its approval of mifepristone altogether. Women deserve better than the abortion pill.

1 Danco Laboratories, "The Safe and Effective Abortion Pill | Mifeprex (mifepristone)," https://www.earlyoptionpill.com (accessed April 14, 2025)
2 Page 7 of the drug label states, "Serious adverse reactions were reported in <0.5% of women." Effectiveness data are reported in Table 3 on page 13. See Mifeprex (mifepristone) drug label, January 2023, https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s026lbl.pdf

Repeated Abortion Attempts Following Failure of Mifepristone Abortion Regimen

According to the insurance data, 5.26 percent of women undergo a second abortion attempt within 45 days of the first, indicating that the first mifepristone abortion attempt failed.[3] Curiously, although the drug label does not appear to contemplate the possibility of a second abortion attempt using mifepristone for the same pregnancy, we regularly observe this in the insurance claims database. *See Table 1.*

The real-world failure rate of mifepristone abortion—at least 5.26 percent,[4] or about one in 19 cases—is double the failure rate of 2.6 percent from the U.S. clinical trials and roughly two-thirds higher than the combined failure rate of 3.2 percent from all clinical trials reported on the FDA-approved drug label.[5]

Safety and Effectiveness

As we previously reported, 10.93 percent of women—roughly one in ten—experience sepsis, infection, hemorrhaging, or another serious adverse event within 45 days following a mifepristone abortion.[6] Combined with the 5.26 percent of women who undergo a second abortion attempt following the failure of the mifepristone abortion regimen and adjusting to avoid double-counting, we find that 13.51 percent of women—roughly one in seven—experience at least one serious adverse event or repeated abortion attempt within 45 days of first attempting a mifepristone abortion. *See Table 2.*

Table 1

Repeated Abortion Attempts After Failed Mifepristone Abortion Attempts

Type	Number of pregnancies with repeated abortion attempts	Rate of occurrence
Repeated mifepristone abortion attempt after failed mifepristone abortion attempt	27,896	3.22%
Surgical abortion procedure after failed mifepristone abortion attempt	24,563	2.84%
Both	6,961	0.80%
Either	45,498	5.26%

Note: The insurance claims database includes 865,727 pregnancies with prescribed mifepristone abortion. These rates of occurrence are per pregnancy. The repeated abortion attempts in this table are subsequent attempts to abort the baby after the first attempt failed. Some patients had multiple pregnancies with abortion attempts in the database; this is *not* what is being measured in this table.

3 We also observe that 1.58 percent of women are prescribed a second dose of misoprostol but not a second dose of mifepristone, a possibility suggested on the drug label for cases in which the woman is no longer pregnant but fetal remains have not been fully expelled from her body. These are not counted as repeated abortion attempts, but repeated use of misoprostol has side effects that pose further harm to women.

4 We do not consider here those cases in which a woman gave birth following a mifepristone abortion attempt, which in a technical sense also indicate that the regimen failed to perform as intended. If these cases were also included, the failure rate would be slightly higher.

5 Table 3 on page 13 of the drug label reports surgical intervention in 2.6 percent of 16,794 cases in U.S. trials and 3.8 percent of 18,425 cases in non-U.S. trials. This averages to 3.2 percent of 35,219 cases overall. See Mifeprex (mifepristone) drug label, January 2023, https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s026lbl.pdf.

6 Jamie Bryan Hall and Ryan T. Anderson, "The Abortion Pill Harms Women: Insurance Data Reveals One in Ten Patients Experiences a Serious Adverse Event," Ethics and Public Policy Center, April 28, 2025.

Table 2

Safety and Effectiveness of Mifepristone Abortion

Type of event	Number of pregnancies	Rate of occurrence
Serious adverse event following mifepristone abortion attempt	94,605	10.93%
Repeated abortion attempt following failed mifepristone abortion attempt	45,498	5.26%
Both	23,165	2.68%
Either	116,938	13.51%

Note: The insurance claims database includes 865,727 pregnancies with prescribed mifepristone abortion. These rates of occurrence are per pregnancy.

Conclusion

Mifepristone abortion as currently practiced in the U.S. is not safe or effective. As our previous paper showed, the real-world rate of serious adverse events following mifepristone abortions is at least 22 times as high as reported on the drug label. Now we also find that its failure rate is significantly higher than reported on the drug label. Altogether, roughly one in seven women who are prescribed a mifepristone abortion experiences a severe adverse event or undergoes a repeated abortion attempt soon afterwards due to the failure of the mifepristone abortion regimen.

In light of these findings, the FDA should immediately reinstate its earlier, stronger patient safety protocols to ensure physician responsibility for women who take mifepristone under their care, as well as mandate full reporting of its side effects. The FDA should further investigate the harm this drug causes to women and, based on objective safety and effectiveness criteria, reconsider its approval altogether. Women deserve to know the truth. Women deserve better than the abortion pill.

This paper is the second in a series investigating women's health and abortion using real-world data. It is based on the same data and follows the same methodology as described in "The Abortion Pill Harms Women: Insurance Data Reveals One in Ten Women Experiences a Serious Adverse Event" and its accompanying documentation.

You can read the first paper and accompanying documentation at eppc.org/stop-harming-women.

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FEBRUARY 2025

Maternal Mortality Rates in the United States, 2023

by Donna L. Hoyert, Ph.D.

This report presents maternal mortality rates for 2023 based on data from the National Vital Statistics System. A maternal death is defined by the World Health Organization as "the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes" (1). Maternal mortality rates—the number of maternal deaths per 100,000 live births—are shown in this report by age group and race and Hispanic origin.

This report updates a previous one that showed maternal mortality rates for 2018–2022 (2). In 2023, 669 women died of maternal causes in the United States, compared with 817 in 2022 (2) (Figure 1, Table). The maternal mortality rate for 2023 decreased to 18.6 deaths per 100,000 live births, compared with a rate of 22.3 in 2022.

In 2023, maternal mortality rates decreased significantly for White non-Hispanic (subsequently, White) and Hispanic women (Figure 2, Table). The observed decrease for Asian non-Hispanic (subsequently, Asian) and increase for Black non-Hispanic (subsequently, Black) women was not statistically significant. In 2023, the maternal mortality rate for Black women was 50.3 deaths per 100,000 live births and was significantly higher than rates for White (14.5), Hispanic (12.4), and Asian (10.7) women.

Rates decreased significantly for women ages 25–39 and age 40 and older between 2022 and 2023 (Figure 3, Table). Rates in 2023 were 12.5 deaths per 100,000 live births for women younger than age 25, 18.1 for those ages 25–39, and 59.8 for those age 40 and older. The rate for women age 40 and older was nearly five times higher than the rate for women younger than age 25. Differences in the rates between age groups were statistically significant.

Data sources and methods

Data are from the National Vital Statistics System mortality file (3). Consistent with previous reports, the number of maternal deaths does not include all deaths during pregnancy or among recently pregnant women but only those deaths with the underlying cause of death assigned to *International Statistical Classification of Diseases, 10th Revision* codes A34, O00–O95, and O98–O99. Maternal mortality rates are per 100,000 live births, based on data from the

National Vital Statistics System natality file. Maternal mortality rates fluctuate from year to year because of the relatively small number of these events, and possibly because of issues with the accuracy of reporting maternal deaths on death certificates (4). Efforts to improve data quality are ongoing, and these data will continue to be evaluated for possible errors. Data are shown for only the four largest race and Hispanic-origin groups for which statistically reliable rates can be calculated, and numbers and rates are suppressed for those groups for which statistically reliable rates cannot be calculated (5). Additional details and data on provisional maternal mortality rates are available (6,7).

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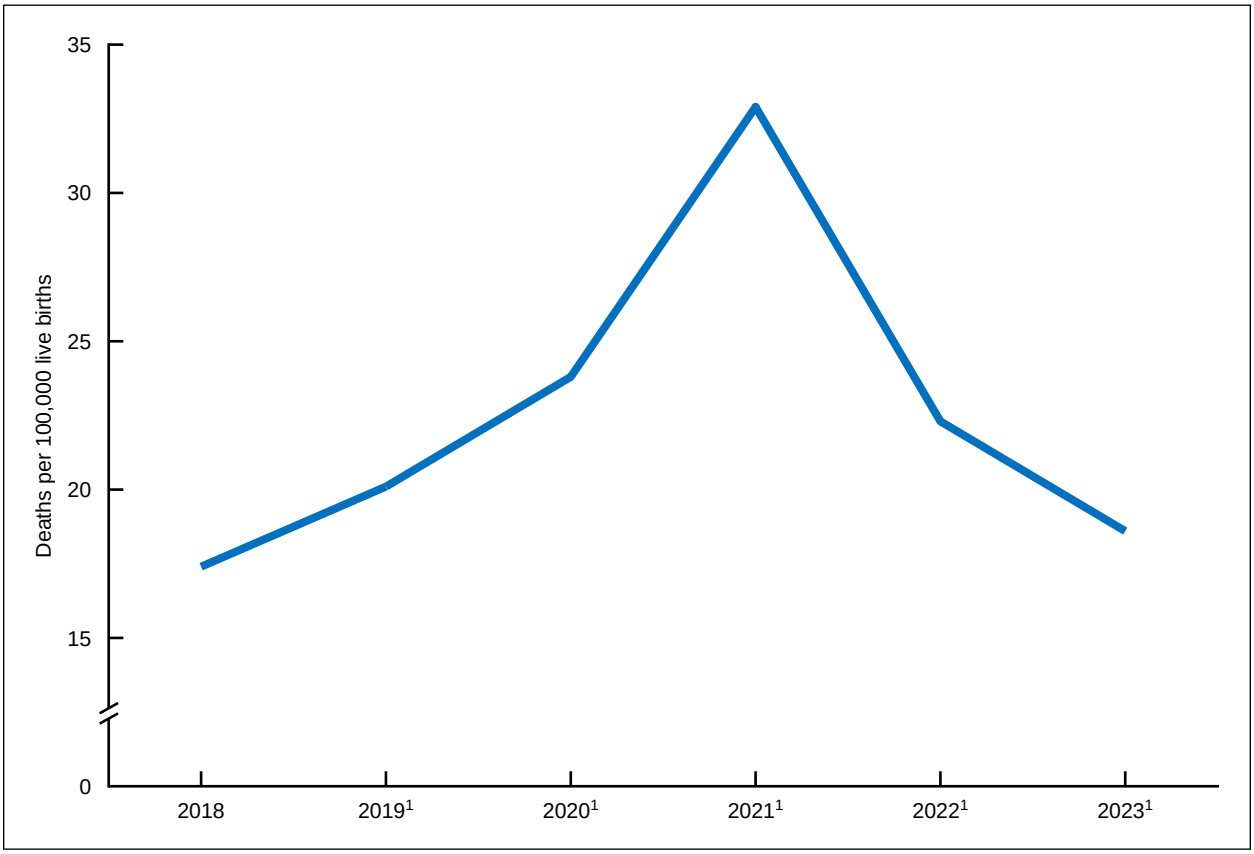
Suggested citation

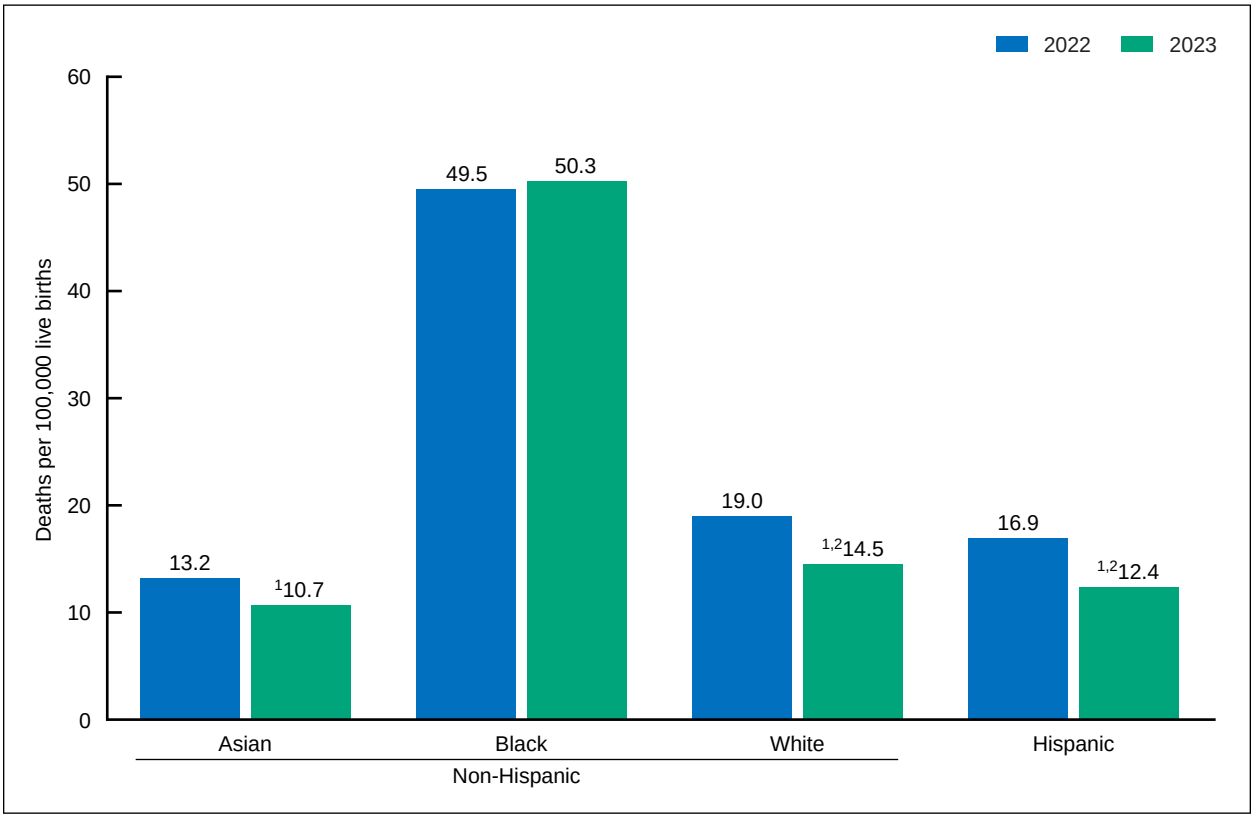
Hoyert DL. Maternal mortality rates in the United States, 2023. NCHS Health E-Stats. 2025. DOI: https://dx.doi.org/10.15620/cdc/174577.

Figure 1. Maternal mortality rate: United States, 2018–2023



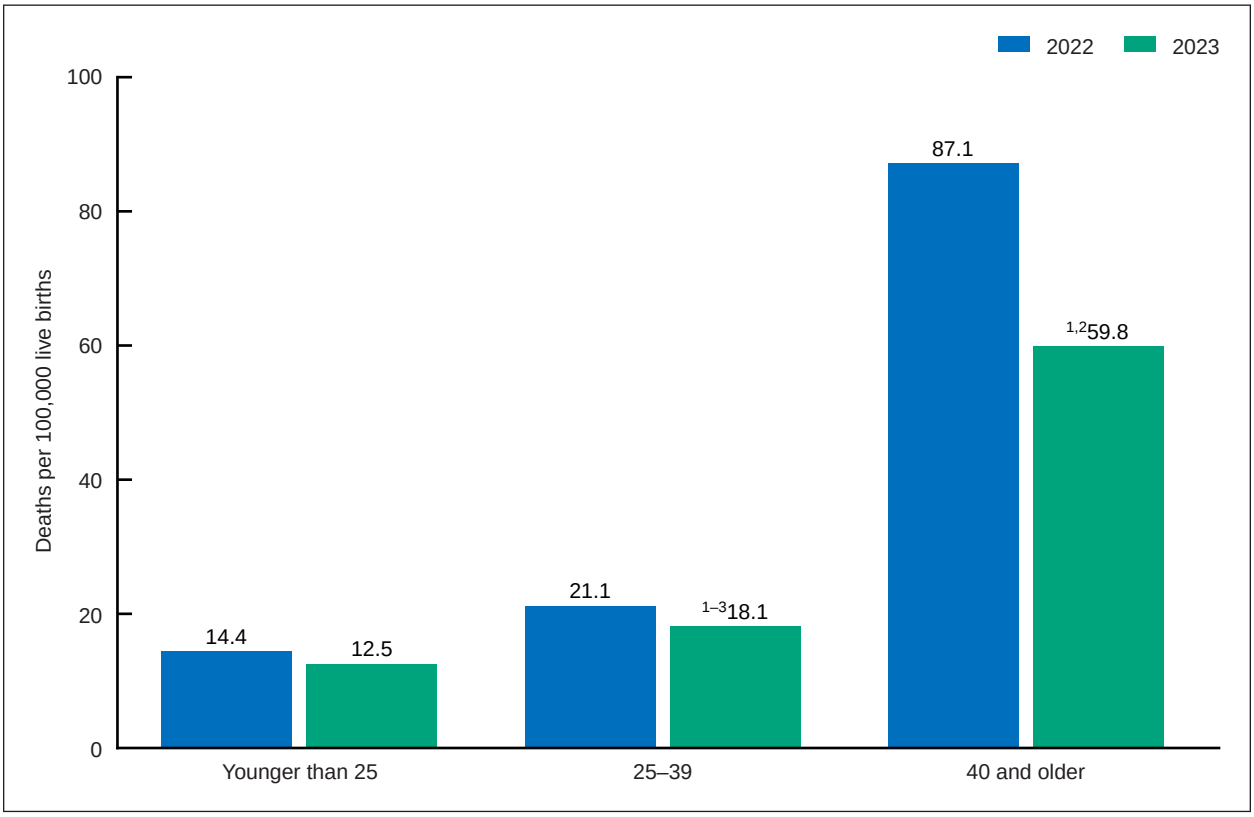
[1]Statistically significant change in rate from previous year ($p < 0.05$).
SOURCE: National Center for Health Statistics, National Vital Statistics System, mortality data file.

Figure 2. Maternal mortality rate, by race and Hispanic origin: United States, 2022 and 2023



[1]Statistically significant difference from Black non-Hispanic women ($p < 0.05$).
[2]Statistically significant decrease in rate from previous year ($p < 0.05$).
NOTES: Race groups are single race. People of Hispanic origin may be of any race.
SOURCE: National Center for Health Statistics, National Vital Statistics System, mortality data file.

Figure 3. Maternal mortality rate, by age: United States, 2022 and 2023



[1]Statistically significant decrease in rate from previous year ($p < 0.05$).
[2]Statistically significant difference from younger than 25 ($p < 0.05$).
[3]Statistically significant difference from 40 and older ($p < 0.05$).
SOURCE: National Center for Health Statistics, National Vital Statistics System, mortality data file.

Table. Number of live births and maternal deaths, and maternal mortality rate, by race and Hispanic origin and age: United States, 2018–2023

Race and Hispanic origin and age	2018	2019	2020	2021	2022	2023
			Number of live births			
Total[1]	3,791,712	3,747,540	3,613,647	3,664,292	3,667,758	3,596,017
Younger than 25	907,782	877,803	825,403	797,334	784,299	759,713
25–39	2,756,974	2,739,976	2,658,445	2,731,223	2,738,802	2,689,250
40 and older	126,956	129,761	129,799	135,735	144,657	147,054
Asian, non-Hispanic[2]	240,798	238,769	219,068	213,813	218,994	215,738
Younger than 25	16,338	15,071	12,993	11,149	11,002	10,352
25–39	211,331	210,177	193,139	189,405	193,025	190,128
40 and older	13,129	13,521	12,936	13,259	14,967	15,258
Black, non-Hispanic[2]	552,029	548,075	529,811	517,889	511,439	491,494
Younger than 25	176,243	169,853	159,541	149,435	140,498	131,977
25–39	358,276	360,206	351,648	349,170	349,740	337,697
40 and older	17,510	18,016	18,622	19,284	21,201	21,820
White, non-Hispanic[2]	1,956,413	1,915,912	1,843,432	1,887,656	1,840,739	1,787,051
Younger than 25	391,829	374,129	348,666	336,792	324,604	309,033
25–39	1,504,888	1,480,595	1,433,839	1,486,249	1,449,365	1,410,849
40 and older	59,696	61,188	60,927	64,615	66,770	67,169
Hispanic	886,210	886,467	866,713	885,916	937,421	945,200
Younger than 25	275,553	270,948	258,635	255,806	264,310	266,416
25–39	579,553	584,109	576,690	597,703	637,735	642,429
40 and older	31,104	31,410	31,388	32,407	35,376	36,355
			Number of maternal deaths			
Total[1]	658	754	861	1,205	817	669
Younger than 25	96	111	114	163	113	95
25–39	458	544	607	854	578	486
40 and older	104	98	140	188	126	88
Asian, non-Hispanic[2]	32	33	27	36	29	23
Younger than 25	*	*	*	*	*	*
25–39	25	28	20	24	21	17
40 and older	*	*	*	*	*	*
Black, non-Hispanic[2]	206	241	293	362	253	247
Younger than 25	27	32	46	62	44	37
25–39	137	179	198	242	172	181
40 and older	42	30	49	58	37	29
White, non-Hispanic[2]	291	343	352	503	350	259
Younger than 25	41	49	40	57	35	26
25–39	207	248	253	364	259	195
40 and older	43	46	59	82	56	38
Hispanic	105	112	158	248	158	117
Younger than 25	21	23	20	36	25	27
25–39	72	71	111	184	108	77
40 and older	12	18	27	28	25	13

See footnotes at end of table

Table. Number of live births, maternal deaths, and maternal mortality rates, by race and Hispanic origin and age: United States, 2018–2023—Con.

Race and Hispanic origin and age	2018	2019	2020	2021	2022	2023
			Maternal mortality rate[3]			
Total[1]	17.4	20.1	23.8	32.9	22.3	18.6
Younger than 25	10.6	12.6	13.8	20.4	14.4	12.5
25–39	16.6	19.9	22.8	31.3	21.1	18.1
40 and older	81.9	75.5	107.9	138.5	87.1	59.8
Asian, non-Hispanic[2]	13.3	13.8	12.3	16.8	13.2	10.7
Younger than 25	*	*	*	*	*	*
25–39	11.8	13.3	10.4	12.7	10.9	8.9
40 and older	*	*	*	*	*	*
Black, non-Hispanic[2]	37.3	44.0	55.3	69.9	49.5	50.3
Younger than 25	15.3	18.8	28.8	41.5	31.3	28.0
25–39	38.2	49.7	56.3	69.3	49.2	53.6
40 and older	239.9	166.5	263.1	300.8	174.5	132.9
White, non-Hispanic[2]	14.9	17.9	19.1	26.6	19.0	14.5
Younger than 25	10.5	13.1	11.5	16.9	10.8	8.4
25–39	13.8	16.8	17.6	24.5	17.9	13.8
40 and older	72.0	75.2	96.8	126.9	83.9	56.6
Hispanic	11.8	12.6	18.2	28.0	16.9	12.4
Younger than 25	7.6	8.5	7.7	14.1	9.5	10.1
25–39	12.4	12.2	19.2	30.8	16.9	12.0
40 and older	38.6	57.3	86.0	86.4	70.7	35.8

* Estimate does not meet National Center for Health Statistics standards of reliability.
[1]Total includes deaths for race and Hispanic-origin groups not shown separately, including women of multiple races and Hispanic origin not stated.
[2]Race groups are single race.
[3]Maternal mortality rates are deaths per 100,000 live births.

NOTES: Maternal causes are those assigned to codes A34, O00–O95, and O98–O99 of the *International Classification of Diseases, 10th Revision*. Maternal deaths occur while pregnant or within 42 days of being pregnant. People of Hispanic origin may be of any race.

SOURCES: National Center for Health Statistics, National Vital Statistics System, mortality and natality data files.

Test or No-Test: Comparison of Medication Abortion Outcomes and Adverse Events When Forgoing Ultrasound, Laboratory Testing, and Physical Examination

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ABSTRACT

Objectives: This study aimed to compare demographics and clinical outcomes between patients who did not undergo investigations and those who underwent investigations before receiving a prescription for medication abortion (MA) during the first 6 months of the COVID-19 pandemic. Outcomes include success rates, adverse events, pathways to completion, and loss to follow-up rates.

Methods: We conducted a retrospective medical record review of 1452 patients presenting for MA between 23 March 2020 and 30 September 2020. Descriptive statistics, 2 × 2 chi-square tests, and Fisher exact tests were used to compare characteristics and outcomes between groups.

Results: Of the 1307 patients who received a prescription, 895 (68.5%) were in the no-test group and 412 (31.5%) were in the test group. The success rate was 95.2%, with no significant difference between groups (94.0% and 95.8%, $P = 0.194$). Rates of adverse events were low, with 28 patients presenting for emergency department visits (2.1%), 62 having clinically significant retained products of conception (4.7%), 5 with heavy bleeding requiring treatment (0.4%), 16 with ongoing pregnancy (1.2%), and 3 requiring ectopic pregnancy management (0.2%). Completion of abortion was verified in 1034 patients (80.5%), and the loss to follow-up rate was 22.6%, with no difference between the groups (82.1% vs. 79.8%, $P = 0.341$; and 21.4% vs. 23.1%, $P = 0.477$; respectively).

Conclusions: We found that clinical outcomes were consistent across the 2 groups, with high success rates and low adverse event rates. Our study contributes to the growing body of evidence that allows for individualized care implementing selective use of low- and no-test MA protocols.

Keywords: induced abortion; mifepristone; misoprostol; COVID-19; telemedicine; ultrasound

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Each author has indicated they meet the journal's requirements for authorship.

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RÉSUMÉ

Objectif : Comparer les données démographiques et les résultats cliniques entre les patientes qui ont eu ou non des évaluations avant de recevoir une ordonnance d'avortement médicamenteux (AM) dans les six premiers mois de la pandémie de COVID-19. Les critères de jugement sont le taux de réussite, les événements indésirables, les voies d'accès jusqu'à l'avortement complet et le taux de perte au suivi.

Méthodes : Nous avons réalisé une étude rétrospective des dossiers de 1452 patientes ayant demandé un AM entre le 23 mars 2020 et le 30 septembre 2020. Des statistiques descriptives, des tests chi-carré au format 2 × 2 et des tests exacts de probabilité de Fisher ont été utilisés pour comparer les caractéristiques et les résultats entre les groupes.

Résultats : Des 1307 patientes qui ont reçu une ordonnance, 895 (68,5 %) étaient dans le groupe sans évaluation et 412 (31,5 %) dans le groupe avec évaluation. Le taux de réussite était de 95,2 %,

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sans différence significative entre les groupes (94,0 % p/r à 95,8 %; $P = 0,194$). Le taux d'événements indésirables était faible : 28 patientes se sont présentées à l'urgence (2,1 %), 62 ont eu une rétention cliniquement significative du produit de conception (4,7 %), 5 ont eu des saignements abondants nécessitant un traitement (0,4 %), 16 ont eu une grossesse évolutive (1,2 %) et 3 ont eu besoin d'une prise en charge de grossesse ectopique (0,2 %). L'avortement complet a été vérifié chez 1034 patientes (80,5 %), et le taux de perte au suivi était de 22,6 %, sans différence entre les groupes (82,1 % p/r à 79,8 %; $P = 0,341$; et 21,4 % p/r à 23,1 %; $P = 0,477$, respectivement).

Conclusion : Nous avons constaté que les résultats cliniques étaient comparables entre les deux groupes, que le taux de réussite était élevé et que le taux d'événements indésirables était faible. Notre étude contribue au nombre croissant de données probantes qui permettent d'individualiser les soins en mettant en œuvre l'utilisation de protocoles sélectifs d'AM avec ou sans évaluation.

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INTRODUCTION

The COVID-19 pandemic introduced novel challenges and significantly exacerbated the current and historic threat to abortion access, a critical and time-sensitive health care service. While there are a variety of appropriate protocols for providing medication abortion (MA), the first step is generally confirming a likely intrauterine pregnancy (IUP) before prescribing medication through some combination of in-clinic physical examination, medical imaging, and/or laboratory testing. Despite evidence that medical imaging is not always needed to ensure a successful and safe MA,[1–14] many providers express concern with proceeding without first verifying gestational age (GA) through ultrasound examination.[15]

In a survey of 100 abortion clinics in the United States, most (87.0%) implemented protocol changes in response to the COVID-19 pandemic. A large proportion of clinics reported changes to telehealth for follow-up (71.0%), initial consultation and screening (41.0%), and reducing the frequency of Rhesus factor testing (43.0%). A much smaller proportion of clinics (15.0%) were able or willing to forgo ultrasound assessment before medication administration.[16] A similar study reviewing protocol changes at 55 sites in the United States during the COVID-19 pandemic revealed that only 27.0% reported proceeding with MA without first confirming eligibility via ultrasound.[17]

In response to the COVID-19 pandemic, numerous professional organizations endorsed protocols for medication abortion requiring minimal or no testing (hereafter referred to as 'low/no-test protocols') to support providers' ability to continue providing MAs while abiding by local/provincial restrictions to in-person care.[18–21] A survey of Canadian abortion providers reported a transition away from in-person provision of MA, with most respondents indicating a rapid uptake of low/no-test protocols.[22] Willow Reproductive Health Centre ("Willow"), a high-volume family planning clinic in Vancouver, British Columbia, Canada, had provided telemedicine MAs for patients living outside of Vancouver Coastal Health Authority for many years, using various low-test protocols.[11] Responding to the shift in health care due to the COVID-19 pandemic, Willow initiated a clinic-wide no-test protocol for MA provision.

Regarding terminology, various protocols categorized as low/no-test abortion protocols fall under the umbrella of telemedicine abortion. Generally, a no-test protocol refers to those that forgo all testing (laboratory testing, medical imaging, and physical examination) through the entire course of an MA and determine completion using only an at-home urine pregnancy test (UPT). Protocols that forgo routine dating ultrasound but include any other testing during the process would be considered low-test. The initiation of a fully no-test protocol at Willow in response to the COVID-19 pandemic allowed a unique research opportunity to provide a Canadian perspective on safety and effectiveness of a no-test MA protocol. For the sake of our study, we analyzed the outcomes of patients who received a prescription without any prior testing (herein referred to as the "no-test group") and compared them with those of patients who did have testing before being provided a prescription (herein referred to as the "test group").

Our study aimed to describe demographics and clinical outcomes, including success rates and adverse events, of the no-test group and test group during the first 6 months of the COVID-19 pandemic. Secondary outcomes included analysis of methods through which patients were confirmed to have completed the MA process (pathways to completion) and loss to follow-up rates compared between these 2 groups. This analysis contributes to a growing body of evidence informing clinical decisions and counselling for eligible people seeking abortion, and provides further information on the risks and benefits of no-test MA as an alternative option to in-clinic abortion care.

GBP-PET00334

METHODS

We conducted a retrospective chart review of all 1452 MA patients presenting to Willow between 23 March 2020 and 30 September 2020. The study was approved by the University of British Columbia Clinical Research Ethics Board (UBC CREB number H21-00104), with additional permission granted by the Executive and Medical Directors of Willow.

Protocol Outline

A change to a clinic-wide no-test MA protocol was initiated in late March 2020 and became the primary method of providing MA until late September 2020, when some regional pandemic restrictions eased, and more patients could be safely seen in the clinic again. During a virtual consultation, patients were deemed eligible and provided with a mifepristone and misoprostol prescription. Eligibility was based on a positive at-home UPT, GA of $<10^{0}$ weeks as determined by patient-reported certain last menstrual period (LMP) in those with a regular cycle and no history of hormonal contraception within the last 6 months, and the absence of ectopic pregnancy symptoms or risk factors (no severe/unilateral pain, vaginal bleeding or spotting, previous ectopic pregnancy, previous pelvic inflammatory disease, previous tubal surgery, assisted reproductive technology, or intrauterine device [IUD] in situ). Patients were then scheduled for 2 virtual follow-up appointments (at 1 week and 4 weeks after mifepristone administration). Consultations were provided virtually and patients were advised to call the clinic or on-call doctor if there were any concerns between appointments. Completion of abortion was determined with either a negative at-home UPT or a negative UPT during IUD insertion at the clinic.

Data Extraction

For each patient, we recorded age, place of residence, and payment method. Clinical data points collected were GA at time of abortion, method of GA determination, anemia risk, ectopic pregnancy risk, obstetric history, date of initiation, confirmation of completion, method of determining completion, number of patients lost to follow-up, and adverse events. The chart review was performed by 2 data abstractors who were familiarized with the clinic policies and processes during the study period.

Data Analysis

We developed and used a standard form within the REDCap platform[23] and extracted all study variables, assigning a project-specific identification number in place of potentially identifying personal information. The resulting data set was then assessed for completeness and accuracy by one of the listed authors, who served a prescribing physician throughout the study period. Of the initial sample, 145 patients failed to attend their initial appointment or did not receive medication for other reasons and were excluded from further data analysis (Figure). The remaining 1307 medical records were included in further data analysis. Primary outcomes were success rates and adverse events of MA. Secondary outcomes were pathways to completion and loss to follow-up rates.

Characteristics and outcomes were compared across 2 groups: (1) "no-test group"—those who did not have any laboratory testing, ultrasound, or physical examination before receiving the prescription, and (2) "test group"—those who had laboratory testing, ultrasound, and/or physical examination before receiving the prescription. Of note, some patients sought care at Willow with pre-existing investigations ordered by an external physician who does not provide abortions. These patients were assigned to the test group despite potential eligibility for no-test MA if initially assessed by a Willow physician. Descriptive statistics were generated for the study cohort, and 2×2 chi-square tests and Fisher exact tests (where cell counts were <5) were used to investigate the associations between the 2 groups and our outcomes of interest. Data analysis was conducted using Microsoft Excel (Microsoft Corp.), Stata v17 (StataCorp),[24] and Social Science Statistics.[25]

RESULTS

Of the 1452 patients presenting to Willow and requesting MA during our study period, a total of 1307 patients were given a prescription for mifepristone and misoprostol. Of the 1307 patients who received a prescription, the no-test group comprised 895 (68.5%) patients, with 882 ultimately initiating the MA process. The test group consisted of 412 (31.5%) patients, with 402 initiating the MA process. The MA process was not initiated for 23 patients (13 no-test group vs. 10 test group) who self-reported that they did not take the medications for various reasons (Figure).

Demographics

Patient age ranged from 15 to 46 years, with a median of 29 years. A total of 718 (54.9%) patients had a home address listed within Fraser Health, while only 444 (34.0%) patients had a home address listed within Vancouver Coastal Health. Most patients (94.0%) had these services covered by provincial insurance. GA determined by LMP was significantly associated with whether patients were assigned to the test or no-test group ($P < 0.000$), with

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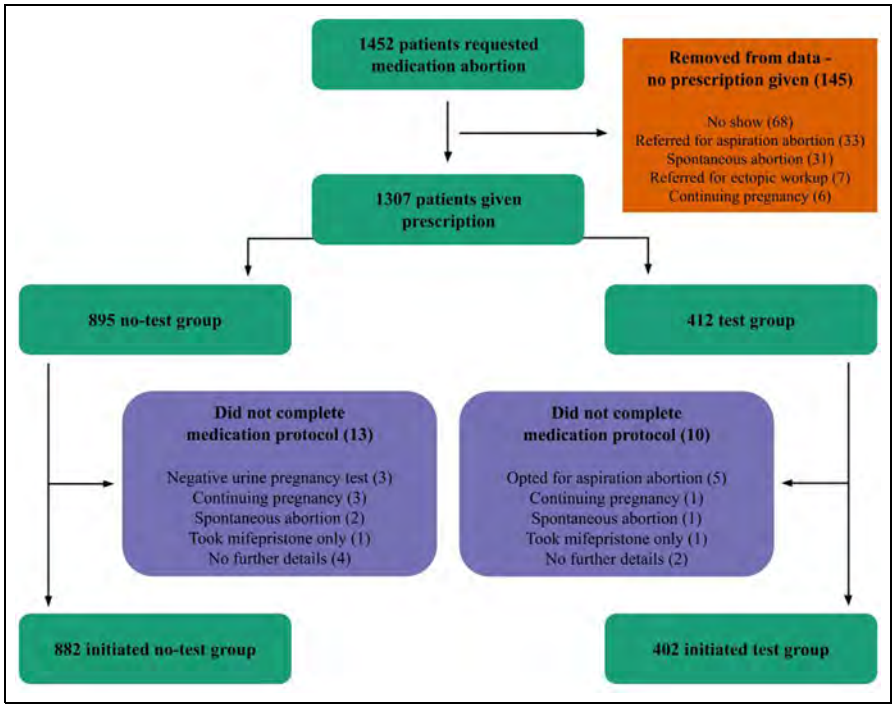
Figure. Summary of medication abortions performed at Willow between 23 March 2020 and 20 September 2020.



higher GA correlating with a lower likelihood of receiving a no-test abortion. As expected, the test group had a significantly higher proportion of patients with elevated risk for anemia or ectopic pregnancy compared with the no-test group (21.1% vs. 1.3% and 29.6% vs. 0.9%, respectively, $P < 0.000$ for both variables) (Table 1).

Success Rates and Adverse Events

Successful MA was defined as no ongoing IUP and no retained products of conception (RPOC) requiring aspiration. The success rate was 95.2% overall, with no significant difference in the likelihood of having a successful MA between the test and no-test groups (94.0% and 95.8%, $P = 0.194$) (Table 2). Rates of adverse events were low overall, with 28 patients presenting for emergency department visits (2.1%), 62 patients having clinically significant RPOC (4.7%), 5 patients with heavy bleeding requiring treatment (0.4%), 16 patients diagnosed with ongoing IUP (1.2%), and 3 patients requiring ectopic pregnancy management (0.2%). Of note, 3 patients in the no-test group were identified at some point during the process to have been beyond the 10^0 week gestational limit at the time of medication administration. There were no statistically significant differences between the no-test and test groups for any of these adverse events (Table 3).

Pathways to Completion and Loss to Follow-Up

Completion of abortion was verified in 1034 patients (80.5%), with no statistically significant difference between the test and no-test groups (82.1% vs. 79.8%, $P = 0.341$) (Table 4). The overall loss to follow-up rate was 22.6%, with no statistically significant difference between the test and no-test groups (21.4% vs. 23.1%, $P = 0.477$). The highest rate of loss to follow-up occurred after the 1-week visit in both the test group (72.7%) and the no-test group (61.8%) (Table 5).

DISCUSSION

We found that pertinent demographic information and clinical outcomes were consistent for all patients receiving MA throughout our study period, regardless of whether tests were ordered before prescribing the medication. Patients access abortion services at all ages throughout their reproductive years, as reflected in the distribution of patient age in our findings. Within the Canadian context of single-payer health care, the cost of MA was covered through provincial insurance for the vast majority of patients, with the remaining patients paying out of pocket.

Unexpectedly, most patients receiving MA during this study period had a home address listed within Fraser Health Authority, despite Willow being located within

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Table 1. Demographics and pertinent obstetric history in patients requesting medication abortion through Willow Clinic between 23 March 2020 and 30 September 2020

Characteristics	No-test = 895, n (%)	Test = 412, n (%)	Total = 1307, n (%)	*P* value
Age, y				0.721
15–19	38 (4.2)	15 (3.6)	53 (4.1)	
20–24	203 (22.7)	94 (22.8)	297 (22.7)	
25–29	242 (27.0)	111 (26.9)	353 (27.0)	
30–34	207 (23.1)	92 (22.3)	299 (22.9)	
35–39	152 (17.0)	68 (16.5)	220 (16.8)	
40+	53 (5.9)	32 (7.8)	85 (6.5)	
Location (Health Authority)				0.474
Vancouver Coastal Health	306 (34.2)	138 (33.5)	444 (34.0)	
Fraser Health	481 (53.7)	237 (57.5)	718 (54.9)	
Interior Health	91 (10.2)	33 (8.0)	124 (9.5)	
Northern Health	9 (1.0)	3 (0.7)	12 (0.9)	
Island Health	4 (0.4)	0 (0.0)	4 (0.3)	
Out of province	4 (0.4)	1 (0.2)	5 (0.4)	
Payment method				0.883
Provincial insurance	841 (94.0)	388 (94.2)	1229 (94.0)	
Cash	54 (6.0)	24 (5.8)	78 (6.0)	
Gestational age by last menstrual period, wk				0.000
<5	158 (17.7)	48 (11.7)	206 (15.8)	
5	346 (38.7)	99 (24.0)	445 (34.0)	
6	240 (26.8)	111 (26.9)	351 (26.9)	
7	99 (11.1)	75 (18.2)	174 (13.3)	
8	40 (4.5)	40 (9.7)	80 (6.1)	
9	11 (1.2)	20 (4.9)	31 (2.4)	
>/=10	1 (0.1)	12 (2.9)	13 (1.0)	
Uncertain	0 (0.0)	7 (1.7)	7 (0.5)	
Anaemia risk				0.000
Low	879 (98.2)	299 (72.6)	1178 (90.1)	
High	12 (1.3)	87 (21.1)	99 (7.6)	
Not documented	4 (0.4)	26 (6.3)	30 (2.3)	
Ectopic risk				0.000
Low	879 (98.2)	266 (64.6)	1145 (87.6)	
High	8 (0.9)	122 (29.6)	130 (9.9)	
Not documented	8 (0.9)	24 (5.8)	32 (2.4)	
Obstetric history				
Never pregnant before	352 (39.3)	178 (43.2)	530 (40.6)	0.185
Previous pregnancy/ies	543 (60.7)	234 (56.8)	777 (59.4)	
Previous medication abortion[a]	199 (36.6)	89 (38.0)	288 (37.1)	0.062
Previous aspiration[a]	169 (31.1)	60 (25.6)	229 (29.5)	0.252

[a]Among people with previous pregnancies.

Vancouver Coastal Health Authority. This is likely influenced by the regional lack of access to abortion outside of the Vancouver Coastal Health Authority. This illustrates the importance of increasing access to abortion for patients within their home community, who must otherwise travel longer distances to access this care. Although no-test MA is an excellent way to improve this health disparity for eligible patients, those needing testing for their abortion would benefit from clinics and services within their own health region.

A 2010 prospective trial of 4484 patients seeking MA found that of those determined to be within the 9^0 week GA limit, only 1.6% were over the limit on ultrasound, supporting the safety of forgoing routine ultrasound.[12] A systematic review found that only 2.5% to 11.8% of

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Table 2. Success rates in patients accessing medication abortion through Willow Clinic between 23 March 2020 and 30 September 2020

Successful medication abortion	No-test = 882, n (%)	Test = 402, n (%)	Total = 1284 n (%)	*P* value
Yes	845 (95.8)	378 (94.0)	1223 (95.2)	0.194
No	37 (4.2)	24 (6.0)	61 (4.8)	
Retained products of conception requiring aspiration	27 (3.1)	18 (4.5)	45 (3.5)	
Ongoing intrauterine pregnancy	10 (1.1)	6 (1.5)	16 (1.2)	

patients who would have been eligible to receive medication on the basis of LMP alone were ineligible by ultrasound, which provides further support that LMP alone can be used to determine eligibility for MA.[13,14] Appropriately, in our study, patients with GA by LMP approaching the 10^0 week cutoff and those deemed high-risk for anemia or ectopic pregnancy were more likely to receive tests before receiving a prescription. Of note, another 7 patients were not eligible for MA (under either test or no-test protocol); therefore, no prescription was given and they were referred for workup of ectopic pregnancy. Accurately determining high-risk individuals for complications such as those related to ectopic pregnancy, anemia, and misdating, and excluding them from no-test MA eligibility enhances the safety profile of these protocols. This has also been observed in previous studies on low/no-test MA,[1,3–7,9,10] and highlights the importance of a thorough and focused individualized history when considering provision of MA under these protocols.

Patients seeking abortion at Willow who had undergone previous investigations were assigned to the test group, which may account for a slight inflation in the number of patients in that group. However, we found that these pre-existing investigations might influence the prescribing physician's decision-making when determining eligibility for no-test MA. Maintaining strict eligibility criteria for assigning no-test versus test groups during data analysis was essential to assessing the safety of proceeding with a prescription without ordering any investigations.

Early findings from the United States[5,9] and Scotland[7] suggest that no-test protocols are safe and effective, with low complication rates. An analysis of over 52 000 MAs performed in the United Kingdom bolstered these findings, highlighting not only the safety and effectiveness, but also the acceptability and enhanced accessibility of low/no-test MA for patients.[1] Furthermore, a systematic review including 21 studies with a total of 10 693 patients

Table 3. Adverse events in patients accessing medication abortion through Willow Clinic between 23 March 2020 and 30 September 2020

Adverse event	No-test = 895 n (%)	Test = 412 n (%)	Total = 1307 n (%)	*P* value
Emergency room visit	18 (2.0)	10 (2.4)	28 (2.1)	0.629
Retained products of conception	36 (4.0)	26 (6.3)	62 (4.7)	0.071
Expectant	4 (0.4)	4 (1.0)	8 (0.6)	
Misoprostol	5 (0.6)	4 (1.0)	9 (0.7)	
Aspiration	27 (3.0)	18 (4.4)	45 (3.4)	
Heavy bleeding[a]	4 (0.4)	1 (0.2)	5 (0.4)	1.000
Transfusion	1 (0.1)	0 (0.0)	1 (0.1)	
Tranexamic acid	3 (0.3)	1 (0.2)	4 (0.3)	
Ongoing intrauterine pregnancy following medications	10 (1.1)	6 (1.5)	16 (1.2)	0.625
Repeat medications (mifepristone/misoprostol or misoprostol alone)	2 (0.2)	3 (0.7)	5 (0.4)	
Repeat medications followed by aspiration	2 (0.2)	0 (0.0)	2 (0.2)	
Aspiration only	5 (0.6)	3 (0.7)	8 (0.6)	
Other	1 (0.1)	0 (0.0)	0 (0.0)	
Ectopic[a]	2 (0.2)	1 (0.2)	3 (0.2)	1.000
Surgery	0 (0.0)	1 (0.2)	1 (0.1)	
Methotrexate	2 (0.2)	0 (0.0)	2 (0.2)	
Gestational age > 10^0 wk[a]	3 (0.3)	0 (0.0)	3 (0.2)	0.556

[a]The Fisher exact test was used where cell counts were <5.

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Table 4. Pathways to completion in patients accessing medication abortion through Willow Clinic between 23 March 2020 and 30 September 2020

Completion	No-test = 882, n (%)	Test = 402, n (%)	Total = 1284, n (%)	*P* value
Verified[a]	704 (79.8)	330 (82.1)	1034 (80.5)	0.341
Ultrasound before and after medication	N/A	53 (13.2)	53 (4.1)	
Negative urine pregnancy test	506 (57.4)	212 (52.7)	718 (55.9)	
Negative urine pregnancy test at intrauterine device insertion	97 (11.0)	0 (0.0)	97 (7.6)	
Aspiration	34 (3.9)	20 (5.0)	54 (4.2)	
Serial human chorionic gonadotropin	35 (4.0)	28 (7.0)	63 (4.9)	
Subsequent appointment	28 (3.2)	14 (3.5)	42 (3.3)	
Other	4 (0.5)	3 (0.7)	7 (0.5)	
Not verified	178 (20.2)	72 (17.9)	250 (19.5)	

[a]Completion could be verified in multiple ways for 1 patient. The first definitive verification of completion was included in these data.

N/A: not applicable.

also found no-test MA to be a safe and effective option.[8] We defined a successful MA as no ongoing IUP or RPOC requiring aspiration following medication administration. Unsurprisingly, success rates and adverse events in our sample were generally consistent with other data on no-test MA protocols.[1,5,7–9]

We found a high success rate and a low adverse event rate, with no significant difference between the test and no-test groups. A potential limitation to our findings is that adverse events were self-reported at the time of follow-up or determined through retrospective medical record review, and may have been documented inconsistently across providers at the clinic. Records exterior to the clinic (e.g., patient hospital records) were not obtained. The reasons for emergency department visits were not analyzed and may include visits during which only supportive measures were provided to assist the patient through the normal and expected clinical course of an MA. However, we believe that most clinically significant adverse events were captured, as this topic was discussed with patients at all follow-up appointments, providing ample opportunity for them to share this information.

We were able to verify completion in most cases through various means, including ultrasound before and after medication, negative at-home UPT, negative UPT at the time of IUD insertion, aspiration (for RPOC or ongoing IUP), serial human chorionic gonadotropin testing, or subsequent unrelated appointment(s) at Willow. There were no notable differences in pathways to completion between the test and no-test groups. This provides further evidence that multiple pathways to determining completion are safe and appropriate[26,27] as long as close follow-up is initiated for rare instances of complication or MA failure. Willow has continued to offer virtual follow-up options for patients, despite moving away from no-test MA as the standard protocol for most patients because of the easing of pandemic restrictions. This approach allows for safe, trauma-informed, patient-centred care by increasing options for patients who prefer virtual follow-up. Some reasons for this preference may include travel time, associated travel cost, cost of childcare, ability to follow-up discreetly (e.g., abusive or controlling partners), work and life commitments, avoidance of pelvic ultrasound, or patient preference to avoid medicalized environments (e.g., due to previous trauma within the medical system).[28]

Table 5. Loss to follow-up rates in patients accessing medication abortion through Willow Clinic between 23 March 2020 and 30 September 2020

Follow-up	No-test = 895, n (%)	Test = 412, n (%)	Total = 1307, n (%)	*P* value
Loss to follow-up	207 (23.1)	88 (21.4)	295 (22.6)	0.477
After counselling	38 (18.4%)	14 (15.9)	52 (17.6)	
After 1-wk visit	128 (61.8)	64 (72.7)	192 (65.1)	
After 4-wk visit	30 (14.5)	10 (11.4)	40 (13.6)	
After intrauterine device insertion	11 (5.3)	N/A	11 (3.7)	
Completed follow-up	688 (76.9)	324 (78.6)	1012 (77.4)	

N/A: not applicable.

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The overall loss to follow-up rate was 22.6%, which is higher than the rates reported in other similar studies, ranging from 4.2% to 18.5%.[5,6,9,11,29,30] There were no differences in loss to follow-up rates between the test and no-test groups. Loss to follow-up was most likely to occur after the 1-week visit in both groups. This may be explained by the patient's confidence in completion based on their history and discussion with an abortion provider at the 1-week visit. Given this reassurance at the first follow-up visit and the well documented success rate of medication abortion, patients may have assumed completion upon resuming regular menstruation, felt it unnecessary to confirm completion with a UPT, and/or failed to provide these results to the clinic.

CONCLUSION

Our study findings provide further data about the risks and benefits of forgoing ultrasound or laboratory testing before initiating MA. The safety of no-test MA protocols continues to be documented and studied. However, some providers may remain hesitant because of ongoing fears of litigation or disciplinary action from governing bodies when faced with complications or unfavourable outcomes, hostility from colleagues practising outside the field of abortion care, and more widely the potentially violent political environment surrounding abortion care. Abortion access is not equitable in low-resource settings, marginalized communities, rural and remote areas, and for patients with low access to health care services. Our study findings contribute to the growing body of evidence that allows for individualized care implementing selective use of low and no-test protocols, particularly in situations where the risks of the aforementioned legal or professional ramifications are outweighed by the benefits of increasing accessibility to patients. Accessibility is a cornerstone of providing equitable care. Therefore, it is important to offer flexibility in providing various aspects of in-person, low-test, or no-test protocols on an individualised basis. This approach prioritizes patients by centring their unique and often complex circumstances, which is essential when considering the safety of their care.

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ETHICS

INSTITUTION/DEPARTMENT: UBC/Medicine, Faculty of Family Practice.

UBC CREB NUMBER: H21-00104-A002.

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ORIGINAL ARTICLE

A direct-to-patient telemedicine abortion service in Australia: Retrospective analysis of the first 18 months

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Background: In 2015, the Tabbot Foundation launched a nationwide direct-to-patient telemedicine service to enable women to obtain medical abortion without visiting an abortion provider.

Aims: We aimed to describe results from the first 18 months of this service.

Materials and Methods: To have an abortion through the Foundation, a woman obtained screening tests locally and had a telephone consultation with a Foundation doctor. If she was eligible, mifepristone, misoprostol and other medications were sent to her by mail. After taking the drugs, the woman obtained follow-up tests at local facilities and had a consultation with Foundation professionals. The Foundation charged $250 to patients with Medicare eligibility and $600 otherwise. We summarised clinical data collected by the service.

Results: Between June 2015 and December 2016, 1010 women received medications, of whom 56% lived outside of major cities. Ninety-five percent of packages were sent within 15 days after registration. Of the 965 women who took misoprostol, outcomes were definitively documented for 754 (78%), of whom 96% had a complete abortion without surgical intervention, and 95% had no face-to-face clinical encounter after treatment. Of women with Medicare cards, 72% paid no out-of-pocket charges other than to the Foundation. Nearly all women (781/802; 97%) were highly satisfied.

Conclusions: The direct-to-patient telemedicine medical abortion service was effective, safe, inexpensive and satisfactory. It disproportionately served women in parts of Australia with limited access to abortion facilities. This experience may be instructive for others desiring to use telemedicine to enhance access to abortion.

KEYWORDS

abortion, access, Australia, telemedicine

INTRODUCTION

Although surgical abortion has been available in Australia for decades, the introduction of medical abortion has been slow. Mifepristone was effectively banned until 2006, when a limited number of providers were authorised to import and distribute the drug under strict conditions. In 2012, 23 years after approval was given to market the drug in France, a registered mifepristone product finally became available in Australia. Measures were instituted to facilitate access: in particular, unlike most other countries, Australia allowed distribution of the drug by prescription in pharmacies, dramatically increasing the number and distribution of certified dispensers.[1] In 2013 mifepristone and misoprostol were added to the Pharmaceutical Benefits

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Scheme, which subsidises the cost of the drugs. Nevertheless, by 2016 use of medical abortion was substantially less than anticipated,[2] and obtaining medical abortion remains difficult for many Australian women.[3–5]

To address this problem, the Tabbot Foundation, based in Sydney, New South Wales, launched a direct-to-patient telemedicine service in June 2015 to enable women to obtain medical abortion without visiting a medical practitioner. In this paper, we present observations from the first 18 months of this service.

MATERIALS AND METHODS

The Tabbot Foundation Service

The specific procedures for providing abortion evolved somewhat over the course of the first 18 months (http://www.tabbot.com.au/). A basic description of the service follows.

Each woman who contacted the Foundation was screened by telephone to confirm that she desired an abortion and met preliminary criteria. These criteria included the following: she had a positive pregnancy test, was <8 weeks gestation by menstrual dating, lived ≤60 minutes from a medical facility, had no major medical illnesses or history of severe dysmenorrhea, identified someone to be with her during treatment, spoke English and could pay by electronic fund transfer. In addition, because laws in the Australian Capital Territory, Northern Territory and South Australia specified that abortions must be performed in an approved medical facility, women from those jurisdictions were required to have an address in another state where they could receive and ingest the abortifacients.

If preliminary criteria were met, Foundation staff referred the patient to facilities of her choice for a screening ultrasound, haemoglobin, blood type and quantitative serum human chorionic gonadotropin (HCG) concentration. The results were reviewed by a Foundation doctor (a gynaecologist or general practitioner with training in abortion provision), who then spoke with the patient by telephone to confirm eligibility, discuss instructions and expectations, and agree on a follow-up plan. A woman was considered eligible if she was projected to have an intrauterine pregnancy of ≤63 days gestation by ultrasound at the proposed abortion date and no medical contraindications (chronic adrenal failure, haemorrhagic disorder, current anticoagulant or long-term corticosteroid therapy, inherited porphyria, allergy to the abortifacient drugs or intrauterine device in place). If the patient was deemed eligible for the service, the Foundation charged $250 if she had a Medicare card or $600 otherwise. The service then authorised a central pharmacy to send a package containing abortifacient drugs, ancillary medications and a urine pregnancy test to her specified address by express mail. Initially, a few patients chose to receive their drugs at a surgical abortion clinic in Tasmania that shared a medical director with the Foundation or at a pharmacy. Rh-negative patients were referred to local hospitals to receive Rh(D) immunoglobulin. A 24-h toll-free phone number was provided to all patients.

A Foundation nurse contacted each patient on the planned misoprostol ingestion date to check her status. Each patient was instructed to obtain a second serum quantitative HCG concentration seven days after misoprostol ingestion. Abortion outcomes were assessed by reviewing these results and through scheduled phone calls with Foundation staff. Complications such as excessive or insufficient bleeding and inadequate pain relief were actively managed with additional misoprostol or analgesics; hospital referrals were made when necessary. Active follow-up was discontinued when Foundation clinicians determined that no further care was needed. All patients were instructed to perform the urine pregnancy test at home 28 days after treatment and to contact the Foundation if the results were positive.

In the first year of the service, the standard abortifacient regimen was mifepristone 200 mg orally followed 40-45 h later by misoprostol 800 μg buccally. In August 2016, all patients were provided with additional misoprostol 200 μg to take sublingually thrice daily for two days. A specific combination of analgesics, anti-emetics and an antibiotic was also recommended.

Analysis

De-identified information was transferred from the electronic medical record into an analysis database. Some data from six patients were obviously invalid: three patients had recorded dates of registration, drug shipment authorisation and misoprostol ingestion that did not occur in that order, one had an interval of 273 days between registration and drug shipment authorisation, and two had intervals of ≥274 days between registration and ultrasound. Our analyses considered these dates as missing. Patients' addresses were classified according to the 2011 Australian Statistical Geography Standard Remoteness Area classification, which reflects relative access to services.[6] For this analysis, we defined a complete medical abortion as one that met any of these criteria: serum HCG concentration declined by ≥80%, urine pregnancy test was negative, ultrasound showed complete abortion, or a clinician diagnosed complete abortion without surgery. We defined a patient to have had full follow-up if she had had a complete medical abortion according to the analysis definition, a uterine evacuation, or an ongoing pregnancy that she planned to continue. We used descriptive statistics to describe the women who accessed the service, the process indicators and the outcomes. We used χ^2 tests to test associations between remoteness area classification and source of initial introduction to the service and between abortifacient regimen and outcomes. We considered a P-value <0.05 as statistically significant. The Allendale Investigational Review Board (Old Lyme, CT, USA) approved the analysis.

RESULTS

Between 11 June, 2015 and 23 December, 2016, 1409 people registered with the Foundation (Table 1). Most lived outside

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TABLE 1 Patient characteristics

	Registered N = 1409 n (%)	Sent drugs N = 1010 n (%)
Age at registration†		
14–24	354 (25%)	240 (24%)
25–34	732 (52%)	523 (52%)
35–49	319 (23%)	243 (24%)
Unknown	4	4
Insurance status		
Medicare	1348 (96%)	973 (96%)
Other	61 (4%)	37 (4%)
Remoteness area class		
Major city	614 (44%)	406 (40%)
Inner regional Australia	557 (40%)	427 (42%)
Outer regional Australia	203 (14%)	153 (15%)
Remote Australia	27 (2%)	20 (2%)
Very remote Australia	8 (0.5%)	4 (0.4%)
State		
Tasmania	445 (32%)	351 (35%)
New South Wales	443 (31%)	301 (30%)
Victoria	203 (14%)	127 (13%)
Queensland	187 (13%)	143 (14%)
Western Australia	102 (7%)	69 (7%)
Australian Capital Territory	23 (2%)	16 (2%)
Northern Territory	5 (0.4%)	3 (0.3%)
South Australia	1 (0.1%)	0
Referral source		
Web search	804 (57%)	576 (57%)
Tabbot-associated surgical abortion clinic‡	131 (9%)	112 (11%)
Other clinical provider or advisory service	344 (24%)	232 (23%)
News media	72 (5%)	48 (5%)
Personal contact	58 (4%)	42 (4%)
Gestational age by ultrasound at registration§		
28–35 days	353 (31%)	315 (31%)
36–42 days	439 (38%)	399 (40%)
43–49 days	256 (22%)	221 (22%)
50–56 days	82 (7%)	64 (6%)
57–63 days	17 (1%)	7 (1%)
64–70 days	2 (0.2%)	0 (0%)
>71 days	5 (0.4%)	0 (0%)
Had ultrasound but gestational age undetermined	6	4
No ultrasound recorded	249	
Rh status¶		
Positive	1005 (86%)	862 (85%)
Negative	164 (14%)	148 (15%)
Unknown	240	0

†Percents exclude women in whom age at registration could not be determined due to data errors.
‡A clinic in Tasmania that shared a medical director with the Tabbot Foundation.
§Percents exclude women who had ultrasound but gestational age could not be determined due to data errors and women who did not have any ultrasound recorded.
¶Percents exclude women with unknown Rh status.

major cities; a third lived in Tasmania. Overall, 57% discovered the service through the internet, and a third were referred either by a surgical abortion clinic in Tasmania that shared a medical director with the Foundation (9%) or by another clinical provider or advisory service (24%). Registrants in major cities were significantly more likely than other women to have used the internet (69% vs 48% respectively; $P < 0.001$), and less likely to have been referred by medical professionals (20% vs 45%, respectively, $P < 0.001$).

A total of 399 registrants (28%) withdrew from the screening process before medications were sent. The records of 200 (50%) of these women include no screening test results or Foundation doctor consultation; 178 (45%) were missing at least one test and/or the doctor consultation; and 21 (5%) had all tests and the doctor consultation but did not provide payment. Only seven of the valid ultrasound results received showed gestational ages of >63 days at registration. Most women who withdrew did not report a reason for discontinuing, but some indicated that they decided to continue the pregnancy or to have an abortion elsewhere. Some were deterred by harassment when obtaining the required screening tests or by misinformation about medical abortion in the community. A few had suspected ectopic or molar pregnancies.

The Foundation provided medications to 1010 of the 1409 registrants (72%). The characteristics of these women were similar to those of the full registrant population (Table 1). All women who were sent packages had recorded gestational ages of <63 days by ultrasound at drug shipment authorisation, except one whose recorded gestational age was 66 days and four whose gestational ages were unavailable. Nearly all (970/1010; 96%) had at least one contact with Foundation staff after drug shipment authorisation.

Progress through the process was efficient (Table 2). Patient evaluation and drug shipment authorisation were completed within 15 days for more than 95% of women who ultimately

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TABLE 2 Process indicators among women to whom drug packages were mailed†

	N	Minimum	Median	95th percentile	Maximum
Intervals between events (days)					
Registration to drug shipment authorisation	1006	0	6	15	34
Registration to ultrasound	1006	−14	1	9	21
Shipment of drug to misoprostol ingestion‡	962	0	5	10	16
Misoprostol ingestion to final contact§	948	1	11	19	66
Gestational age in days by ultrasound on day of misoprostol ingestion‡	962	33	51	62	69

†Table excludes three cases in which registration, drug prescription and misoprostol ingestion if any were not recorded as having occurred in that order and one case in which an interval of 273 days was recorded between these dates.
‡Row excludes 44 who did not take misoprostol or provided no relevant information after shipment.
§Row excludes 44 who did not take misoprostol or provided no relevant information after shipment, 12 whose last contacts were on the day of misoprostol ingestion, and two whose last contacts were recorded as having occurred >100 days after misoprostol ingestion.

TABLE 3 Abortion outcomes among women who took misoprostol and had full follow up

	***N* = 754** ***n* (%)**
Abortion outcome	
Complete abortion without surgical evacuation	727 (96%)
Surgical uterine evacuation†	26 (3%)
Continuing pregnancy	1 (0.1%)
Clinical encounters after package mailed	
Hospital admission†	21 (3%)
Outpatient face-to-face encounter	16 (2%)
No clinical encounter	717 (95%)

†One woman had a transfusion

received medications. This interval was shorter for the 16% of women who had ultrasounds before registration than for those who had ultrasounds on or after registration (median three vs seven days, respectively). Of the 962 women who had a valid date of misoprostol ingestion recorded, nearly all took the drug within 10 days after drug shipment authorisation. Sixteen women reported having taken the misoprostol at gestational ages of more than 63 days, but all were less than 70 days.

Of the 1010 women who were sent medications, 31 (3%) provided no relevant information after shipment, and 14 (1%) reported that they did not take the misoprostol. Most of the latter group reported that they had either miscarried or decided not to have a medical abortion. Of the other 965 women, full follow-up according to our analysis definition was accomplished in 754 (78%). Of those, 96% had a complete abortion without surgical uterine evacuation, and 95% had no face-to-face clinical encounter (other than for providing the HCG specimen) after the package was sent (Table 3). Neither abortion outcomes nor the incidence of face-to-face encounters changed significantly after the introduction of the extended misoprostol dosing in August 2016 (data not shown).

A total of 211 women who took misoprostol did not have full follow-up by the analysis definition. Of these women, seven were known to have been admitted to hospital and seven had outpatient consultations with outside providers for symptoms related to the abortion. The outcomes of these encounters were not ascertained. Foundation clinicians using clinical judgment (i.e., criteria other than those defined for this analysis) determined that 75 of the 211 women (35%) ultimately had complete medical abortions without a face-to-face clinical encounter.

From February 2016, the Foundation began asking each woman at discharge how much she had spent on abortion-related tests and other care in addition to the Foundation charge. Of the 584 women with Medicare cards who had full follow-up by the analysis definition and provided this information, 421 (72%) paid no additional costs. The other 163 women reported additional costs ranging from $30 to $310 with a median of $130.

Women were asked at the last contact to rate their satisfaction with the process. Of the 802 who responded, 781 (97%) rated it a 1 (highly satisfied) on a scale of 1–5.

DISCUSSION

Telemedicine is increasingly recognised as an important approach for increasing access to abortion and for enhancing patients' privacy and autonomy.[7] For more than a decade, several international organisations have been mailing abortifacient drugs across international boundaries to women in countries where abortion is illegal or severely restricted.[8,9] In the United States of America, videoconferencing is being used in several states to evaluate patients and authorise provision of these drugs at clinics that have no authorised prescribers on site.[10] A Canadian doctor instituted a program that counsels and evaluates women by videoconference and then sends medications to their homes by mail.[11] Research has shown that these programs are safe and well accepted by patients.

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The Tabbot Foundation program is the first known nationwide telemedicine service to legally offer abortion directly to patients without an in-person visit to an abortion provider. Our analysis of data from the first 18 months of this service indicates that it worked well. It provided abortions to over 1000 women from all but one of the Australian states and territories. Nearly all of these women were counselled, screened and sent the medications within 15 days after initial registration. Of those with full follow up, 96% completed the abortion without surgical evacuation, consistent with outcomes of in-person medical abortion.[12–14] Only 5% of treated women required any subsequent face-to-face clinical encounter. Of women with Medicare cards, 72% paid only $250 total out of pocket, considerably less than the median of $470 for medical abortion obtained from a large provider organisation in Australia.[3] Nearly all patients were highly satisfied.

The service was used disproportionately by women outside of major cities: 60% of women who received abortion drugs from the Foundation lived in regional and remote communities, compared to 29% of the Australian population (Fig. 1).[15] This finding is encouraging because these communities are underserved by abortion clinics[5,16,17] and constitute a priority population group for health interventions in Australia.[18] Notably, whereas most registrants from major cities discovered the service from internet websites, fewer than half of non-urban women did so; for the latter group, referrals from medical providers were relatively more important. Ensuring that health professionals in non-urban settings inform patients about the option of telemedicine is key to realising its potential for enhancing service in these areas.

One limitation of our study is that only 76% of the women who were sent medications either had full follow-up according to our analysis definition or reported not having taken the misoprostol. This proportion is somewhat lower than the 87% reported in a recent series of in-person medical abortions in Australia.[14] Also, information about outcomes after face-to-face encounters was incomplete. However, 96% of patients had at least one post-treatment contact with the Foundation, and every patient was sent a urine pregnancy test to perform at home four weeks after treatment. Symptom-based follow up with or without pregnancy testing has been validated in several studies[19,20] and is now routinely offered after in-person medical abortion by organisations in the UK, Norway and Australia.[14,21,22] Nevertheless, our analysis may have missed some abortion failures or complications. In addition, our dataset lacked some information of potential interest, such as confirmation of mifepristone ingestion, the number of misoprostol doses taken, confirmation of receipt of Rh(D) immunoglobulin and incidence of side effects.

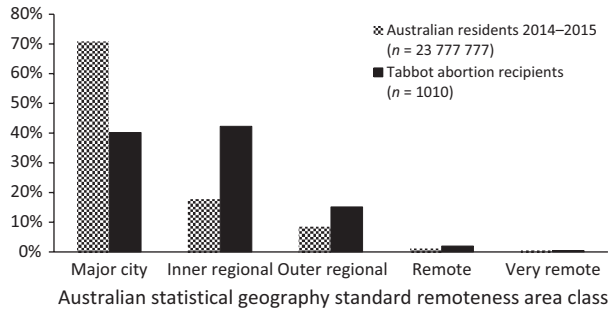

FIGURE 1 Australian resident population and Tabbot abortion recipients by Remoteness Area class. Australian resident population data estimated by Australian Bureau of Statistics.[17]

The Foundation encountered several challenges in implementing its service. From the outset, considerable planning was needed to ensure compliance with the unique regulations in each Australian state and territory. Finding facilities that would administer Rh(D) immunoglobulin to Rh-negative women promptly and nonjudgmentally has been problematic. Some surgical abortion providers dissuaded women from choosing medical abortion, citing excessive pain and bleeding.

The Foundation's experience yields recommendations for maximising the efficiency and success of a direct-to-patient telemedicine service. Standardised protocols and an electronic medical record are essential to effectively managing large numbers of patients. A well-designed website that provides full information to patients before and after treatment facilitates registration, screening and follow up. Communication with patients can be accomplished satisfactorily using telephone and text; videoconferencing, which has been required by North American telemedicine abortion services, is unnecessary. Indeed, a videoconferencing requirement can impede access by women who do not have the needed equipment and a reliable internet connection. Sending the medications to patients by mail from a central source can be preferable to issuing prescriptions, particularly in settings with a limited number of pharmacies that stock mifepristone and misoprostol or with high levels of stigma about abortion. Finally, providing adequate analgesics to minimise side effects is critical for acceptability.

The launch of the Tabbot Foundation service in 2015 was a turning point for abortion care in Australia. The following year, a second home-based telemedicine abortion service was introduced that also provides services in most Australian states and territories.[23] With the commencement in July 2017 of the Termination of Pregnancy Law Reform Act in the Northern Territory, which removed the requirement that abortion must be provided in hospitals, in-home abortion through one or both services is now available to over 93% of women in the country, excluding only those in South Australia. We hope that Australia will serve as a model for other nations desiring to use telemedicine to increase access to abortion care.

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Family Planning: *Original Research*

Medical Compared With Surgical Abortion for Effective Pregnancy Termination in the First Trimester

Luu Doan Ireland, MD, MPH, Mary Gatter, MD, and Angela Y. Chen, MD, MPH

OBJECTIVE: To compare efficacy between medical and surgical abortion at 9 weeks of gestation or less.

METHODS: We performed a retrospective cohort study comparing efficacy of medical compared with surgical abortion before 64 days of gestation at Planned Parenthood, Los Angeles, from November 2010 to August 2013. Electronic medical records were reviewed for ongoing pregnancies after the initial abortion procedure. Data were also collected on complications occurring within the immediate postabortal period (8 weeks postabortal) including unanticipated aspiration and major adverse events (emergency department presentation, hospitalization, perforation, transfusion, infection). Chi square test and logistic regression were used to compare the primary outcomes between cohorts.

RESULTS: Data were collected from 30,146 women with pregnancies seeking termination before 64 days of gestation. Sociodemographic and clinical characteristics were similar in the medication and surgical abortion groups. Efficacy of pregnancy termination was 99.6% for medication abortions and 99.8%% for surgical abortions ($P<.001$). The medication abortion group was more likely to undergo an unanticipated aspiration, for ongoing pregnancy or persistent pain, bleeding, or both (2.1% compared with 0.6%, respectively, odds ratio 1.6, 95% confidence interval 1.1–2.3). These rates were unchanged after controlling for gravidity, parity, and body mass index. There was no difference in major adverse events between the two groups.

CONCLUSION: Medication abortion and surgical abortion before 64 days of gestation are both highly effective with low complication rates.

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LEVEL OF EVIDENCE: II

See related editorial on page 3.

Pregnancy termination at 9 weeks of gestation or less accounts for 65.9% of all abortions in the United States.[1] Although surgical abortion remains the mainstay of first-trimester abortion care, the incidence of medical abortion is rising, accounting for 36% of abortions at 9 weeks of gestation or less.[2] In 2000, the U.S. Food and Drug Administration approved the use of mifepristone for medical abortion at 49 days of gestation or less. The approved regimen included 600 mg mifepristone followed by 400 micrograms of misoprostol taken orally 48 hours later.[3] The current evidence-based regimen results in higher efficacy before 64 days of gestation with fewer side effects[4–6] and entails 200 mg mifepristone followed by buccal, sublingual, or vaginal administration of 800 micrograms of misoprostol between 24 and 48 hours later.[7] First-trimester surgical abortion entails uterine aspiration under local anesthesia with oral premedication or intravenous sedation. Both methods are highly effective with failure rates that are below 5% for either method.[8–10] However, there are few comparative studies of efficacy between early surgical and medical abortion.[11] Most used outdated medication regimens and surgical techniques such as sharp curettage. These results may not be generalizable to women currently seeking early pregnancy termination.[12–15] The primary objective of this retrospective cohort study is to compare

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efficacy, the proportion of pregnancies successfully terminated by the initially chosen method, between medical abortion, using the current evidence-based regimen, and surgical abortion at 9 weeks of gestation or less. We hypothesize that the two methods of pregnancy termination are similar in efficacy.

MATERIALS AND METHODS

This historical cohort study was conducted at Planned Parenthood, Los Angeles, a high-volume health care system providing abortion services at 15 sites throughout the Los Angeles area. The study included a convenience sample of 30,146 women with pregnancies before 64 days of gestation who underwent surgical or medical abortion at Planned Parenthood, Los Angeles, from November 1, 2010, to August 31, 2013. Staff physicians performed or supervised all surgical abortions. These were conducted under local anesthesia with paracervical block and the addition of either oral nonsteroidal antiinflammatory drugs or intravenous sedation. Although women undergoing surgical abortion were not routinely scheduled for follow-up visits,[16] patients were counseled to return for persistent bleeding, pain, or with any other postoperative concerns. Women seen in follow-up and identified to have ongoing pregnancies were offered reaspiration or medical abortion. Advanced practice clinicians provided all medical abortions. The evidence-based regimen of 200 mg mifepristone orally at the time of the clinic visit followed by a single dose of 800 micrograms of buccal misoprostol 24–48 hours later was used for all medical abortions. One-week follow-up appointments were scheduled with advance practice clinicians for repeat ultrasonography to confirm abortion completion. All ongoing pregnancies identified at this visit underwent aspiration by a physician. Women with persistent vaginal bleeding or pain and intrauterine debris on ultrasonography were offered either aspiration with a physician or repeat misoprostol. Provided women met gestational age criteria by ultrasonography on the initial visit and had no contraindications to either method of abortion, they were given the option to choose their preferred method of termination. Contraindications to medical abortion included anemia with a hemoglobin of less than 10, chronic steroid or anticoagulant use, suspected ectopic pregnancy, intrauterine device in place, or inability to adhere to the medical abortion regimen or return for a follow-up visit. Contraindications to surgical abortion included hemoglobin of less than 8, molar gestation greater than 12 weeks in size, or any significant medical comorbidity.[17]

Planned Parenthood, Los Angeles, uses an electronic practice management system that electronically tracks all patients served within our system. Data collected includes visit date, patient demographics, gestational age by ultrasonography, and type of procedure performed. Internal quality assurance studies are routinely performed to ensure accuracy and we have previously published a description of these practices.[18] A separate electronic database stores all information regarding complications associated with abortion, including but not limited to ongoing pregnancies, incomplete abortion, emergency department presentations, and hospital transfers. Complications are recorded into this adverse event database as they occur by clinic staff and are reported by health care providers from outside institutions. This database has been verified by random chart audit.

In this study, data were collected through review of electronic medical records and the electronic practice management system by two of the three authors (M.G. and L.D.I.). Demographic data collected include patient age, racial and ethnic background, and income level. Clinical characteristics recorded include gestational age by ultrasonography, gravidity, parity, body mass index (BMI, calculated as weight (kg)/[height (m)]^2), type of abortion procedure, surgical documentation, and confirmation of medical abortion completion. Complications during the 8 weeks after pregnancy termination were collected through the adverse event database. The study was approved by Planned Parenthood Federation of America and the institutional review board at the University of California, Los Angeles (IRB #13-001941).

The primary outcome of this study was the difference in efficacy between medical and surgical abortion at 9 weeks of gestation or less using the evidence-based medication abortion regimen and aspiration for surgical procedures. This measure was defined as successful termination of pregnancy after the initial abortion procedure. To identify a 1% difference in efficacy between abortion methods with 80% power and $P<.05$, we needed at least 2,319 women per group. Ongoing pregnancies were identified in each group to determine efficacy of each abortion method. Secondary outcomes included complications such as unanticipated aspiration. This measure was defined as aspiration during a separate encounter after the initial procedure in the surgical abortion group and any aspiration in the medical abortion group. With few exceptions, these were performed at Planned Parenthood, Los Angeles, clinics during follow-up visits. These were done for ongoing pregnancy or persistent pain, bleeding, or both, with

ultrasound findings suggestive of retained clot, debris, or products of conception. Persistent bleeding, pain, or both were defined as symptoms that were unacceptable to the patient. The decision to recommend aspiration was based on the discretion of the evaluating physician and individualized for each patient. Patients undergoing medical abortion returning with persistent symptoms were also offered the option of repeat misoprostol. A previously published study with an overlapping data set demonstrated only 1.2% of women chose repeat misoprostol over aspiration.[19] Data were also collected on major adverse events occurring in the 8 weeks after the abortion. Major events included emergency department presentation, hospitalization, perforation, transfusion, and infection.

Statistical analyses were completed using SAS 9.3. For bivariate analyses, *P* values for comparing proportions were computed using Fisher's exact or the permutational χ^2 test. The *P* values for comparing continuous variables between the medical and surgical abortion groups were computed using *t* tests in cases in which the data followed a normal distribution and nonparametric Wilcoxon rank-sum test otherwise. Differences were regarded as statistically significant if $P<.05$. Multivariate logistic regression was used to determine associations of the simultaneous associates of age, race–ethnicity, income level, gravidity, parity, gestational age, and BMI with the risk of ongoing pregnancy. Because there were few ongoing pregnancy events, a simultaneous multivariate evaluation of all seven covariates was not possible so a bivariate screening was carried out using abortion type with each of the six covariates. Regression analyses were repeated with respect to the risk of unanticipated aspiration. A hierarchical, backward stepdown regression with a liberal $P<.10$ variable retention criterion was carried out using all seven potential predictors and the six two-way interactions with medical compared with surgical abortion. Restricted cubic splines were used to determine if the relation of age or BMI to the log odds was linear. Adjusted ongoing pregnancy risk and aspiration risk were computed using the logistic regression model to adjust for these covariates.

RESULTS

After a thorough review of medical records, a total of 30,146 women who met our inclusion criteria were identified with 13,221 undergoing medical abortion and 16,925 undergoing surgical abortion (Fig. 1). The groups had similar sociodemographic characteristics (Table 1). The mean age at abortion was 25.7 years (25.4 years and 25.9 years in the medical and surgical abortion groups, respectively). The mean gestational age at the time of abortion was nearly identical between the two groups (6.7 weeks compared with 6.9 weeks, respectively). Body mass index, gravidity, and parity were similar for both groups (Table 1).

Eighty-four percent of patients undergoing medical abortion received follow-up within 8 weeks for their initial visit (Fig. 1). Of 13,221 women undergoing medical abortion, 15.9% were lost to follow-up. Women who underwent surgical abortion only returned if they had persistent symptoms or postoperative concerns. Eighteen percent of these women returned for a follow-up visit. Women in the medical abortion group who did not return to the clinic within 8 weeks of their initial abortion procedure were considered lost to follow-up. Women who were lost to follow-up were considered to have undergone uncomplicated, complete abortions. Additional analyses showed no significant differences in demographic or clinical characteristics between patients undergoing medical abortion who followed up and those who did not.

There were a total of 79 ongoing pregnancies after the initial abortion procedure accounting for 0.2% of the total sample. There were 52 ongoing pregnancies in the medical abortion group for an efficacy of 99.6%. Surgical abortion was 99.8% effective with 27 ongoing pregnancies in this group (Table 2). Although the rate of ongoing pregnancy was low, women undergoing medical abortion had a four times higher risk of abortion failure than those undergoing surgical abortion (unadjusted odds ratio [OR] 4.0, 95% confidence interval [CI] 3.1–5.1) (Table 3). All ongoing pregnancies in the medical abortion group underwent aspiration. In the surgical abortion group, 22 of 27 women with ongoing pregnancies underwent repeat aspiration. Of the remaining five women, three opted to undergo medical abortion for ongoing pregnancy and two opted to continue their pregnancies. We attempted to assess the effect of clinical and demographic variables on efficacy. However, the rate of ongoing pregnancy was too low to simultaneously evaluate all eight clinical and demographic characteristics. Nevertheless, we found that abortion type and gestational age had a significant effect on efficacy. In the medical abortion group, the risk of ongoing pregnancy increased by 50% for each week of gestational age (adjusted OR 1.5, 95% CI 1.1–1.9) (Table 4). Conversely, the risk of ongoing pregnancy decreased by 60% with each week of gestational age among women undergoing surgical abortion (adjusted OR 0.4, 95% CI 0.3–0.5).

There were a total of 382 unanticipated aspirations, accounting for 1.3% of our sample. Of the

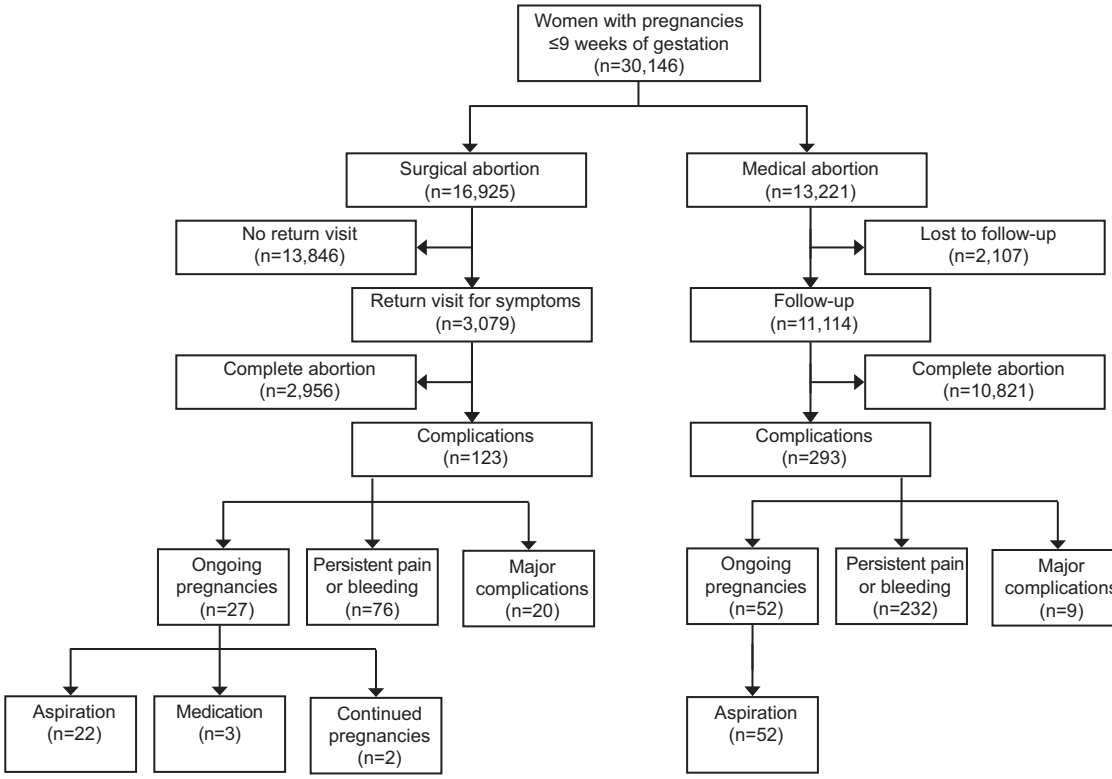

Fig. 1. Flowchart of patients undergoing medical or surgical abortion at 9 weeks of gestation or less.
Ireland. First-Trimester Medical vs. Surgical Abortion. Obstet Gynecol 2015.

13,221 women who underwent medical abortion, 2.2% underwent unanticipated aspiration. Of the 16,925 women who underwent surgical abortion, 0.6% underwent unanticipated aspiration (unadjusted OR 1.6, 95% CI 1.1–2.3) (Table 3). Persistent pain, bleeding, or both was the most common reason for an unanticipated aspiration. Among women seeking medical abortion, 1.8% underwent unanticipated aspiration for these reasons compared with 0.4% in the surgical abortion group ($P<.001$) (Table 5). A smaller proportion of aspirations occurred as a result of pregnancies ongoing after the initial procedure (0.4% medical abortion compared with 0.1% surgical abortion, $P<.001$). In the medical abortion group, four women requested surgical completion of abortion after initiation of the medication regimen.

In our regression analysis, only abortion type, patient age, and gestational age had a significant effect on a woman's risk of unanticipated aspiration (Table 4). In both the medical and surgical abortion groups, the risk of unanticipated aspiration increased by 3% with each year of patient age (adjusted OR 1.03, 95% CI 1.01–1.04). Gestational age had a more significant effect on the risk of unanticipated aspiration. With each advancing week of gestational age, this risk increased in the medical abortion group (adjusted OR 1.3, 95% CI 1.1–1.4) and decreased in the surgical abortion group (adjusted OR 0.7, 95% CI 0.6–0.8).

We reviewed chart data on major complications occurring in the 8 weeks after pregnancy termination. These complications included emergency department presentation, hospitalization, uterine perforation, infection, and hemorrhage requiring transfusion. Overall, 29 women, or 0.1% of the total sample, experienced one of these complications with no significant difference between treatment groups (OR 1.2, 95% CI 0.7–1.8) (Table 4). Frequency of any adverse events including unanticipated aspiration for persistent symptoms, ongoing pregnancies, and major complications was low at 1.9% of the total sample. This risk was higher in the medical abortion group than the surgical abortion group (OR 6.6, 95% CI 5.5–8.0).

DISCUSSION

Medical and surgical abortion at 9 weeks of gestation or less is similar in efficacy with success rates of greater than 99% in both groups. Although there is a statistically significant difference in the risk of

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Table 1. Characteristics of Women Undergoing Abortion at 9 Weeks of Gestation or Less

Characteristic	Total	Medical Abortion	Surgical Abortion
n (row %)	30,146	13,221 (44)	16,925 (56)
Age at abortion (y)	25.7±6.0	25.4±5.8	25.9±6.2
Race–ethnicity			
Latina	14,851 (49)	6,735 (51)	8,116 (48)
White	5,491 (18)	2,604 (20)	2,887 (17)
Black	4,423 (15)	1,433 (11)	2,990 (18)
Asian	2,060 (7)	982 (7)	1,078 (6)
Native American	106 (<1)	55 (<1)	51 (<1)
Other	3,215 (11)	1,412 (11)	1,803 (11)
Income (% FPL)			
0–100	22,930 (76)	9,902 (75)	13,038 (77)
101–200	4,695 (16)	2,115 (16)	2,580 (15)
201–300	1,307 (4)	617 (5)	690 (4)
Greater than 300	1,208 (4)	584 (4)	624 (4)
BMI (kg/m^2)	25.8±5.8	25.7±5.9	25.9±5.7
Gestational age at abortion (wk)	6.8±1.2	6.7±1.2	6.9±1.2
Gravidity	2.0 (1–27)	2.0 (1–18)	2.0 (1–27)
Parity	1.0 (0–9)	1.0 (0–9)	1.0 (0–9)

FPL, federal poverty level; BMI, body mass index.
Data are n (%), mean±standard deviation, or median (range).

unanticipated aspiration between the two methods of pregnancy termination, this risk is overall low in both groups. There is no difference in the risk of major complications between medical and surgical abortion at this gestational age with a rate of 0.1% for both groups (P=.19).

Table 2. Characteristics of Women With Ongoing Pregnancy After an Initial Abortion Procedure

Characteristic	Medical Abortion	Surgical Abortion	*P*
n (row %)	52 (0.4)	27 (0.2)	<.001
Age at abortion (y)	25.9±5.8	25.0±5.4	.57
Race–ethnicity			.81
Latina	21 (40.4)	12 (44.5)	
White	12 (23.1)	5 (18.5)	
Black	5 (9.6)	4 (14.8)	
Asian	4 (7.7)	3 (11.1)	
Native American	0	0	
Other	10 (19.2)	3 (11.1)	
Income (% FPL)			.54
0–100	39 (79.5)	20 (74.1)	
101–200	4 (8.2)	5 (18.5)	
201–300	2 (4.1)	1 (3.7)	
Greater than 300	4 (8.2)	1 (3.7)	
BMI (kg/m^2)	24.7±5.9	25.6±6.4	.69
Gestational age at abortion (wk)	7.2±1.4	5.1±1.1	<.001
Gravidity	2.0 (1–10)	2.0 (1–5)	.74
Parity	0.5 (0–5)	0 (0–4)	.64

FPL, federal poverty level; BMI, body mass index.
Data are n (%), mean±standard deviation, or median (range).

There are few comparative studies of medical and surgical abortion in the first trimester. One retrospective cohort study of 932 women comparing medical and surgical abortion found completion rates of 90.2% and 94.5%, respectively.[20] Higher completion rates of 96.5% for medical abortion and 99.9% for surgical abortion[21] were found in a prospective cohort study of 2,550 women seeking early abortion in family medicine clinics. The remaining comparative studies utilize outdated regimens for medication abortion or surgical techniques that are not generalizable to women currently seeking early pregnancy termination.

One of the greatest strengths of this study is a robust and diverse sample of urban women from 15 Planned Parenthood, Los Angeles, affiliate clinics. The surgical and medical abortion protocol is uniform throughout each site, thus minimizing potential bias from variation in abortion provision. Planned Parenthood's electronic medical record and practice management system provides a reliable and validated way to track patients served within the system. Internal quality assurance studies are routinely performed to maintain integrity of the data. This standardized method of data entry and documentation was critical to minimize information bias.

There are several limitations to this study. Women were not randomized to abortion type. Therefore, selection bias may explain some of the variation in efficacy and complications between the two cohorts. Sixteen percent of the medical abortion group failed to follow-up in the clinic to confirm completion of abortion. This may have resulted in an overestimate of efficacy and underestimate of complications related to medical abortion. Additionally, although we sought to identify the effect of BMI, gravidity, and parity on efficacy, the frequency of ongoing pregnancy in our sample was too low to define these relationships.

Given Planned Parenthood, Los Angeles' uniform and comprehensive reporting system, we are confident that we successfully captured all of the abortion failures and complications in women who return to us for care. It is a limitation of our study, however, that we cannot capture complications that occurred in patients who sought follow-up at other health care facilities. However, because most patients who obtained abortions at Planned Parenthood, Los Angeles, would have had to pay for follow-up medical care delivered outside of the system, but not within the system, patients were financially incentivized to return to our

Table 3. Complications in Women Undergoing Abortion at 9 Weeks of Gestation or Less

Outcome	Rate/1,000 Pregnancies (95% Confidence Bounds)			Unadjusted OR (95% CI)	
	Total	Medical Abortion	Surgical Abortion	Medical or Surgical Abortion	*P*
n	30,146	13,221	16,925		
Ongoing pregnancy	2.6 (2.1–3.3)	3.9 (2.9–5.2)	1.6 (1.1–2.3)	4.0 (3.1–5.1)	<.001
Unanticipated aspiration	12.7 (11.4–14.0)	21.5 (19.0–24.1)	5.8 (4.7–7.1)	1.6 (1.1–2.3)	<.001
Persistent pain, bleeding, or both	10.2 (9.1–11.4)	17.6 (15.4–20.0)	4.5 (3.5–5.6)	5.8 (4.7–7.1)	<.001
Major complication*	1.0 (0.6–1.4)	0.7 (0–1.3)	1.2 (0.7–1.8)	1.2 (0.7–1.8)	.192
Any adverse event	13.2 (11.9–14.5)	21.6 (19.1–24.2)	6.6 (5.5–8.0)	6.6 (5.5–8.0)	<.001

OR, odds ratio; CI, confidence interval.
* Major complication includes emergency department presentation, hospitalization, infection, perforation, and hemorrhage requiring transfusion.

institution for care. Furthermore, Upadhyay et al[22] recently evaluated outcomes for all Medicaid-funded abortions in California in 2011 by examining billing codes for the abortion procedure as well as any complications treated at any institution in the 6 weeks after pregnancy termination. They identified a rate of ongoing pregnancy in patients undergoing medical abortion of 0.13% and 0.04% in patients undergoing first-trimester surgical abortion. These numbers are comparable to our present findings.

In conclusion, our findings on efficacy and complication rate of first-trimester medical and surgical abortion are consistent with prior findings.[8,9] Efficacy was greater than 99% in both groups. In the medical abortion group, efficacy decreased with gestational age, corresponding to previously published literature.[19] Efficacy increased with advancing gestational ages in the surgical abortion cohort, likely related to earlier gestations being smaller and easier to miss during an aspiration procedure. The rate of serious complications was 0.1% in each group. In this study, we evaluated a third, and perhaps the most common, adverse event: unanticipated aspiration. A repeat or unanticipated aspiration is a safe and readily available procedure to manage persistent postabortal symptoms or ongoing pregnancy. However, this adverse event comes with increased cost, patient time, discomfort and inconvenience, and clinician time. Although an infrequent event in either group, we did find the risk of unanticipated aspiration to be more than three times higher in the medical abortion group.

Overall, the efficacy of medical and surgical abortion at 9 weeks of gestation or less is extremely high and complications are infrequent. Provided they are appropriate candidates for either method, they should be counseled on both medical and surgical options when seeking pregnancy termination.

Table 4. Logistic Regression Model

Variable	Adjusted OR (95% CI)	*P*
Predictors of ongoing pregnancy		
Medical abortion vs surgical abortion*	4.5 (2.3–8.6)	<.001
Gestational age (/wk)†		
Medical abortion	1.5 (1.1–1.9)	.003
Surgical abortion	0.4 (0.3–0.5)	<.001
Predictors of unanticipated aspiration		
Medical abortion vs surgical abortion*	3.9 (3.1–5.0)	<.001
Patient age (/y)‡	1.03 (1.01–1.04)	.002
Gestational age (/wk)		
Medical abortion	1.3 (1.1–1.4)	<.001
Surgical abortion	0.7 (0.6–0.8)	<.001

OR, odds ratio; CI, confidence interval.
* At average gestational age of 6.8 weeks.
† At average patient age of 25.7 years.
‡ Effect of patient age on unanticipated aspiration was the same for both medical and surgical abortion.

Table 5. Reasons for Unanticipated Aspiration in Women Who Underwent Abortion at 9 Weeks of Gestation or Less

Aspiration	Medical Abortion	Surgical Abortion	*P*
n (%)	13,221 (43.9)	16,925 (56.1)	
Aspiration for ongoing pregnancy	52 (0.4)	22 (0.1)	<.001
Aspiration for persistent pain, bleeding, or both*	232 (1.8)	76 (0.4)	<.001
All aspirations	284 (2.1)	98 (0.6)	<.001

* Aspiration for persistent pain, bleeding, or both in the presence of ultrasound findings concerning for retained products of conception or intrauterine debris.

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EXHIBIT B-3

APPENDIX TO PETITIONER GENBIOPRO, INC.'S CITIZEN PETITION DATED JULY 3, 2025[1]

Source	Appendix Starting Page
Appendix Volume I	
108 Cong. Rec. 17366 (Aug. 23, 1962)	GBP-PET00001
Aiken, Abigail R.A. et al., *Safety and Effectiveness of Self-Managed Medication Abortion Provided Using Online Telemedicine in the United States: A Population Based Study*, 10 Lancet Reg'l Health – Ams. 1 (2022), https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(22)00017-5/fulltext	GBP-PET00010
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[1] This Appendix includes all documents cited in the accompanying July 3, 2025 Citizen Petition with the exception of certain documents not required by 21 C.F.R. § 10.20(c). Volumes I, II, III, IV, V, and IX contain copyright restricted materials.

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The efficacy, safety and acceptability of medical termination of pregnancy provided by standard care by doctors or by nurse-midwives: a randomised controlled equivalence trial

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Objective To assess nurse-midwife provision of early medical termination of pregnancy (TOP) in a high-resource setting where ultrasound examination for dating of pregnancy is part of the protocol.

Design Randomised controlled equivalence trial.

Setting Out-patient family planning unit at a university hospital.

Population Women seeking early medical TOP.

Methods A total of 1180 women were randomised, without any prior examination, to counselling, examination, and treatment by either nurse-midwife or gynaecologist. Ultrasound was performed in all cases by the allocated provider.

Main outcome measures The primary outcome was efficacy, defined as the successful completion of TOP without need for vacuum aspiration. Secondary outcomes were safety, defined as need for hospitalisation or blood transfusion, and acceptability, defined as preferred provider were the women to have a medical TOP in the future.

Results A total of 481 women in the nurse-midwife group and 457 women in the doctor group were available for the final analysis. The effectiveness of provision of medical TOP by nurse-midwife providers was superior to that provided by doctors (risk difference 1.6%, 95% confidence interval 0.2–3.0%, which was within the set margin of equivalence). There were no significant differences in safety parameters. Women examined and counselled by a nurse-midwife were significantly more likely ($P < 0.001$, 95% confidence interval 0.308–0.394) to prefer seeing a nurse-midwife for the consultation were they to have another medical TOP in the future.

Conclusions These findings show that nurse-midwife provision of early medical TOP in a high-resource setting, where ultrasound is part of the protocol, is effective, and can be safely implemented with high acceptability among women.

Keywords Abortion, medical abortion, midlevel provision.

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Introduction

According to the World Health Organization (WHO) and the Guttmacher Institute, approximately 47 000 women die every year as a result of unsafe termination of pregnancy (TOP). Almost all these deaths occur in developing countries where access to safe TOP services is limited.[1] In addition to legal limitations, access to providers may be a limiting factor in gaining access to safe TOP. Task shifting is defined as a process of delegating appropriate tasks from doctors to specialised providers, and has been found to increase productivity within healthcare systems.[2] Studies from Africa show that the training of specialised non-doctor healthcare providers to perform tasks traditionally

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reserved for doctors can help build sustainable, cost effective, and equitable healthcare services in both maternal healthcare and post-TOP services.[3–5] In developing countries TOP services may or may not include pregnancy tests and/or ultrasound examination. Midlevel provision of medical TOP in Nepal, where ultrasound is not routine, has recently been shown to be effective and acceptable.[6] The midlevel provision of surgical TOP has been shown to be equally safe and effective as that performed by doctors.[7]

In high-resource settings where TOP is legal it is generally a safe procedure; however, access to TOP may be limited by the scarcity of doctors willing to perform TOPs. In the USA, midlevel provision of medical TOP is becoming increasingly common. A wide variety of healthcare provider categories are involved in this care.[8] The physical and pelvic examination before a TOP is traditionally performed by a doctor, and an ultrasound for dating of pregnancy is usually part of the protocol. Also, increased access to induced TOP in high-resource settings could thus be achieved by task sharing/shifting in TOP care.

The primary objective of this trial was to show that nurse-midwives can provide early medical TOP as effectively as doctors in a high-resource setting where TOP services are provided by doctors and ultrasound dating of pregnancy is part of the protocol. To show this the trial was designed as a randomised equivalence trial. Secondary objectives were to assess the safety and acceptability of nurse-midwife provision of medical TOP.

We could show that task shifting in medical TOP in high-resource settings, where vaginal ultrasound dating of pregnancy is part of the protocol, is highly effective. The results will be important for healthcare systems and the provision of safe TOP in many settings.

Methods

In Sweden, TOP is legal upon request by the woman up to 18 weeks and 0 days of gestation, and must be performed by a doctor. Permission was granted by the National Board of Health and Welfare and by the Ethical Review Board of Stockholm to allow midwives to independently provide medical TOP according to the study protocol. Nurse-midwives in Sweden may prescribe doxycycline for *Chlamydia trachomatis* infection but not antibiotics for bacterial vaginosis.

The study was registered at Clincaltrials.gov, NCT01612923, and followed the modified CONSORT (Consolidated Standards of Reporting Trials) reporting guidelines for equivalence trials.

The trial was conducted at the out-patient family planning clinic of the Karolinska University Hospital, Sweden. Women made an appointment by calling the clinic by telephone, and were informed about the study at that time and asked if they would be willing to participate. If they were healthy, had a pregnancy of 63 days or less according to their last menstrual period, and wanted a medical TOP they were further informed of the study at the first visit to the clinic. Women were eligible to participate if they were 18 years or older, had no contraindication for medical TOP, and were in good general health with no continuing medication for chronic disease. If the women were eligible after interviewing and accepted participation they signed informed consent before they were randomised and prior to any examination had been performed. Women were allocated to the nurse-midwife arm or to the standard-care arm. In the nurse-midwife arm the examination, including the ultrasound dating of pregnancy and contraceptive counselling, was performed by the nurse-midwife. In the standard-care arm the examination, including the ultrasound dating of pregnancy and contraceptive counselling, was performed by a doctor, and further information and dispensation of medication was performed by a nurse-midwife. The gestational length was determined by measurement of gestational sac diameter or crown–rump length of the fetus, in all cases. The ultrasound was performed by the allocated provider. All women were screened for *Chlamydia trachomatis* and bacterial vaginosis according to Swedish clinical practice.

Women were excluded from both groups after examination if the ultrasound showed predefined exclusion criteria, such as a gestational length of over 63 days, evidence of pathological pregnancy, or an adnexal mass.

Two nurse-midwives experienced in medical TOP and contraceptive counselling received theoretical and practical training in vaginal ultrasound examination of early pregnancy. These nurse midwives were the sole providers in the nurse-midwife arm. There were a total of 34 doctors in the standard-care arm, reflecting the number of doctors involved in TOP care in the clinic. These doctors had varying training and experience. Some had only a few months of training, whereas others were senior consultants with long experience. The recruitment for the study began on 28 February 2011 and ended on 25 July 2012.

Randomisation was achieved through the consecutive opening of numbered opaque and sealed envelopes containing a computer-generated randomisation allocation code, in blocks of ten women, at a ratio of 1 : 1. The study was not blinded.

A woman randomised to the nurse-midwife group (intervention) was examined, counselled, informed, and treated by one single nurse-midwife. Women allocated to the standard-care group (control) were examined and counselled by a doctor, and then received additional information about the practical details and medication from a nurse-midwife, according to clinical routine. Participating nurse-midwives did not perform any regular nurse-midwife

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tasks during the study period, to avoid possible bias. Medical TOP was performed according to the WHO recommended protocol, and did not differ between the groups.

All women received mifepristone 200 mg (Mifegyne®; Nordic Drugs, Limhamn, Sweden) given in the clinic according to Swedish law. The women had a free choice to administer 800 μg of misoprostol (Cytotec®; Pfizer, Sollentuna, Sweden) vaginally at home or in the clinic 24–48 hours after mifepristone administration. If no bleeding occurred within 3 hours, women were instructed to take an additional dose of 400 μg of misoprostol orally.[9] Women were advised to take prophylactic pain treatment consisting of acetaminophen (paracetamol) 1 g (Alvedon®; Astra Zeneca, Södertälje, Sweden) and Diclofenac 100 mg (Voltaren®; Novartis, Täby, Sweden) at the time of vaginal misoprostol administration.

Contraceptive counselling and prescription was performed by a nurse-midwife or by a doctor, according to allocation. Follow-up in all cases was by low-sensitivity urinary human chorionic gonadotropin (hcg) test (cut-off 500 iu/ml; ANL-produkter AB, Alvsjo, Sweden), performed by a nurse-midwife not involved in the study, according to clinical routine, after approximately 3 weeks. Two attempts to contact women were made if women did not attend for follow-up, after which they were considered lost to follow-up.

If the urinary hCG test was positive, a serum hCG test was performed and the patient was referred for evaluation with vaginal ultrasound to rule out continuing pregnancy. The primary outcome measure was efficacy, assessed through the successful completion of TOP without the need for vacuum aspiration. Secondary outcome measures were safety, defined as the need for hospitalisation or blood transfusion, and acceptability of the procedure. The efficacy and safety were assessed by self-administered questionnaires and electronic patient records, which were completed after the initial examination and counselling, and also at the follow-up visit. Records were also checked if the patient was lost to follow-up. Complication was defined as the need for causal treatment at an unscheduled visit up to 6 weeks after the TOP, such as treatment with misoprostol, antibiotics, or treatment for anaemia. Acceptability was assessed in self-adminstered questionnaires by women stating whether they would prefer standard treatment by a gynaecologist or a nurse-midwife were they ever to have another medical TOP.[10,11]

In addition, the need for a second opinion from a doctor for nurse-midwives, or from another doctor in the case of the standard-care arm, and the reasons for this were recorded. Second-opinion consultations were performed immediately by other doctors in the clinic to avoid any delay of the TOP. The contraceptive method prior to the TOP and the prescribed method intended to start after the TOP were reported, as well as the actual method started (e.g. intrauterine contraception/implants inserted).

This study was designed as a two-sided equivalence trial with the overall efficacy of medical TOP assumed to be 95% in both groups. A clinically significant margin of equivalence was set to 5% based on what was believed to be of clinical importance to the patients. To demonstrate two-sided equivalence within a margin of 5%, with 80% power, and a confidence interval of 95% ($\alpha = 0.05$), 400 women in each group would be sufficient. To compensate for loss to follow-up and patients not completing the medical TOP, 1180 patients were randomised. All statistical calculations except the generalised estimating equation were made using SPSS 20 (IBM Corporation, Somers, NY, USA). For comparison of groups with regard to skewed data the Mann–Whitney *U*–test was used. For variables with a normal distribution the Student's *t*–test was used. For categorical variables, comparison between groups were made using the chi-square test. The equivalence between nurse-midwife providers and doctors was assessed using a generalised estimating equation. The generalised estimating equation allows for treatment as a fixed factor and provider as a random factor, and thereby enables adjustment for the difference in providers' enthusiasm and competence. This analysis was performed in the PROC GENMOD procedure of SAS 9.3 (SAS Institute, Gary, NC, USA).[12] In addition, the risk ratio (risk of failure in the standard group divided by risk of failure in the nurse-midwife group) for the primary outcome was added. Results were regarded as statistically significant for $P < 0.05$. Analysis was per protocol, according to recommendation, and followed the CONSORT guidelines for equivalence trials.[13]

Results

A total of 1180 women were randomised, with no prior physical examination, to examination and counselling by a nurse-midwife ($n = 597$) or by a doctor ($n = 583$). A total of 105 women in both groups were excluded after examination but prior to mifepristone intake, for predefined reasons, with the numbers and reasons not differing between the groups (Table S1). Seven women in the standard-care group did not receive the allocated treatment because of sudden illness of the allocated provider. Unfortunately, these women were not followed-up and no results are available. Thus, 1068 women received and completed the allocated intervention. In the nurse-midwife group 54 women were lost to follow–up, compared with 76 women in the standard-care group (130 women in total, $P = 0.038$). The flow of patients is presented in Figure 1. Analysis was performed per protocol. There were no significant demographical differences between the groups (Table 1).

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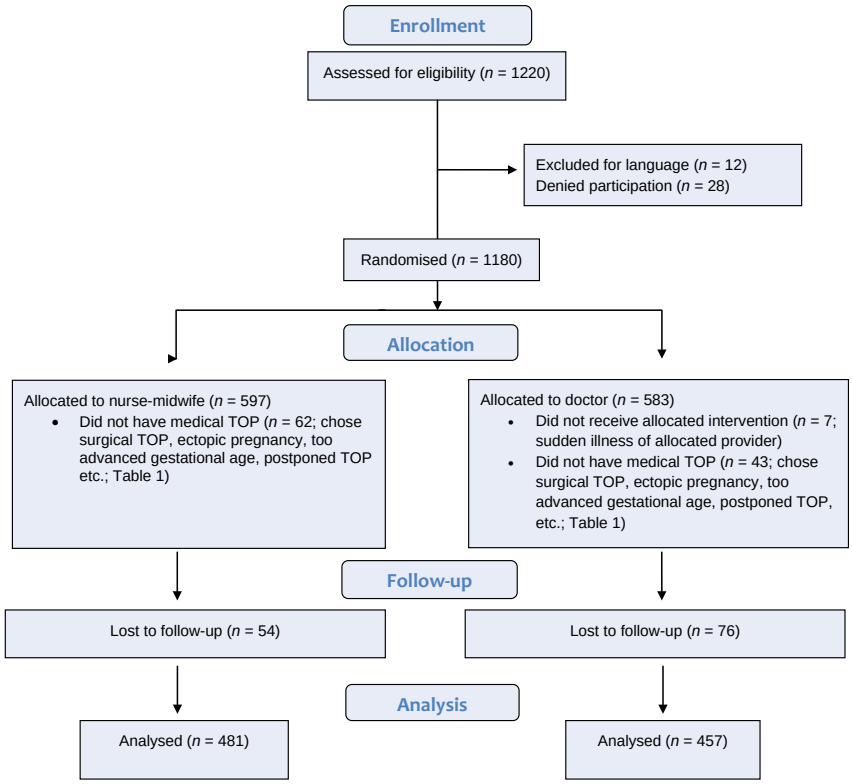

Figure 1. Consort flow chart.

Table 1. Demographic characteristics of women

	Allocated to nurse-midwife *n* = 535 Median (range)	Allocated to doctor *n* = 533 Median (range)
Age	27 (18–47)	27 (18–46)
Gestational age at ultrasound (days)	45 (30–63)	45 (28–63)
Gravidity	2 (0–13)	2 (0–14)
Parity	0 (0–5)	0 (0–6)
Miscarriage	0 (0–4)	0 (0–5)
TOP, surgical	0 (0–3)	0 (0–5)
TOP, medical	0 (0–4)	0 (0–5)
Vaginal deliveries	0 (0–5)	0 (0–6)
Caesarian section	0 (0–3)	0 (0–3)

There were no statistically significant differences between the groups.

An overview of primary and secondary outcome measures is given in Table 2. Reasons for surgery are given in Table S2. The risk difference for efficacy was 1.6%, with a 95% confidence interval (95% CI) of 0.2–3.0% ($P = 0.027$). Although the trial was designed to show equivalence, the results show superiority for the nurse-midwife group, with a risk ratio for the primary outcome of 2.5 (95% CI 1.4–4.3) for the doctor group.

The overall complication rate was 4.1% for the women randomised to a nurse-midwife (20/493, 41 missing), and 6.1% for women randomised to a doctor (29/472, 61 missing, 95% CI −0.7 to 5%, $P = 0.14$). Reasons for complications are given in Table S3. There were no serious complications and no blood transfusions were given.

The percentage of unscheduled visits was 9% among women randomised to nurse-midwives (44/489, 45 missing), and 9.7% for women randomised to doctors (46/473, 60 missing, 95% CI −3 to 4.5%, $P = 0.7$). One patient had a continuing pregnancy at an unscheduled visit. She was successfully treated with a repeat medical TOP, according to her choice.

No significant differences existed between the groups in satisfaction with information, contraceptive counselling, feeling of calm and safety before, during, or after the TOP, with high satisfaction rates above 92% for all variables in both groups. There were no significant differences in perceived bleeding or worse pain experience on day of expulsion, or in the experience of the procedure, as compared with expectation (data not shown).

Women randomised to doctors were significantly more likely to choose home administration of misoprostol (310/

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Table 2. Overview of primary and secondary outcome measures

Outcome measure	Allocated to nurse-midwife (%)	Allocated to doctor (%)	Total (%)	95% CI
Efficacy	476/481 (99)	445/457 (97.4)	923/940 (98.2)	−0.002 to 0.036
Safety	453/473 (95.8)	414/443 (93.5)	867/916 (94.7)	−0.006 to 0.054
Acceptability	200/535 (37.4)	12/533 (2.3)	212/1068 (19.9)	0.308–0.394

Efficacy defined as no need for surgical intervention, safety defined as no complication, and acceptability defined as women preferring their allocated provider.

Table 3. Reason for second opinion consultation

Reason for consultation	Allocated to nurse-midwife *n* (%)	Allocated to doctor *n* (%)	Total *n* (%)
Multiple pregnancy	7 (1.3)	1 (0.2)	8 (0.7)
High serum hCG*	0 (0)	1 (0.2)	1 (0.9)
Information	3 (0.6)	1 (0.2)	4 (0.4)
Medical reasons	13 (2.4)	4 (0.8)	17 (1.6)
Ultrasound	59 (11)	8 (1.5)	67 (6.3)
Unknown	3 (0.6)	4 (0.8)	7 (0.7)
Prescription/second opinion for suspected bacterial vaginosis	54 (10)	4 (0.8)	58 (5.4)
Total	535	533	1068

*hCG, human chorionic gonadotropin.

Table 4. Preference in case of future TOP

Future preference	Allocated to nurse-midwife (%) (*n* = 534)	Allocated to physician (%) (*n* = 533)	95% CI	*P*
Midwife	200 (37.5)	108 (20.3)	0.118–0.225	<0.001
Physician	5 (0.9)	12 (2.3)	−0.003 to 0.030	0.06
Indifferent	271 (50.7)	320 (60)	0.033–0.152	<0.001
Missing	58 (10.9)	93 (17.4)	0.024–0.108	0.002

533) compared with women randomised to nurse-midwives (266/535, 95% CI 2.5–14.3%, $P = 0.006$).

Doctors needed a second opinion in 4% of cases (21/533) compared with 26% of cases (139/535) for nurse-midwives (95% CI 18–26%, $P < 0.001$); however, the frequency of ultrasound consultations for nurse-midwives went down as the study progressed, indicating a learning curve. Reasons for consultations are given in Table 3. The women allocated to nurse-midwives spent significantly shorter time in the family planning unit during the first visit (mean 42 minutes, SD 18.3 minutes), compared with the doctor group (mean 60 minutes, SD 24.1 minutes, $P < 0.001$). Women randomised to nurse-midwives were significantly more likely (95% CI 11.8–22.5%, $P < 0.001$) to prefer seeing a nurse-midwife again were they to have another TOP, although the majority were indifferent (Table 4). Patients randomised to nurse-midwives were more likely (200/535 women, 37.4%) to prefer their allocated provider than women randomised to doctors (12/533 women, 2.3%, 95% CI 30.8–39.4%, $P < 0.0001$).

Women who were examined and counselled by nurse-midwives had long-acting reversible contraceptives (LARCs) inserted within 3 weeks of the TOP (intrauterine contraception and implant, 290/532, three missing), significantly more often than women examined and counselled by doctors (241/528, five missing, 95% CI 3.2–15.2%, $P = 0.004$).

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Discussion

Main findings

In this equivalence trial we showed the superior efficacy of nurse-midwife provision of early medical TOP in healthy women, when compared with standard doctor provision, in a setting where vaginal ultrasound examination for the dating of pregnancy is part of the protocol. We also found that nurse-midwives were significantly more likely to prescribe LARCs as post-TOP contraception.

Strengths and limitations

One strength of this study is that women were randomised after standard telephone screening without any prior examination. An additional strength is that the results can be generalised to high-resource settings, as ultrasound dating of the pregnancy was part of the protocol to confirm gestational length. Furthermore, women were able to choose home administration of misoprostol. To help women avoid another unwanted pregnancy, the provision of post-TOP contraception is crucial. The LARCs (intrauterine contraception and implants) have been shown to decrease the rate of repeat TOPs.[14] Therefore, the prescribed contraceptive method was studied.

This study also has limitations. As this is the first study on task shifting to the midlevel provision of induced TOP, including ultrasound dating of pregnancy, we limited participation to healthy women. The study was not blinded. It is possible that acceptability was influenced by the involvement of highly motivated nurse-midwives, but blinding of the provider did not seem feasible. The deeper involvement in family planning may also have influenced these midwives to prescribe more LARCs to women, compared with the doctors who only performed TOP as part of their training or rotations. The results our study also show that at follow–up, a larger proportion of women in the nurse-midwife group had returned to the clinic to have the LARCs inserted. The rate of patients lost to follow-up is comparable with a recent study from Scotland,[15] and is comparable with most studies in TOP practice.

Interpretation

Previous studies have shown that task shifting has a place in caesarean section provision, and in the provision of surgical TOP;[3,4,7] however, task shifting has so far been limited to low-resource settings. A recent study from Nepal investigated the midlevel provision of medical TOP;[6] however, in the Nepal study randomisation was undertaken after bimanual pelvic examination to estimate uterine size. Thus, women were already examined before the randomisation. It is well known that midlevel providers can provide the TOP drugs and the counselling. In our present study, women were self-referred and randomised before any part of the consultation had been performed. Furthermore, vaginal ultrasound dating of pregnancy was part of the routine protocol. This is another important difference to the study from Nepal, in which ultrasound examination for dating of pregnancy was not part of the protocol.[6] It is well documented that medical TOPs can be performed without any ultrasound examination;[16–18] however, ultrasound dating of the pregnancy is part of the protocol in many high-resource settings, and the results of the Nepal study may therefore not be applicable. In contrast to other studies on task shifting in TOP care, we also studied the provision of post-TOP contraception. The equivalence trial model was purposely chosen instead of the approach of inferiority trial, as midlevel provision of medical TOP may have profound advantages for women, such as being able to access TOP services where there are none available today, and shorter waiting periods to receive an appointment. A lower efficacy could therefore be tolerated; however, the study showed superiority for the nurse-midwife group.

This study showed that although a majority of patients were indifferent to the provider being a nurse-midwife or doctor, the women who expressed a preference preferred nurse-midwives to a larger extent in both randomisation groups. A possible explanation of this result may be that an uncomplicated TOP is not necessarily viewed as a medical condition that warrants the attention of a doctor. It is likely therefore that women prefer a nurse-midwife to a doctor for the examination and counselling; however, nurse-midwives do not prescribe contraceptives to women with intercurrent disease, and nor do they oversee complicated pregnancies or deliveries. In this study, women with complications or women who made unscheduled visits for fear of complications were therefore examined by doctors. The doctor on call also performed any necessary surgery. Women in the nurse-midwife group received significantly shorter consultations, but this did not reflect in lower satisfaction rates among women concerning the information received. In the nurse-midwife group the nurse-midwife was the sole provider of information and also handed out all medication. It may be that the group allocated to standard care received duplicate information or had waiting times between seeing the nurse-midwife and the doctor. More women allocated to doctors chose home administration of misoprostol, which may have impacted on the time allocated for counselling. Decreasing the time patients spend in the family planning clinic must be seen as something that is beneficial to the patient and to the healthcare system. As midwives have lower salaries than doctors, the results also have economic implications.

Conclusion

This study shows that task shifting in medical TOP in high-resource settings, where vaginal ultrasound dating of

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pregnancy is part of the protocol, is highly effective. In addition, nurse-midwives spent shorter time on the consultation, which has potential economic impact on the healthcare system. Furthermore, women examined and counselled by nurse-midwives received LARCs to a greater extent than women examined and counselled by doctors. This may have an impact on repeat TOP rates. Task shifting in medical TOP may therefore have a positive impact on TOP care in low- as well as in high-resource settings. The increased involvement and responsibilities of nurse-midwives in medical TOP should be encouraged. Further studies should include an exentended gestational range.

Disclosure of interests

All authors declare that they have no conflicts of interest to report.

Contribution to authorship

The study was initiated by KGD, who had overall responsibility for the study. KGD, LM, RG, ES, and MJ were responsible for the project plan and planning, and KGD and LM were responsible for the training programme. HKK and KGD were responsible for conducting the study, the database design, analysis, and writing of the article. All authors assisted with writing the article.

Details of ethics approval

Permission was granted by the National Board of Health and Welfare and by the Ethical Review Board of Stockholm (permission number 2010/1828-31/3, 23 December 2010) to allow midwives to independently provide medical TOP, according to the study protocol. The study protocol was submitted with the ethics application on 11 November 2010, and was approved on 23 December 2010. Patient recruitment started in April 2011. No amendments were made to the protocol following ethics approval. Once approved by the regional ethics committee at Karolinska Institutet, all applications are publicly available. In addition, the protocol was also made available prior to and at a meeting convened by the WHO, Geneva, which was a consultation on the midlevel provision of medical abortion, with relevant material being circulated and shared before beginning the recruitment of patients for the trial. The trial was also registered at ClinicalTrials.gov after starting the study, but before recruitment had been completed (NCT01612923).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Reasons for not completing treatment.

Table S2. Reasons for surgery.

Table S3. Reason for complication, defined as an unscheduled visit for symptoms that led to further treatment. ■

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Time to streamline access to termination of pregnancy

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Unplanned and unwanted pregnancy is one of the major problems facing women worldwide. Although some may wish to continue unintended pregnancy, many will choose a termination of pregnancy (TOP). Most authorities now accept that access to safe TOP is a prerequisite for reproductive health (WHO 2007). Modern methods of TOP are extremely safe and effective, particularly in the first few weeks of pregnancy.

The major problem in providing safe TOP is not the method but its availability. As predicted in early publications, the simplicity of medical TOP provides the opportunity for widening the provision by using relatively unskilled health care workers (Rodger & Baird *Lancet* 1987;ii:1415–8). Several studies have reported that in low income countries, suitably trained mid-level providers (MLP) can provide safe and efficient TOP using both medical and surgical methods (Renner et al. *BJOG* 2013;120:23–31). This issue of BJOG reports the results of an RCT that examines the facilities necessary to deliver safe medical TOP in a high income country – Sweden (Gemzell et al. *BJOG* 2014;122:511–8). Women were randomised to care by either a team of doctors and nurses (standard service) or a team of trained midwives/nurses (MLP). Both groups achieved over 95% complete TOP with few complications. There was some evidence that women in the MLP arm were more satisfied with their experience and had a higher uptake of contraception. The authors suggest that this model could be more widely used in high income countries as a cost-effective service.

The suggestion of re-examining the 'skill mix' required for provision of medical services including TOP is topical and welcome, but the current trial leaves unanswered several questions about its general applicability. All women had a routine ultrasound to determine gestation. One asks how necessary this routine investigation is when safe TOP can be provided by assessing suitability on clinical grounds alone? (Warriner et al. *Lancet* 2012;377:1155–61). In the MLP arm, care was provided by one of two specially trained MLPs, compared with the standard arm with numerous doctors with variable levels of training. Furthermore, in the MLP arm, 26% of women were referred for a second opinion to a doctor, so clearly the MLP provision is limited to settings where both providers are readily available. While superficially it may appear cheaper for women to be seen by MLP, a rigorous examination of the cost-effectiveness of providing the service in different settings is needed before this model could be generally recommended.

In many countries, legal constraints severely limit access to safe TOP. Even in countries such as Sweden and the UK, the law requires TOP to be authorised by a registered medical practitioner and conducted in a hospital or registered premises. In the UK, repeated attempts to update the 1967 Abortion Act to accommodate developments in methods of TOP have failed. Only when there has been radical reform of the legal conditions surrounding TOP will it be possible to provide a safe and cost-effective service for unwanted pregnancy.

Disclosure of interests

I declare no conflicts of interest. ■

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4

Modern methods to induce abortion: Safety, efficacy and choice

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A B S T R A C T

Abortion care is a fundamental part of women's reproductive health care. Surgical and medical abortion methods are safe and effective throughout the gestational age range wherein abortions are performed. Although risks increase with the gestational age of the pregnancy being terminated, rates of complications remain low and comparable between surgical and medical techniques. A high-quality abortion service should offer women a choice between abortion methods and provide the one they prefer.

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Introduction

Abortion is a common event in women's reproductive lives, affecting approximately 25% of all pregnancies [1]. Globally, 56 million induced abortions are estimated to occur each year for a rate of 35 abortions per 1000 women aged 15–44 years [1]. Safe services to terminate a pregnancy are, therefore, an essential aspect of women's health care.

Induced abortion using modern methods is very safe [2]. The chance of a woman dying from an induced abortion, when performed by a trained clinician, is manyfold lower than dying from a pregnancy carried to term [3]. However, abortions performed by unskilled providers or in environments lacking minimal medical standards, have high rates of maternal death and injury [4,5]. The informal use of misoprostol, which has become widespread, has decreased risks historically associated with unsafe methods of abortion [6]. Ensuring the safe provision of abortion – whether by training in

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medical and surgical methods, securing the supply chain of quality medicines and equipment, or expanding access to services, is essential in reducing maternal morbidity and mortality worldwide.

Methods of induced abortion

Advances in abortion technologies now mean that either medical or surgical methods can be offered throughout a range of gestational ages of pregnancy. Surgical abortion methods include uterine aspiration, by manual or electric vacuum, and dilation and evacuation (D&E). Aspiration techniques are sufficient to evacuate the uterus up to about 14 weeks' gestation. As the pregnancy advances, safe removal of the increasing volume and density of tissue requires advanced cervical preparation, and the use of a combination of forceps and aspiration to remove the products of conception from the uterus through the cervix. D&E is used from 14 to approximately 24–26 weeks' gestation. Medical abortion relies on the use of medications: primarily a combination of mifepristone and misoprostol. This drug combination has been recommended in World Health Organization (WHO) guidance for safe abortion care since 2003 and included in the WHO Essential Medicines List since 2005. Where both drugs are available, they should be used in combination [2]. Misoprostol, mainly due to its various other non-obstetric and obstetric indications, is widely available; however, mifepristone, is not. Mifepristone is registered in only about 70 countries; where it is not available, misoprostol alone may be used to induce abortion.

In countries with reliable data, official statistics demonstrate that about half of all abortions are performed with medications [7]. The comparative proportions of surgical and medical methods vary by country [7]. In countries with few restrictions on abortion and with well-developed services, terminations occur early in pregnancy, at least 90% before 13 weeks' gestation [7]. In more restricted settings or in the immediate period after legal status changes, the proportion of women undergoing abortion at later gestations is greater [8–10].

Over the past 10 years, the proportion of abortions occurring at under 13 weeks' gestation, as well as those occurring under 9 weeks' gestation, and the proportion that are medically induced have all increased [7]. Trends of women seeking abortion care at earlier gestations have been documented in concert with the introduction and increasing popularity of medical abortion; whether this is a causal effect is unknown, but it is a positive one as the risk attributed to induced abortion is lower in earlier gestations [11]. Abortion-related mortality increases with gestational age from a rate of 0.1 per 100,000 procedures at 8 weeks gestation to 8.9 per 100,000 procedures at 21 weeks; thus, the earlier the abortion procedure takes place, the safer it is likely to be [12–14].

Safety and efficacy of surgical abortion techniques

Uterine aspiration is safer and less painful than the older technique of dilation and sharp curettage, and is therefore, the most widely recommended and utilized method of inducing abortion surgically in the first trimester [2,15]. There are two aspiration techniques: manual vacuum aspiration (MVA) and electric vacuum aspiration (EVA). In both, the uterus is evacuated using a rigid or flexible plastic cannula inserted through the cervix and attached to a vacuum source. During an MVA procedure, the vacuum is created by manually charging a 60 ml hand-held syringe (Fig. 1), whereas an electric pump creates an EVA's vacuum. The MVA procedure is quieter than an EVA, which is preferred by many women and may contribute to lower anxiety and pain levels [16]. Its low cost and portability make it more accessible, particularly to primary care or low-resource settings. The largest cannula that can be used with an MVA device is 12 mm. Thus, EVA is useful at higher gestational ages when larger cannulae are needed, and the sustained level of vacuum obviates the need to repeatedly empty a hand-held syringe.

A systematic review of 10 randomized controlled trials comparing MVA and EVA found no significant differences in efficacy as measured by the complete abortion rate, reported to be between 98 and 99% in both groups [15,17]. Less blood loss, albeit unlikely to be clinically significant, was reported among MVA patients under 50 days' gestation, as was less severe pain when compared with EVA. As gestational age increased, blood loss increased, and differences between the procedures in pain and blood loss disappeared. Procedure times averaged 5–6 min with either device; although EVA



Fig. 1. Manual vacuum aspirator.

procedures were statistically of shorter duration, the difference was about 30 seconds and unlikely to be clinically significant. Satisfaction with procedure and preference, as measured by electing to have the same procedure again if needed in the future, were similar between the two methods.

Major complications requiring an intervention or procedure, such as hemorrhage requiring transfusion, or uterine perforation or cervical laceration requiring repair occur in less than 0.1% of aspiration abortions, according to a recent systematic review of 57 studies [18]. In current practice, providers understand MVA and EVA are comparable in terms of efficacy and safety, and generally choose between them for reasons such as their preferences, characteristics of their facility, availability of supplies, and cost.

As the gestational age of pregnancy increases, surgical techniques require more than aspiration to remove the tissue. D&E primarily rely on the use of strong, elongated grasping forceps to remove the pregnancy (Fig. 2). The D&E technique requires the use of cervical priming agents, such as misoprostol over a period of hours, mifepristone over a day, or osmotic dilators over 1–2 days before the procedure [19]. By softening and opening the cervix, priming reduces the risk of cervical or uterine trauma and need for further mechanical dilation, and facilitates fetal extraction [13,20]. The amount of preparation required increases with gestational age and with certain patient characteristics, such as nulliparity and young age [19].

After cervical preparation is deemed adequate, and appropriate anesthesia or sedation is initiated, aspiration of the amniotic fluid is performed [20]. Following removal of the amniotic fluid, the uterus begins to contract, and forceps are used to remove the fetus in parts and the placenta. When all parts of the pregnancy are removed, a final aspiration is performed to ensure complete evacuation of the uterus, and hemostasis is achieved. Generally, the procedure takes 10–25 min, and after a short recovery, women return home the same day [21].

Safe provision of D&E requires advanced training and ongoing provision [2,20,22]. D&E is highly effective with minimal rates of complications, ranging from 0.05 to 4%, reported in various studies [13,20,22–26]. D&E is almost always effective; in rare cases additional time or agents for cervical preparation or mechanical dilation is needed to facilitate the procedure. The most common complications remain rare; hemorrhage, requiring transfusion occurs in approximately 0–1% of cases [26–28]. Infection occurs uncommonly following surgical abortion with routine prophylactic antibiotics, which are recommended by organizations, such as the American College of Obstetricians and Gynecologists, the Royal College of Obstetrics and Gynaecology, and the WHO, and ranges from 0 to 2% of cases [29]. When cervical preparation is undertaken, the complication of cervical laceration is low, and ranges from 0.02 to 3.3% [24,27]. Risk of cervical laceration, as in the first trimester, is increased with need for mechanical dilation, nulliparity, advanced gestation, and provider inexperience [23]. Uterine perforation occurs more commonly than in first trimester procedures, approximately in 0.2–0.8% of cases [27,30].

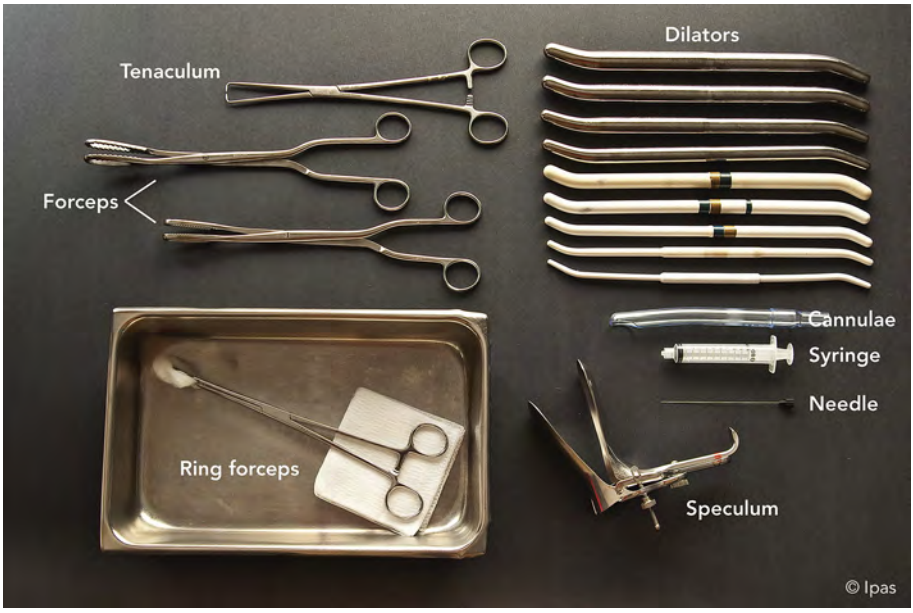

Fig. 2. Dilation and evacuation equipment.

Safety and efficacy of medical abortion techniques

Medical abortion, as for the surgical techniques, may be used at any gestational age [2]. The most effective regimen utilizes a combination of mifepristone, a progesterone receptor antagonist, followed by misoprostol, and a prostaglandin analog [31]. Changes to the regimen with increasing gestational age involve lowering the dose of misoprostol and repeating its administration, until the abortion is complete [32,33].

There are few contraindications to medical abortion drugs, primarily: confirmed or suspected ectopic pregnancy, hemorrhagic disorder, allergy, or intrauterine device (IUD) in place (after removal, medical abortion may be pursued) [2]. Additional contraindications for mifepristone include chronic adrenal failure, long-term systemic corticosteroid use, or inherited porphyria [34]. After administration of misoprostol, women typically experience bleeding and uterine cramping and pain; these symptoms are considered a normal part of the medical abortion process.

Medical abortion with mifepristone and misoprostol

A substantial body of evidence has documented the safety and efficacy of medical abortion with mifepristone and misoprostol in early pregnancy. Initial studies included gestational ages up to 7 weeks; subsequent research expanded the age range up to 9 and 10 weeks. A recent systematic review of 200 mg oral mifepristone followed by 800 mcg misoprostol administered buccally 24–48 h later in pregnancies up to 63 days gestation, documented an effectiveness of 96.7% among 33,846 women [35]. A prior review, which considered all administrative routes (buccal, oral, sublingual, and vaginal) and doses for misoprostol following 200 mg mifepristone up to 63 days' gestation, noted failure (defined as the need for surgical treatment) occurred in fewer than 5% of subjects among more than 45,000 abortions, and ongoing pregnancy was 1.1% [36]. Those who took misoprostol less than 24 h after mifepristone had a higher failure rate than among those employing a 24- to 48-h interval between medications (OR 2.1; 95% CI, 1.4–3.2) [36]. Oral administration of misoprostol at each dose level was associated with significantly higher failure rates than each of the other routes (sublingual, buccal, and

vaginal), while there was no difference between three nonoral routes. Finally, failure was also more likely among groups using 400 mcg misoprostol, when compared with 600 or 800 mcg.

Complications following medical abortion are rare: hemorrhage requiring a blood transfusion is reported at an estimated rate of 0.03–0.6% [35–37]; serious infection reported in recent systematic reviews range from 0.01 to 0.5% [30,35] and serious infection with fatal sepsis is extremely rare (<1/100,000, [64]). The most common adverse outcome from medical abortion is the need for a surgical uterine aspiration for treatment of retained products of conception, persistent pain, prolonged bleeding, or ongoing pregnancy [35,36]. Rates vary by the study population, gestational age, and regimen used, but are also influenced by providers' experience and comfort with medical abortion [30,35,36].

More recent data from two prospective trials comparing outcomes of the combination regimen between 57 and 63 days with 64–70 days, found that rates of successful abortion did not differ between the two gestational weeks, and there were likewise no differences in adverse events [38,39]. These data provided the evidence to extend outpatient medical abortion services globally through 70 days gestation in practice, and also through a regulatory pathway change in the label of one mifepristone drug (Mifeprex) [34].

Beyond 10 weeks' gestation, effectiveness of the combination regimen with only one misoprostol dose falls, making it necessary to repeat the dosing [32]. Available studies are fewer, reflecting that abortion for most women occurs early in pregnancy. Mifepristone followed 24–48 h later by misoprostol is the most effective regimen, up to 94% success within 24 h of initiation of misoprostol, and with a significantly shorter interval to abortion and fewer adverse effects than using misoprostol alone [32,40–43]. Median induction to abortion intervals range between 6 and 10 h; longer intervals are associated with higher gestational ages, as well as among nulliparous and older women [41,44–46]. While most abortions will be successful within 24 h, a small proportion will require several days to complete. Minor complications, such as needing a procedure for heavy bleeding or to remove a retained placenta, occur at a higher rate in more advanced gestations. In the largest cohort study of mifepristone-misoprostol abortion, including 1002 women between 13 and 21 weeks gestation, 8.1% required a uterine evacuation to remove a retained placenta, while two women needed an evacuation to terminate the pregnancy [44]. In this study, serious complications such as hemorrhage and blood transfusion were uncommon; they occurred in 8 women (<1%).

Uterine rupture, a serious complication of labor in obstetric literature associated with prostaglandin use in women with prior cesarean sections, is rare among abortion patients in the second trimester. In a meta-analysis of data from medical abortion studies in the midtrimester using the combined regimen or misoprostol alone, the overall rate of rupture was 0.08% with a rate among women with prior cesarean/hysterotomy of 0.28% [47].

Medical abortion with misoprostol alone

A recent systematic review of misoprostol-only regimens identified 38 trials contributing data from 12,829 women undergoing medical abortion up to 13 weeks gestation [48]. In the meta-analysis, 22% (95% CI, 18.8–25.5%) resulted in a surgical uterine evacuation; the odds of needing a surgical procedure decreased significantly as the amount of misoprostol in the initial dose increased and was lower in the trial groups that administered the dose vaginally, sublingually, or buccally compared with orally. Among groups receiving 800 mcg vaginally, surgical intervention occurred less commonly if women were permitted to take at least four doses, if they were taken over a period of 48 h, and if the tablets were moistened before vaginal insertion. Among 20 study groups comprised of 5338 women, which utilized at least 3 doses of misoprostol, with an initial dose of 800 mcg administered buccally, sublingually, or vaginally, the success rate (abortion without surgical intervention) was 87%.

Misoprostol-only medical abortion is associated with a low risk of complications: from the 38 trials included in the systematic review, 14 women were hospitalized, and 12 received blood transfusions, for an estimate of 0.2% rate of serious complications [48]. No death was reported in more than 12,000 women.

Beyond 13 weeks' gestation, misoprostol-only regimens continue to be both safe and effective with repeat misoprostol doses. The largest trial enrolled women from 13 to 20 weeks gestation in 7

countries, and found a fetal expulsion rate of 85% at 24 h and 94% at 48 h among those who had vaginally administered misoprostol [49]. The median time to fetal expulsion was 12 h (4.1–61.8 h) and parous women had significantly shorter abortion intervals. Other randomized trials with smaller sample sizes report abortion intervals between 10 and 15 h, and no difference in efficacy between vaginal and sublingual administration [50,51]. With a dosing interval of 6 h, compared with 3 h, the time to abortion is increased [52]. Major complications occurred in about 1% of women; in the largest trial of 681 women, 10 (1.5%) required a blood transfusion [49].

The value of choice between abortion methods

Contraindications to either medical or surgical abortion are few; therefore, most women will be eligible for either method throughout the first and second trimesters. Both methods can be provided in an outpatient setting, which further facilitates offering a choice. For medical abortion, as the gestational age progresses, some women may require an overnight stay but a recent study estimated its occurrence among only 11% of those undergoing abortion up to 18 weeks [53]. D&E can be safely provided as a day case, even when general anesthesia or deep sedation is used [22,54]. As the characteristics of the methods are markedly different, a woman's informed choice is the best decision-maker between surgical and medical abortion. Acceptability and satisfaction with the abortion process is greatest when women can choose between methods and receive their preferred method [2,55–58].

Characteristics of surgical abortion that are attractive to some are the short duration of the procedure, completion within an expected timeframe, low complication rate, and comfort with options for pain management during the procedure ranging from local anesthesia and oral analgesia to general anesthesia. Women who prefer medical abortion appreciate the characteristics of privacy – particularly in early gestations when women administer misoprostol and abort at home- the more natural-seeming process, which is akin to having a miscarriage, and avoiding an invasive procedure or administration of anesthesia [55,56,58]. In later gestations, medical abortion techniques allow seeing or holding the fetus after it is expelled, a wish some women have when the pregnancy is terminated for fetal indications [57,59].

Randomizing women between medical and surgical methods has been difficult given many women's strong preference for one method over the other; therefore, comparative trials are few and at least one was prematurely stopped because of slow enrolment [20,60]. The stronger preference in these studies has been for a surgical procedure, which women perceive as less painful, less psychologically traumatic, and faster [60,61]. In studies where women agreed to be randomized and acceptability assessed, higher satisfaction was reported with surgical abortion techniques over medical, primarily because of the length or volume of bleeding and pain associated with medical abortion [20,61–63]. In the most recent of such studies, 100% of those who were randomized to the D&E procedure reported they would choose it again when compared with 53% of those who were randomized to a medical abortion [61]. Additionally, significantly fewer women who had a D&E compared with medical abortion found the experience to be worse than expected. Given the strong preferences women may have regarding the characteristics of abortion techniques and the generally more positive experience women attribute to uterine aspiration and D&E when randomized to it, services should aim to provide both methods. Where trained providers or facility characteristics impede this ideal, referral mechanisms should be in place to best meet women's needs and preferences.

Conclusion

Abortion care is a fundamental part of women's reproductive health care. Surgical and medical abortion methods are safe and effective throughout the gestational age range wherein abortions are performed. Although risks increase with the gestational age of the pregnancy, rates of complications remain low and comparable between surgical and medical techniques. Women should be offered a choice between methods and receive the one they prefer.

Declaration of Conflict of Interest

The authors of this paper have no financial interests or personal relationships that could have created a conflict of interest.

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2 CME REVIEW ARTICLE

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Combination of Mifepristone and Misoprostol for First-Trimester Medical Abortion: A Comprehensive Review of the Literature

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Importance: Several medications have been used to achieve medical abortion in the first trimester of pregnancy. The most commonly used is the combination of mifepristone and misoprostol; however, different doses and routes of administration have been proposed.

Objective: The aim of this study was to summarize published data on the effectiveness, adverse effects, and acceptability of the various combinations of mifepristone and misoprostol in medical abortion protocols in the first trimester of pregnancy.

Evidence Acquisition: This was a comprehensive review, synthesizing the findings of the literature on the current use of mifepristone and misoprostol for first-trimester abortion.

Results: The combination of mifepristone and misoprostol seems to be more effective than misoprostol alone. Regarding the dosages and routes, mifepristone is administered orally, and the optimal dose is 200 mg. The route of administration of misoprostol varies; the sublingual and buccal routes are more effective; however, the vaginal route (800 μg) is associated with fewer adverse effects. Finally, the acceptability rates did not differ significantly.

Conclusions: Different schemes for first-trimester medical abortion have been described so far. Future research needs to focus on identifying the method that offers the best trade-off between efficacy and safety in first-trimester medical abortion.

Target Audience: Obstetricians and gynecologists, family physicians

Learning Objectives: After participating in this activity, the learner should be better able to discuss available combinations of mifepristone and misoprostol for first-trimester medical abortion; describe the recommended doses of misoprostol for first-trimester medical abortion; and assess the adverse effects caused by misoprostol when administered by different routes.

Early pregnancy failure and the associated induction of abortion are common complications in the first trimester of pregnancy, with a reported incidence of 15% to 20% of confirmed pregnancies.[1–4] In the last decades, medical abortion or medical management of missed miscarriage has emerged as an attractive alternative to surgical evacuation[5] and has a high level of patient acceptability without increasing the risk of infection.[4,6,7] To date, several guidelines recommend medical termination of pregnancy as a secure, efficient, and acceptable

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option.[8,9] Furthermore, first-trimester medical abortion adds privacy and convenience to the procedure of abortion, is less invasive, and has a lower complication rate compared with the surgical approach.[10] Initially, regular prostaglandins and their analogs were used alone for medical abortion and resulted in a high rate of adverse effects and failure; therefore, there was a need of a new regimen that would optimize the effect, pending the use of mifepristone.[11]

The most broadly used prostaglandin for medical abortion is misoprostol. Misoprostol is a synthetic prostaglandin E_1 analog, originally established for the prevention and treatment of peptic ulcers; because of the uterine contractions that develop as an adverse effect, it is widely used in medical abortion, especially in the first trimester.[12] Misoprostol presents many advantages, including the fact that it is stable at room temperature, has fewer systemic adverse effects compared with other prostaglandins, and is inexpensive.[4,12–15] Misoprostol's uterotonic properties, including ripening and dilatation of the cervix and myometrial contractions, make it ideal for medical abortion, especially in developing countries because of its low cost.[4,16]

Mifepristone (previously known as RU 486) is a synthetic steroid with strong antiprogester-1 activity, originally established for its potential antiglucocorticoid activity.[4,17] Mifepristone's antiprogesterone activity on the decidua and myometrium[11] upsurges the production of endogenous prostaglandins by the endometrium, the sensitivity of the pregnant uterus to exogenic prostaglandins, the contractility of the myometrium, and the cervical softening and dilatation[16] and leads to decidual necrosis and uterine contractions, thus facilitating the medical abortion.[11] Initially, when mifepristone was used alone for first-trimester medical abortion, the success rate was relatively low (73%).[11] The finding that mifepristone can sensitize the myometrium to prostaglandins drove to the hypothesis that the combination of mifepristone and prostaglandins may provoke an enhanced effect on uterine contractions and, in turn, first-trimester medical abortion.[5,8,11,16,18–22] Therefore, mifepristone could be used to prime the myometrium and cervix before the use of a prostaglandin, to improve the success rate of medical abortion.[4] A series of studies have since found a high effectiveness and acceptability of mifepristone combined with misoprostol, for first-trimester abortion, using various routes and dosages; however, the optimal approach remains undetermined.[10,23–25]

The scope of this narrative review was to synthesize available data on the effectiveness, adverse effects, and acceptability of the various combinations of mifepristone and misoprostol in medical abortion protocols in the first trimester of pregnancy.

EVIDENCE ACQUISITION

The most relevant published studies on the combination of mifepristone and misoprostol for the first-trimester medical abortion were retrieved and analyzed, and a state-of-the-art review was conducted. An overview of the included studies is presented in Table 1, and a summary of best practices for first-trimester medical abortion is presented in Table 2.

COMBINATION OF MIFEPRISTONE AND MISOPROSTOL

The combination of mifepristone and misoprostol has been found to be the most effective for abortion than the use of misoprostol alone or the use of another regimen.[4,12,16,40–45] There is strong evidence supporting the use of mifepristone-misoprostol combination as an efficient regimen for medical abortion up to 70 days of gestation, and it has been approved by the US Food and Drug Administration.[20,46,47] On the other hand, there is no absolute lower gestational age limit.[46] Furthermore, failure of medical abortion in the first trimester of pregnancy (ongoing pregnancy or retained tissue) upturns with progressing gestational age through 70 days of gestation; patients should be informed for the possibilities of failure, particularly when the gestational age approaches 10 weeks.[47]

The use of 200 mg of oral mifepristone followed by 400 μg oral or 800 μg vaginal misoprostol for ≤49 or ≤63 days of gestation, respectively, is recommended by the World Health Organization.[48] The effectiveness of this combination ranges between 92% and 99% among women in the first trimester of pregnancy.[5,49] Chawdhary et al[10] found a success rate of 94% in the combination group (200 mg mifepristone, 800 μg misoprostol) versus 86% in the misoprostol alone group (total 1600 mg) for up to 63 days of gestation. Jain et al[50] compared the effect of 200 mg mifepristone combined with 800 μg vaginal misoprostol with that of 200 mg placebo in combination with 800 μg vaginal misoprostol (misoprostol doses were repeated if needed for up to 3 times). The success rate was higher in the first group (95.7% vs 88%; $P < 0.05$). In another similar study, the effectiveness was 83.8% in the combination compared with 67.1% in the misoprostol alone group; the difference referred to the outcome was noted after only 1 dose of misoprostol.[44] Blum et al[40] reported an efficacy rate of 92.9% of the combined regimen in contrast with 78% of the misoprostol-alone regimen; the ongoing pregnancy frequency in the misoprostol-only arm was 13.8%. In a study accomplished by Ngoc et al,[41] a success rate of 96.5% was estimated in the combination arm versus 76.2% in the misoprostol-only arm (relative risk [RR], 0.79; 95% confidence interval [CI], 0.73–0.86).

TABLE 1
Comparison of Findings on Misoprostol Route of Administration

First Author	Year	Gestational Age	Mife Dose, mg	Miso Dose, μg	Miso Route	Success, %	Adverse Effects	Acceptability, %
Oral vs vaginal								
El-Refaey*[26]	1995	<63 d	600	800	Oral	87	Gastrointestinal↑	—
				800	Vaginal	95	—	
Schaff*[27]	2002	<63 d	200	400	Oral	84	Same	89
				800	Oral	92		
				800	Vaginal	96		
Von Hertzen[28]	2003	<63 d	200	800	Oral + oral	92,3	—	—
				800	Vaginal	93.5		
				800	Vaginal + oral	94.7		
Honkanen[23]	2004	<63 d	200	800	Oral	—	Gastrointestinal, pain ↑	84
				800	Vaginal + oral	—	—	
				800	Vaginal	—	Fever↑	
Arvidsson[29]	2005	<49 d	600	400	Oral		Gastrointestinal↑	76
				800	Vaginal		—	48
Shannon[30]	2006	<56 d	200	400	Oral	94.7	Same	92.4
				600	Oral	93.4		91.2
				800	Vaginal	94.3		88.1
Sublingual vs vaginal								
Tang[31]	2003	<63 d	200	800	Sublingual	98.2	Fever, chills, gastrointestinal↑	—
				800	Vaginal	93.8	—	
Hamoda*[32]	2005	<63 d	200	600	Sublingual	98.1	Gastrointestinal↑	70
				800	Vaginal	97.4	—	68
Von Hertzen[33]	2010	<63 d	200	400	Sublingual	91.5	Symptoms less frequent in vaginal/400	92.5
				400	Vaginal	89.6		93.6
				800	Sublingual	93.9		93.7
				800	Vaginal	94.5		94.6
Oral vs buccal								
Winikoff*[34]	2008	<63 d	200	800	Oral	91.3	Same	91.9
				800	Buccal	96.2		
Oral vs sublingual								
Dahiya[12]	2011	<56 d	200	400	Oral	87.5	Gastrointestinal↑	93.5
				400	Sublingual	95.5	—	
Fekih[35]	2010	<56 d	200	400	Oral	94.5	Gastrointestinal↑	96
				800	Sublingual	92.1	—	92
Sublingual vs buccal								
Raghavan[36]	2010	<63 d	200	400	Sublingual	97.4	Same	90
				400	Buccal	97.1		
Chai*[37]	2013	<63 d	200	800	Sublingual	97.8	Chills↑	—
				800	Buccal	95.4	Chills	
Buccal vs vaginal								
Middleton[38]	2005	<56 d	200	800	Buccal	95	Same	92
				800	Vaginal	93		95
Garg*[39]	2015	<49 d	200	800	Buccal	96	Altered taste↑	100
				800	Vaginal	88	—	92

*Statistical significance found.
Mife, mifepristone; miso, misoprostol.

Importantly, the percentage of ongoing pregnancies in the first group was 16.6% compared with only 1.5% in the second group (RR, 1.62; 95% CI, 0.68–3.90).[41]

Moreover, regarding the need of additional surgical intervention, it is less common in the mifepristone pretreatment group than in the misoprostol-alone group (8.8% vs 23.5%).[44] Chu et al[45] found a 17% rate of surgical intervention for completing the abortion in the combination group and 25% in the placebo-misoprostol group (RR, 0.71; 95% CI, 0.53–0.95).

With regard to late first-trimester medical abortion, Dalenda et al[5] concluded that the combined regimen is as effective as the misoprostol-only regimen for medical abortion between 9 and 12 weeks of gestation; successful abortion occurred in 80.8% in the combination group and 77.4% in the misoprostol-only group ($P = 0.66$).

TABLE 2
Summary of the Best Practices for First-Trimester Medical Abortion

Parameters	Findings
Combination	• Mifepristone combined with misoprostol is the most effective.
Mifepristone dosage	• 200 mg oral, single dose • Lower doses for earlier gestations
Misoprostol route of administration	• The vaginal route is equally effective with the sublingual and buccal. • The vaginal route has the least adverse effects. • The oral route is the least effective and with most adverse effects. • The acceptability rates are almost the same.
Misoprostol dosage	• 800 μg for vaginal and sublingual • Second and third dose can amplify the effectiveness.
Administration intervals	• 48 h is widely accepted. • Flexibility can be effective too (24 or 48 or 72 h). • Simultaneous administration can be used for up to 49 d of gestation. • The acceptability rate has been found to be the same.

However, other studies that investigated late first-trimester medical abortions found a higher success rate in the combination groups: 94.6% in the study by Ashok et al[24] (10–13 gestational weeks) and 94.8% in the study by Hamoda et al[51] (64–91 days of gestation).

As for the adverse effects, misoprostol on its own is related to more adverse effects including fever, shivering, and gastrointestinal effects such as nausea, vomiting, and diarrhea; mifepristone has appeared to cause fewer complications.[5] Dalenda et al[5] emphasized the higher occurrence of abdominal pain in the misoprostol-only arm (71.4% vs 43.8%), probably due to the fact that misoprostol was used in a higher dosage to achieve successful results. On the contrary, Chu et al[45] found no difference in the presence of adverse effects, as did Ngoc et al,[41] except for the higher rate of diarrhea reported by the women in the misoprostol-only regimen group. One of the most significant adverse effects in medical abortion, which could also affect acceptability, is the longer duration of bleeding.[10] Nevertheless, the incidence of heavy bleeding resulting in blood transfusion is rare in both the combined and misoprostol-only regimens (2% vs 0.7%, respectively).[44] Regarding patient acceptability, both the combined and misoprostol-only groups seem to be acceptable for medical abortion (75.5% and 75.7%, respectively).[5] Moreover, Wiebe[52] showed that privacy of aborting at home and emotional support are very important for women (71.3% and 61% acceptability, respectively). In another report, 91.3% of patients who underwent medical abortion were satisfied with the method and would choose it again.[49]

Overall, although mifepristone is a more expensive drug compared with misoprostol, the higher success rate of the combined regimen leads to reduced overall time spent on the process of abortion (time off work, office visits, need of surgical management for ongoing pregnancies), which in turn results in a significantly reduced cost.[22]

It seems that the combination of mifepristone and misoprostol presents with advantages and is the criterion standard for first-trimester medical abortion, at least in high-income countries where mifepristone is available.

MIFEPRISTONE DOSAGE

Several studies have shown that 200 mg of mifepristone is as effective as 600 mg.[11,53] Moreover, a Cochrane review found that both 600 and 200 mg of mifepristone are equally effective in aborting during the first trimester (90.8% and 91.4%, respectively).[20] In a large study including 45,528 women, the use of 200 mg mifepristone followed by misoprostol achieved a complete abortion rate of 95.2%.[54] This equal effect of the 2 dosages may be due to the fact that after ingestion of either 200 or 600 mg, there is no difference in the peak concentration of serum mifepristone, possibly because mifepristone is bound to aracid glycoprotein.[53] Apart from the efficacy using 200 mg of mifepristone, it is also very practical as each tablet of mifepristone consists of 200 mg of mifepristone.[11] Following the finding that 200 mg of mifepristone was equally effective as 600 mg, some studies investigated the possibility that an even lower dose could be as effective. A systematic review compared 150 versus 200 mg of mifepristone (both combined with misoprostol) and found no difference in the efficacy (RR, 0.98; 95% CI, 0.96–1.01) or in the induction to expulsion time and the blood loss (mean difference, 0.01; 95% CI, 0.29–0.27; and 0.05; 95% CI, 0.23–0.32, respectively) between the groups.[55] A trial conducted in women at 63 days of gestation compared the efficacy of 100 versus 200 mg of mifepristone (each group additionally took 800 μg of misoprostol); there was no difference in the complete abortion rate (92.0% vs 93.2%; 95% CI, −1.0 to 3.5) or the incidence of adverse effects.[49] Creinin et al[56] evaluated the efficacy of 100 mg of mifepristone and reported that it is highly dependent on the dosage and route of administration of misoprostol. Moreover, in a study comparing 75 versus 150 mg of mifepristone in pregnancies up to 49 days of gestation, there was no significant difference in the rates of complete abortion (95.4% vs 96.3%).[57] Another study concluded that the use of 75 mg mifepristone followed by 400 μg misoprostol is effective (98.2%) in achieving abortion in up to 35 days of gestation.[58] Li et al[58] suggested that, for up to 35 days of gestation, lower doses of mifepristone

(50 or 75 mg) followed by a lower dose of misoprostol (200 μg oral misoprostol) are also effective and safe as higher doses; they also reported that lower doses of mifepristone and misoprostol lead to reduced adverse effects including bleeding.

Mifepristone is currently recommended at a single dose of 200 mg as this is as effective as the original 600-mg regimen. A lower dose may also be effective in earlier gestations, before 49 days; however, more studies are needed.

MISOPROSTOL ROUTE OF ADMINISTRATION

Several routes of misoprostol administration have been studied to date, including oral, vaginal, sublingual, and buccal (Table 1).

Oral Versus Vaginal

The vaginal application of misoprostol is widely accepted, and the use of 200 mg oral mifepristone followed by 800 μg of vaginal misoprostol 36 to 48 h later is the most commonly used combination regimen, with a reported success rate of 90% to 95%.[24,31,53,59] Oral misoprostol has been found to be less effective in medical abortion and leads to more adverse effects compared with vaginal misoprostol.[26,31] When pharmacologically comparing oral and vaginal administration of misoprostol, the oral route leads to a more rapid absorption and higher peak levels.[13] Moreover, Zieman et al[60] reported a 3 times higher systemic bioavailability of vaginally administered misoprostol compared with that of oral misoprostol. This may be explained by the finding that, although the vaginal route achieved slightly lower peak plasma levels and they developed more slowly, they were persistent for longer, up to 4 hours.[61] Another study compared vaginal (800 μg) with oral misoprostol (800 μg) regarding their efficiency in aborting a pregnancy of up to 63 days (both groups initially received 600 mg of mifepristone) and found higher efficacy (95% vs 87%; $P = 0.03$) and fewer adverse effects in the vaginal group.[26] In similar studies, von Hertzen et al[28] found that women in the oral group had nearly 3 times higher risk of failure than women in the vaginal group (RR, 2.8; 95% CI, 1.3–5.8), and Schaff et al[27] showed the superiority of vaginal misoprostol over 2 regimens of oral misoprostol (400 and 800 μg) for pregnancies up to 9 weeks, also suggesting that a repeated dose of misoprostol is safe and contributes to a better efficacy rate when needed. Accordingly, von Hertzen et al[28] found that a twice-daily repeated dose of 400 μg oral misoprostol increases the efficacy of the regimen, but at the cost of increasing the presence of adverse effects (diarrhea).

Regarding adverse effects, in one study, the incidence of fever, nausea, and vomiting is less with vaginal than with oral administration, but no differences were found in the presence of diarrhea and abdominal pain.[55] However, in another study by Arvidsson et al,[29] nausea was present in 47.9% of the cases in the oral group compared with 34.7% of the vaginal group, and vomiting incidence was double in the oral group (22.9% vs 10.2%). Arvidsson et al[29] also investigated the severity of associated pain by using the VAS assessment method and concluded that there is no statistically significant difference between the oral and vaginal groups. Similarly, regarding the associated bleeding, a series of studies found that it starts within 24 hours after using either oral or vaginal misoprostol with no reported difference in the duration or the quantity.[27,29,55]

With regard to acceptability, it was found higher in the oral group because of its practicality and the avoidance of uncomfortable vaginal examination.[62] Similarly, Arvidsson et al[29] found that 76% of women in the oral and 48% of women in the vaginal group would prefer an oral route in a possible future medical abortion procedure; of note, 4% of women in the vaginal compared with 7% of the women in the oral group would never choose medical abortion again.

The comparison between the vaginal and the oral route shows that the former is more effective and with fewer adverse effects; however, the oral route seems more acceptable to women.

Sublingual Versus Vaginal

In terms of efficacy and safety, researchers have also assessed the possibility of the sublingual route of misoprostol in first-trimester medical abortion (600–800 μg).[63] The sublingual route is more convenient, and dialysis could be easily observed in contrast to vaginal misoprostol.[12,31] Therefore, it can be easily taken at home.[31] Regarding pharmacokinetics, the sublingual route has the briefest onset of action and the highest peak concentration and bioavailability compared with oral and vaginal misoprostol.[12] Tang et al[31] studied the effectiveness of sublingual and vaginal misoprostol in pregnancies up to 9 weeks and found 98.2% (95% CI, 93%–99%) of complete abortion in the sublingual compared with 93.8% (95% CI, 88%–97%) in the vaginal group; this difference was not statistically significant as the study population was too small. Von Hertzen et al[33] reported that the sublingual route causes stronger uterine contractions after a shorter time interval compared with the vaginal group; it may thus lead to a shorter interval to abortion and probably a higher efficacy at later gestational weeks.

Moreover, the rates of adverse effects seem to be higher in the sublingually treated women (gastrointestinal, chills,

and fever).[31,32] However, the satisfaction rate was reported to be similar to that of the vaginal group[33]; both 800 μg sublingual and 800 μg vaginal misoprostol had a similar complete abortion and acceptability rate, although vaginal misoprostol was related to fewer adverse effects.[33] Based on these findings, the authors concluded that, if there is no special preference on the route, the optimal seems to be the vaginal.[33]

The comparison between the vaginal and the sublingual route shows a similar effectiveness and satisfaction rate and a higher rate of mostly mild adverse effects in the sublingual route. The latter may offer some advantages in later gestations; however, more studies are needed.

Oral Versus Sublingual

Fekih et al[35] found a complete abortion rate of 94.5% in the oral versus 92.1% in the sublingual group ($P = 0.7$). Moreover, Dahiya et al[12] found a rate of 95.5% complete abortion in the sublingual and 87.5% in the oral group, in pregnancies up to 56 days of gestation ($P = 0.166$; 95% CI, −0.194 to 0.033); both the rates of ongoing pregnancies and of adverse effects were higher in the oral group. Another study showed that the efficacy was similar in both sublingual and oral groups.[55]

The published data seem to favor the sublingual route over the oral one because the former has at least equal effectiveness and fewer adverse effects.

Buccal Versus Sublingual

With regard to the buccal route of administration of misoprostol, several studies compared its efficacy with that of other routes. The comparison of pharmacokinetics of sublingual and buccal misoprostol showed that the sublingual route achieved higher bioavailability and peak plasma concentration but also higher incidence of adverse effects, as well as lower acceptability.[27,36] Raghavan et al[36] showed that there is no difference in the efficacy (97%) achieved by both the sublingual and the buccal route after mifepristone administration (up to 63 days' gestation), which is in accordance with the results presented by other researchers.[31,34,36–38,64]

As for adverse effects, both sublingual and buccal routes are associated with low rates of adverse effects, with no disparity found between the 2 routes except the higher incidence of chills and shivering among women in the sublingual group.[36,37]

Overall, based on the studies published comparing the buccal and the sublingual route, it seems that there is no clear advantage of the one over the other.

Buccal Versus Oral

Winikoff et al[34] compared buccal versus oral misoprostol and demonstrated that the buccal route (96.2%), administered after mifepristone, is more effective in aborting late first-trimester pregnancies (57–63 days) than the oral route (91.3%) (RR, 0.95; 95% CI, 0.92–0.98). These results are in accordance with previous research.[27,28,30,34,53]

When comparing the adverse effects of buccal versus oral misoprostol, both are found to be acceptable and similar, except for the higher levels of fever and chills found in women taking buccal therapy.[34]

The buccal route seems to be more effective than the oral route, with similar acceptability and safety profile but a possible higher incidence of mild adverse effects.

Buccal Versus Vaginal

Compared with vaginal (93%), buccal administration of misoprostol (95%) has the same efficacy rates ($P = 0.51$).[38] In addition, no differences were found in adverse effects, except for a higher incidence of diarrhea, chills, nausea, and altered taste, which are more common after administering buccal than vaginal misoprostol.[38,39] The overall satisfaction rate was almost similar in the buccal (100%) and vaginal (92%) groups.[38,39]

Based on limited data, the buccal route offers similar effectiveness and satisfaction to the vaginal route, with a possible higher incidence of mild adverse effects.

MISOPROSTOL DOSAGE

Regarding the dosages of vaginal and sublingual routes, using 400 μg in either route led to a higher risk of failure of complete abortion and higher incidence of ongoing pregnancies compared with 800 μg and therefore should not replace the regimen of 800 μg (sublingual or vaginal).[33]

Furthermore, women who received 800 μg of oral misoprostol (2 doses of 400 μg) had a lower rate of ongoing pregnancies in comparison with women who took only 400 μg.[65] Schaff et al[27] found a complete abortion rate of 84% in the 400 μg oral misoprostol group and 92% in the 800 μg oral misoprostol group, which increased after a second dose to 91% and 95%, respectively ($P < 0.001$). In another study that considered different dosages of misoprostol, a similar rate of complete abortion was identified between 800 μg (95%) and 400 μg twice (92%) of oral mifepristone.[66] The women in the single 800-μg-dose group had higher rate of diarrhea (33%) than those in the sequential dose of 400-μg-dose group (22%; $P = 0.05$).[66] Shannon et al[30] compared 400 μg with 600 μg of oral misoprostol and found no difference in the complete abortion rate (94.7% vs 93.4%; $P = 0.975$) and the adverse effects caused.

A dosage of 800 μg of buccal misoprostol was effective for first-trimester medical abortion.[34,42] Moreover, Chong et al[42] suggested that a dose of 400 μg of buccal misoprostol is equally efficacious to the commonly used dose of 800 μg in aborting pregnancies up to 63 days. Raghavan et al[36] found that the combination of mifepristone and 400 μg buccal misoprostol achieved a 97.1% complete abortion rate. Furthermore, a dose of 400 μg buccal misoprostol, besides being equally effective, is more practical (as it consists of only 2 pills of misoprostol) and acceptable and causes fewer adverse effects than 800 μg of buccal misoprostol (nausea: 75.1% vs 54.1%, vomiting: 47.6% vs 22.2%, headache: 41.1% vs 17.7%, fever/chills: 47.6% vs 18.0%).[36,42]

Notably, the administration of a second or, if needed, a third dose of misoprostol was found helpful in achieving complete abortion and has led to an increase of the success rate to approximately up to 98%.[24,67–69] Ashok et al[24] found that approximately 30% of women at 70 to 83 days of gestation needed a second dose of misoprostol to complete the abortion procedure.

Overall, there is not enough evidence to support the reduction of the commonly used dose of 800 mg of misoprostol by any of the routes. However, some of the studies show that lower doses may be associated with equal effectiveness and fewer adverse effects, especially when using the buccal route.

ADMINISTRATION INTERVALS

The most widely used interval time between mifepristone and misoprostol administration is 48 hours and is the one approved by the US Food and Drug Administration.[70] Researchers have investigated shorter time intervals in search of an equally effective, more convenient, and faster regimen with minor adverse effects. Thus, von Hertzen et al[49] found an efficacy rate of 93.5% in the 24-hour interval group compared with 91.7% in the 48-hour-interval group (95% CI, −4.0 to 0.5). Another study determined that the interval can be reduced from 48 to 24 hours when mifepristone was followed by 800 μg vaginal misoprostol, while keeping the same efficacy, supporting the initiation of a more flexible interval time.[71] Heikinheimo et al[69] assessed the alteration from a 48-hour fixed interval to a 24-, 48-, or 72-hour flexible one in first-trimester medical abortion and concluded that there was no significant difference (94.9% vs 94.4%). In addition, Hekinheimo et al[69] found approximately 9% increase in medical abortion acceptance, when flexible intervals were used. Basu et al[72] found that a 72-hour interval had a higher efficacy rate (98.2% vs 94.2% vs 97.2%) after administration of mifepristone alone, and there was a trend to require fewer doses of misoprostol than the 24-/48-hour intervals.

Regarding intervals less than 24 hours, Guest et al[73] studied a 6-hour interval and found lower efficacy compared with the 36- to 48-hour-interval group (79% vs 92%). On the contrary, Creinin et al[74] found an equal efficacy rate in the 6- to 8-hour and the 23- to 25-hour groups (95.8% vs 98.1%). As for the pharmacokinetics, both oral mifepristone and vaginal misoprostol achieve peak plasma concentrations in 1 to 2 hours, but the sensitization to prostaglandins occurs 36 to 48 hours following mifepristone administration.[75,76] Several studies also evaluated the simultaneous administration of mifepristone and misoprostol, with varying efficacy rates of 90% to 98%.[50,76–78] Creinin et al[68] reported that the simultaneous administration offered a 95.1% efficacy compared with 96.9% in the 24-hour-interval group, supporting the noninferiority of one regimen over the other ($P = 0.003$). In another study, an efficacy rate of 94.5% was achieved in the simultaneous compared with 97.1% in the 24- to 48-hour-interval group,[79] which is in accordance with the findings by Goel et al. (95% vs 97.5%; $P = 0.56$).[70] Furthermore, Murthy et al. studied the simultaneous administration of the regimens for up to 49 days of gestation and found a complete abortion rate of 90%.[78] Similarly, Schreiber et al. studied the efficacy rates for pregnancies up to 63 days of gestation and found that expulsion occurred in 93% of women at 50–56 days and in 90% of women at 57–63 days of gestation after simultaneous administration.[77] Li et al, found 92.6% success rate when misoprostol was administered simultaneously.[80]

Regarding adverse effects in the different interval groups, studies have shown a time dependent correlation following mifepristone. More specifically, bleeding occurred in 55% in the 48-hour group,[81] 8% in the 24-hour group,[82] 5% in the 6 to 8-hour group[83] and minimal in the simultaneous group.[78] The duration of bleeding in the study by Chen et al., was the same between the groups of 6 to 8 and 24 hours.[84] Other adverse effects like nausea, vomiting and diarrhea were found significantly lower in the simultaneous group compared with the commonly used 24 and 48-hour interval.[56,68,74] These findings may be explained by the fact that the shorter the interval the lower the sensitivity to misoprostol and as a result fewer adverse effects related to misoprostol occur.[21] On the other hand, Goel et al[70] found no difference in the incidence of adverse effects between different intervals (simultaneous and 24-hour interval). With regard to pain occurrence, there was no difference between the various interval groups.[70]

Satisfaction rates differed in various studies; Guest et al[73] found a higher acceptance rate (97%) among

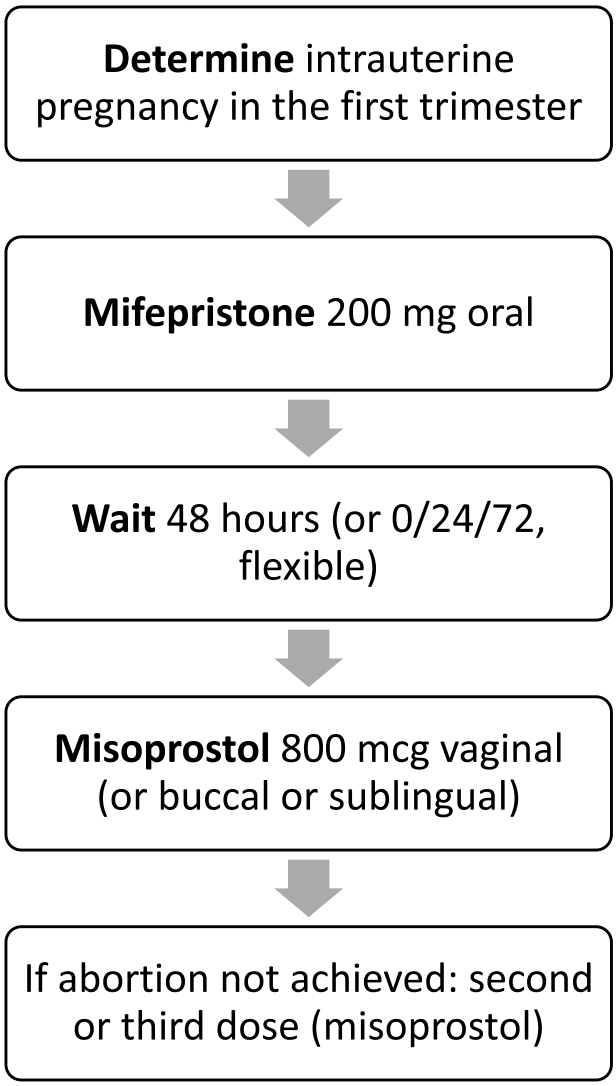

FIGURE 1. Suggested protocol for first-trimester medical abortion.

women in the lower interval (6 hours) compared with the 36- to 48-hour group (90%). Moreover, Schaff et al[67] found satisfaction rates of 86%, 79%, and 76% in the 24-, 48-, and 72-hour groups, respectively. Goel et al[70] found a similar acceptability rate between the different interval groups.

Overall, although this issue is far from resolved, there is some evidence that the shorter interval of administration may not significantly affect the effectiveness and may be associated with fewer adverse effects and a higher satisfaction rate.

CONCLUSIONS

To summarize, there are multiple ways to achieve medical abortion, but (i) the most popular and widely approved is the combination of 200 mg oral mifepristone followed by 800 μg vaginal misoprostol; (ii) the vaginal route is generally not preferred by women, and the buccal and sublingual routes have advantages compared with the originally used oral approach; and (iii) the most widely used interval time between mifepristone and misoprostol administration is 48 hours (Fig. 1). Of note, the dosage of mifepristone and misoprostol and the time intervals are not fully investigated, and there is some evidence that different gestations may require different regimens. It seems that more research is needed, and as in many cases, differences in effectiveness and adverse effects are not large; women's preferences, clinicians' familiarity, and logistics may allow for different regimens to be applied.

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ARTICLE

PERSPECTIVES on Sexual and Reproductive Health

Person-centered, high-quality care from a distance: A qualitative study of patient experiences of TelAbortion, a model for direct-to-patient medication abortion by mail in the United States

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Abstract

Context: Direct-to-patient telemedicine abortion allows people to receive mifepristone and misoprostol for medication abortion in their home without requiring an in-person visit with a healthcare provider. This method has high efficacy and safety, but less is known about the person-centered quality of care provided with telemedicine.

Methods: We interviewed 45 participants from the TelAbortion study of direct-to-patient telemedicine abortion in the United States from January to July 2020. Semi-structured qualitative interviews queried their choices, barriers to care, expectations for care, actual abortion experience, and suggestions for improvement. We developed a codebook through an iterative, inductive process and performed content and thematic analyses.

Results: The experience of direct-to-patient telemedicine abortion met the person-centered domains of dignity, autonomy, privacy, communication, social support, supportive care, trust, and environment. Four themes relate to the person-centered framework for reproductive health equity: (1) Participants felt well-supported and safe with TelAbortion; (2) Participants had autonomy in their care which led to feelings of empowerment; (3) TelAbortion exceeded expectations; and (4) Challenges arose when interfacing with the healthcare system outside of TelAbortion. Participants perceived abortion stigma which often led them to avoid traditional care and experienced enacted stigma during encounters with non-study healthcare workers.

Conclusion: TelAbortion is a high quality, person-centered care model that can empower patients seeking care in an increasingly challenging abortion context.

INTRODUCTION

In the United States, over half of abortions are now medication abortions.[1] Medication abortion with mifepristone and misoprostol is a safe and effective method to end a pregnancy that offers the advantage of not needing the healthcare provider and patient to be in the same space.[2] The simplicity of medication abortion lends itself to telemedicine adaptation since patients already may take the medications at home. Telemedicine has expanded from medication pickup at a clinic distant from the provider to completely remote models with

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medications delivered by mail.[3,4] The challenges of providing abortion care during a global pandemic accelerated the adaptation of telemedicine for medication abortion.[5,6]

Recent evidence shows similar safety and efficacy of medication abortion when the medications were dispensed by mail, rather than in-person, with or without pre-abortion ultrasound.[7–9] The Gynuity TelAbortion project was the first to offer direct-to-patient telemedicine abortion in the United States, with patients receiving medications by mail after videoconference counseling.[10] Of 1157 abortions, 95% successfully completed a medication abortion; 85% of participants were very satisfied with the service, with 97% willing to recommend TelAbortion to a friend.[11]

The person-centered quality of care provided via direct-to-patient telemedicine abortion has not been evaluated as extensively as the efficacy. The Institute of Medicine and World Health Organization (WHO) name person-centeredness as one element of quality care.[12,13] Limited quality markers for abortion care that focus on patient experience exist beyond satisfaction, which typically is high since patients receive the care they present for, but fails to capture nuances of the care.[14,15] The person-centered framework for reproductive health equity (PCFRHE) is one model that emphasizes eight domains: dignity, autonomy, privacy/confidentiality, communication, social support, supportive care, trust, and health facility environment (Table 1).[16] These are placed into context of broader societal and community determinants of health equity, health seeking behaviors, and facility level factors, and can be used as outcome measures in evaluating reproductive healthcare, including TelAbortion.[16,17]

An important societal determinant of reproductive health that impacts person-centered outcomes is abortion stigma, a social phenomenon that ascribes negative attributes to someone seeking an abortion and "marks them as inferior to the ideals of womanhood" (p. 628).[18] In essence, seeking an abortion is seen as violating social expectations, for which people are discredited or discriminated against.[19] Abortion stigma can be further broken down into perceived stigma, or how people expect others will think of them; internalized stigma, like feelings of guilt or shame about having an abortion; and enacted stigma, overt discrimination.[20] Stigma motivates people seeking abortion care to keep it concealed.[21] Telemedicine abortion is unique in that it offers a level of privacy not possible for patients going into a clinic.

Evaluating direct-to-patient telemedicine abortion from a person-centered angle gives insight into patients' values and how all abortion care can be more responsive to patient needs beyond increasing access.[22] TelAbortion provides an ideal example of direct-to-patient telemedicine abortion as it started before and evolved during the COVID-19 pandemic, operated through sites in states with differing abortion access, and was designed to mirror standard abortion care.[11] Qualitative analysis allows for exploration of the entire abortion experience, including abortion stigma, and offers insight into ways to improve abortion care while highlighting the unique impact of telemedicine.[23] By framing our data within the eight domains of the PCFRHE, we aim to show that the experience of TelAbortion is person-centered care and can be a model for other direct-to-patient telemedicine abortion care.

TABLE 1 Definitions of the person-centered outcomes from the person-centered framework for reproductive health equity (adapted from Altshuler and Whaley[17] and Sudhinaraset et al[16])

Dignity	Receiving care in a respectful and caring setting
Autonomy	Supporting people in making their own healthcare decisions
Privacy/confidentiality	Ensuring privacy in the setting where care is provided and confidentiality in records
Communication	Explaining the condition and treatment clearly, providing information that is understandable
Social support	Allowing the companion of the patient's choice to be part of the care
Supportive care	Integrating care to be supportive of all the patient's needs, including pain control
Trust	Providing care that is truthful, ensuing patients are comfortable with their provider's competence
Environment	Offering a welcoming environment, including the full continuum of care

METHODS

We performed qualitative content and thematic analyses of semi-structured participant interviews to evaluate patient experiences of TelAbortion. The University of Hawai'i Institutional Review Board (#2019-00799) granted ethics approval.

Participant selection

We recruited participants from the Gynuity TelAbortion study in the United States who completed a medication abortion by mail without in-person interaction with a clinic. The TelAbortion study operated from existing abortion clinics, some of which had providers licensed in multiple states and therefore provided telemedicine in those states. Patients contacted a participating site and were offered TelAbortion or in-person care, or specifically contacted the clinic after finding out about TelAbortion from its website. If required by their provider, they obtained testing for Rh(D) type and an ultrasound. The ultrasound was often obtained from a healthcare provider in their community unaffiliated with the abortion clinic, typically facilitated by their TelAbortion provider. Participants underwent videoconference counseling with a provider from their site, and if eligible, were mailed the medications to take at home with 1–2 follow-up contacts.[10] Pre-abortion testing and the cost of the abortion were determined per the sites' usual medication abortion protocols and were not covered by the study. Each site slightly varied in how they implemented TelAbortion to fit into their existing abortion protocols.[11]

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During the routine exit questionnaire, sites asked participants if they would be willing to be contacted for future research, then referred those patients to this study. Seven of the eight sites providing TelAbortion in January 2020 referred participants from eight states: two in the East (Maryland, New York), one in the South (Georgia), two in the Midwest (Illinois, Minnesota), and three in the West (Colorado, Hawai'i, Oregon). At the time of the study, the political landscapes in Georgia and Colorado were considered neutral or hostile to abortion care and access.[24]

We contacted interested participants up to three times to schedule an interview. We included English-speaking participants over age 18 who completed a TelAbortion in the previous six months. We capped recruitment at 10 participants per site to maintain geographic diversity, which was important to capture experiences from states with varied availability of abortion clinics and hostility toward abortion.

The initial protocol aimed for 40 participants recruited or until thematic saturation was reached. Because the COVID-19 pandemic started during the data collection timeframe, we increased our recruitment goal to explore the impact that the pandemic had on TelAbortion experiences.

Data collection

Introducing herself as a researcher from the University of Hawai'i, CK conducted semi-structured telephone interviews between January and July 2020. Questions focused on seeking abortion care, sources of information, barriers to abortion care, expectations for care, the abortion process, and ideas for improvement. Interviews lasted 30–75 min. Participants gave oral consent prior to starting the interview and received a $50 gift card to an online retail store for remuneration. We modified the interview guide throughout the interview process iteratively and added additional questions relating to the pandemic after its onset. We wrote notes after each interview and documented research team discussions in memos throughout the course of interviewing. We audio-recorded interviews and had them professionally transcribed verbatim.

Data analysis

Four team members (CK, JE, RD, RS), including two complex family planning physicians and two public health researchers, met regularly to discuss the interview transcripts as the interview process was ongoing, modify the interview guide as needed, and develop a codebook. We developed codes inductively from interview data and categorized them. Once interviews were complete, we further revised the codebook to be comprehensive and eliminate duplicate concepts. Two researchers coded each interview and one researcher coded all interviews. We compared coding between the study team members and resolved discrepancies with the full team. We used ATLAS.ti version 8.4.5 (ATLAS.ti GmbH, Berlin, Germany) for qualitative data management and coding. We use pseudonyms for the quotes presented to preserve confidentiality.

We identified themes with an iterative process using qualitative content analysis, a flexible, reflective, repetitious approach that examines common language, experience, and ideas.[25,26] Triangulation with memos written throughout the interview process and citation of verbatim evidence in this text confirm the credibility of the themes that emerged. Although we did not use PCFRHE to generate the interview guide, develop the codebook, or identify themes, we drew on the PCFRHE to organize the themes and contextualize our findings because person-centeredness emerged as a primary focus of the interviews.[16] This manuscript concentrates on the patient experience of TelAbortion; we presented themes relating to access to abortion care in a separate publication.[22]

RESULTS

We interviewed 45 participants who completed a TelAbortion, 23 prior to March 2020, the start of the COVID-19 pandemic in the United States and 22 after the onset. Study sites referred 124 people; we did not contact 28 due to saturation from their study site, 40 did not respond, eight were no longer interested in participation, two had scheduling conflicts, and one was under age 18 and therefore ineligible. The sample was diverse in age, race/ethnicity, and geography, with a median age of 29. Eighteen (40%) had a prior abortion (Table 2).

The patient experiences of TelAbortion encompassed the PCFRHE outlined by Sudhinaraset et al (Figure 1).[16] With the four themes that emerged, each person-centered outcome was represented as well as the interconnected societal and community determinants of health and health seeking behaviors. Abortion stigma, depicted at the highest level of the PCFRHE, was a thread throughout each of the themes, impacting how participants perceived TelAbortion and their expectations for abortion care, why they preferred staying at home versus going to a clinic, and their lived experiences of interacting with healthcare outside of TelAbortion. Every participant had some interaction with abortion stigma, whether from their personal complicated beliefs about abortion, the beliefs of their family or community, having a sense that they may be judged for their abortion and needed to keep it private, or by being discriminated against because they were having an abortion.

Participants felt well-supported and safe with TelAbortion

Across all sites, participants overwhelmingly reported feeling well-supported throughout their abortion process which created a sense of safety. Three of the person-centered outcomes contributed to the sense of support and safety: communication, supportive care, and environment.

Communication with the TelAbortion study team was frequent and thorough, which many participants noted gave them confidence

TABLE 2 Participant ($N = 45$) characteristics from in-depth interviews of TelAbortion participants

Characteristics	Participants ($N = 45$) *n* (%) or median (range)
Age (years)	29 (18–46)
Gravidity	2 (1–6)
Parity	1 (0–4)
Prior medication abortion	12 (27)
Prior procedural abortion	7 (16)
Gestational age (weeks)	8 (4–10)
Race/ethnicity*	
White	25 (56)
Black	7 (16)
Hispanic	10 (22)
Asian	4 (9)
Native Hawaiian/Pacific Islander	6 (13)
Middle Eastern	2 (4)
State	
Colorado	4 (9)
Georgia	4 (9)
Hawai'i	10 (22)
Illinois	3 (7)
Maryland	2 (4)
Minnesota	8 (18)
New York	5 (11)
Oregon	9 (20)

*Nine participants reported more than one race, so percentages do not add up to 100%.

in the process. In addition to oral communication, many participants appreciated written instructions which contributed to their sense of preparedness and therefore safety.

> I felt really safe…I got so much information in the video call. I did jot some things down, but I still thought like, "Oh, gosh, what if I can't remember when to take this and when to take that." And when the packet came, it was just so full of information, and everything was very clearly laid out. It was like, "Call here if you have an emergency." I felt very safe and very much if something went wrong, I would have help readily available. (Jeanne 40-year old, Illinois)

Most participants did not require any additional care beyond the standard TelAbortion protocol. For the three participants who did require further medical care, they felt like their care team continued to support them.

> I love everybody I spoke to. Even when I went to the downtown area for the D&C [dilation and curettage], the doctor…was very nice. She joked with me. I was like, "I'm dying." She was like, "No." So we joked and stuff. [The team] made me feel comfortable like we'd known each other, not just over a phone, not just over this abortion, but like you've been my doctor for a couple of years, and you know my background. (Amira, 30-year old, Georgia)

TelAbortion provided well-rounded supportive care through providing information for financial resources, giving patients pain medications, sending adjuncts like heating pads and tea, and being responsive to any concerns that arose during or after taking the medications.

> It was super convenient having it ship to your house, and especially everything that they added in it. They put some ibuprofen in there, and they put some condoms in there, they put a heating pack in there. Those little details put you at ease. (Shannon, 37-year old, Illinois)

By recognizing the challenges of obtaining care at a physical clinic and helping patients overcome them by providing an alternative, TelAbortion providers were perceived as highly supportive by many participants. Participants could stay in their home and manage the entire process in an environment in which most participants felt comfortable, which eased the other challenges associated with having a medication abortion.

A fundamental difference between traditional abortion care and direct-to-patient telemedicine abortion is the lack of an in-person interaction with the medical provider. Participants had mixed feelings about not being seen in-person, with some noting initial apprehension. Most participants did not comment on any concerns once they went through the experience. Some even thought it was beneficial not to be face-to-face, allowing them additional anonymity.

> It can be a touchy subject for some people to talk to about. They can feel like they're being judged or looked down upon by sitting in a small office. Being on the phone, I'm like, okay, you're in your safe place, you feel okay. Because at the end of the day, if I didn't want to continue, I could have just hit the End button, and then that's it. It's done. (Sarah, 27-year old, Hawai'i)

Difficulties with mailing delays for the packages and occasional challenges with video connections for the video visits were rare but did occur. Most participants reported that they were well supported by their providers, who stayed in communication and helped resolve these issues. Likewise, participants felt well-equipped to take the medications at home with remote medical supervision. TelAbortion offered person-centered communication and supportive care in a comfortable environment, their home.

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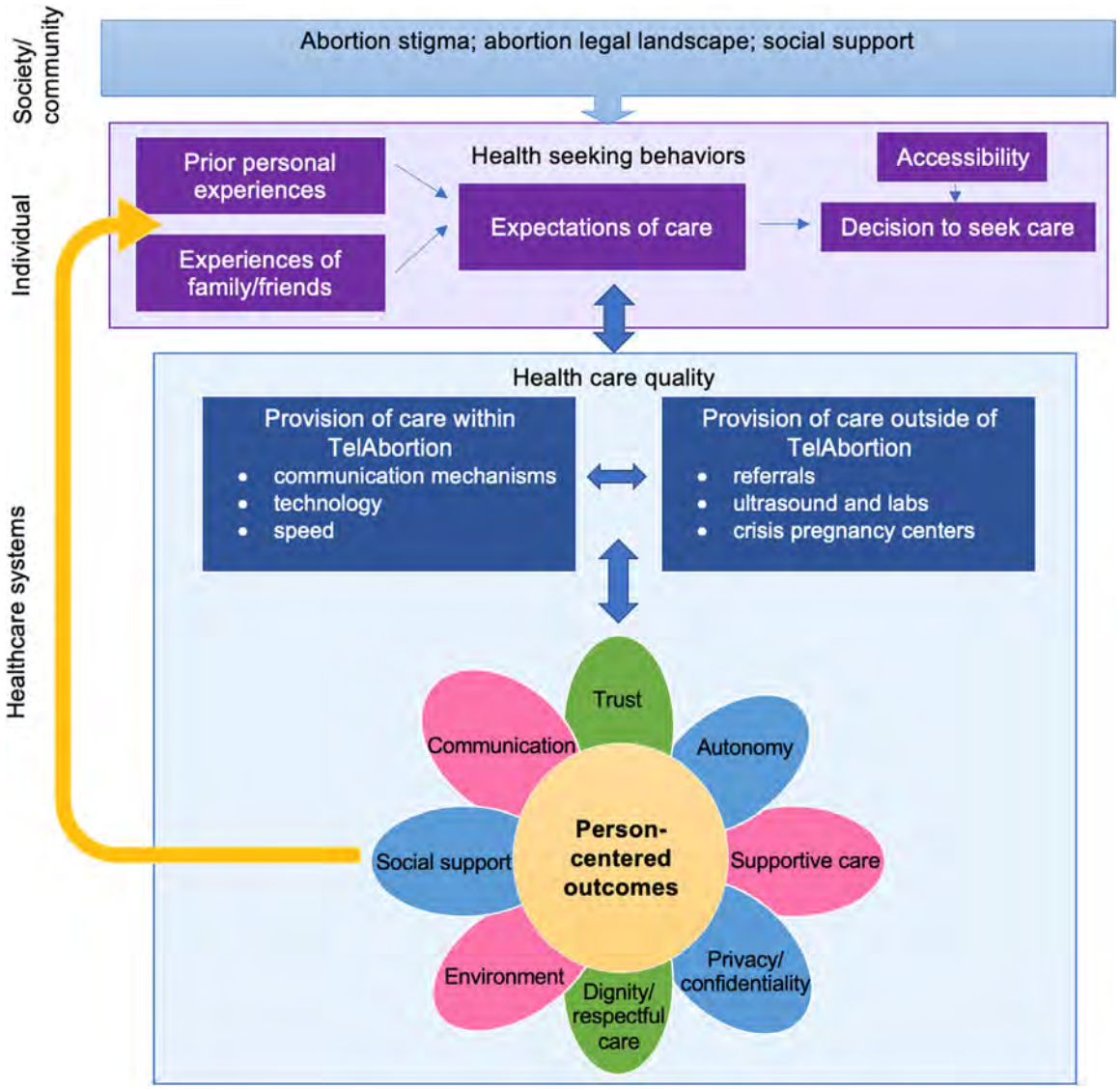

FIGURE 1 Adaptation of the person-centered framework for reproductive health equity (Sudhinaraset et al)[16] for telemedicine. Pink: Participants felt well-supported and safe with TelAbortion; Blue: Participants had autonomy in their care which led to feelings of empowerment; Green: TelAbortion exceeded expectations

Participants had autonomy in their care which led to feelings of empowerment

TelAbortion presented participants with an opportunity to take ownership of their care during a time when they often started by feeling powerless. Nearly all participants commented on how easy the process was once they had found TelAbortion. Being able to plan their visits and take the medications around their own schedule, without missing work or needing additional childcare contributed to the ease. Staying at home also allowed participants to control who was present when they went through the process. Many participants were concerned with a loss of privacy if they had gone into a clinic, so having their abortion entirely at home eliminated this concern. This autonomy meant they could ensure their privacy and involve the social support persons that made them feel most comfortable.

For many participants, completing the abortion quickly was imperative. They identified three main reasons for this urgency: (1) concerns about not being eligible for medication abortion if they waited longer; (2) fears about abortion not being safe later in pregnancy; and (3) emotional and physical difficulties with continuing to be pregnant. TelAbortion often expedited the process so participants received their medication package before they would have had an in-person appointment. They could choose to take medications when it worked best for them, rather than relying on a clinic schedule. Whether it was taking extra time for an intentional process or taking the medications as soon as they arrived in the mail, participants made this decision based on their own needs.

> It was on my own time when I was ready to take the pills in my own comfort zone. If I wanted to cry, I could cry. Nobody was here. That was the most important part of the process for me being able to just be home with the kids and not having to worry about where the kids are going to go, the babysitter and the daycare. (Amira, 30-year old, Georgia)

Having agency in decisions throughout the process transformed the experience into something empowering. TelAbortion not only changed the logistics of the process, but also shaped the emotional experience. It shifted more power to the participant, thus embodying person-centered care. A participant who had a recent in-clinic medication abortion before her TelAbortion compared her experiences:

> I kind of expected it to go like the first time but I felt a little more empowered that I was able to do it on my terms and my time and within the privacy of my own home…It was a sense of like, okay, that this is in my hands. I'm going to do this when I want whereas at [abortion clinic] it was like, okay, "here's this pill, down the hatch." And that's the moment that I'm like, wow, there's no going back once you take the pill. So for me to be able to ritualize that. I was actually with a really close girlfriend. And she supported me through…I think that being able to do it on your terms is a game changer…the freedom of making the choice when you're ready and in the circumstance that is comfortable for you. (Heather, 26-year old, Hawai'i)

The convenience of having medications mailed, ease of being able to work around their own schedule in their own environment, and autonomy of making these decisions was appreciated.

One area of assistance that some participants felt was lacking was emotional support following the abortion. Many participants described this as something that would be helpful for others but that they personally did not need. As 26-year-old Heather from Hawai'i stated, "And I feel like I'm usually pretty good with dealing with the emotional things but a lot of women maybe are not, and maybe this would be something that could be scarring for them and they would find other ways to try to heal that might not be so healthy."

Others did report that they could use additional support.

> I'm only 18, and I really just didn't know how to react to me being pregnant. I just felt really alone, just the fact that I couldn't tell anybody. But for anybody else that gets an abortion and stuff, for the best experience, it would be to always have somebody there, people that understand and accept you and accept the choice you're about to make. I just feel it would make them-- it would have made me more comfortable. (Alanah, 18-year old, Hawai'i)

Some participants felt disconnected from their social support and desired additional external support, but they saw this as more of a problem with society in general than with their abortion care.

> I wish that there was a space for women to speak about this and to process this, but I don't think that can be something attributed to your study…[TelAbortion] did a great job of offering support if I needed it and made it very specific where I can go and who I can talk to about that, which I was very grateful for. But the majority of the healing was talking with the other women, so, in a perfect world, I wish that there was a community around this, to support women in a different or more encompassing way. (Katherine, 29-year old, Oregon)

As the above participants described, this issue of support would likely not have been alleviated with in-person care.

TelAbortion exceeded expectations

Most participants had never received any healthcare via telemedicine and did not have many expectations for telemedicine itself. One participant had a prior TelAbortion and one participant had received medications through the mail from an entirely online service.

Conversely, most participants carried expectations of what an abortion would be like, which then influenced their perceptions and satisfaction with their actual experience. Twelve participants had a prior medication abortion and seven had a procedural abortion, which often shaped expectations. Expectations also arose from stories of other people's abortion experiences, their social spheres, popular culture, and the media. Some participants were unsure of abortion legality, as Aubrey, a 26-year old from Minnesota, explained, "I just wasn't sure if it was legal. I guess I never really thought about it or had to talk about it with anyone and all these politics and politicians were going around about how it's legal in this state and this person's going to make it illegal in this state, so I wasn't sure."

Expectations were heavily influenced by abortion stigma, both internalized and perceived. Table 3 juxtaposes participants' perceptions of abortion care with their actual experience. Stigmatized anti-abortion narratives, such as "you're basically killing a life" (19-year old, Oregon), "you're automatically a slut" (37-year old, Illinois), and "you're being selfish" (34-year old, Georgia) made the process more emotionally distressing, but many participants also embraced the idea of "It's my body, my choice" (26-year old, Illinois).

The resulting experience of TelAbortion was therefore much better than anticipated as seen in Table 3, superseding expectations of shame and judgment with person-centered outcomes of dignity and trust. When asked, all participants reported satisfaction with their care and report that TelAbortion offered a nonjudgmental, safe, and convenient way to access care. It centered the participant by making the process easy, prioritizing their needs, and treating them with respect.

> [I appreciated the] convenience, lack of judgment. And not just lack of judgment, but it was friendlier. It was so much friendlier. It was not just nonjudgmental but just happy to help in the decision that I had had to make, because it's not a pleasant decision. I don't think anybody's like, "Oh, yay. I get to go do this." It's shitty. But at the same time, if you're doing that, you're doing

TABLE 3 Comparison of expectations of what participants might encounter having an abortion and actual experiences of TelAbortion from in-depth interviews with TelAbortion participants

Expectation (participant identification)	Description of expectation	Description of actual experience
Judgmental abortion provider (Katie, 30-year old, Minnesota)	I did think that there would be a lot more judgment and stigma from the medical people that were operating the center.	They just kind of trusted you as an adult that you knew that this decision was right for you and they help in a really nonjudgmental manner, which I wasn't expecting.
Pressure to make a particular decision (Adriana, 34-year old, Maryland)	I really thought it would be extremely negative and that I would second guess my decision and that people would try to convince me to not have the process.	I realized that everybody who was participating and helped were really kind and really supportive, and nobody questioned my decision. And if anything, they just wanted me to feel comfortable while I was doing it.
Community stigma (Amanda, 26-year old, Minnesota)	There's billboards all over my city, just about, how life begins at conception and how babies have heartbeats at two days of—honestly, they're very much not about abortion. So the idea of when they said that there was protestors outside really scared me because I don't know how crazy those people are.	Where I live really played a role in it because of how people are so against it, and so being able to do it at home and nobody knew I was even doing it is very relieving.
Difficulty accessing abortion care (Nora, 29-year old, Oregon)	In Tennessee, I would have had to drive to Nashville, a 45-minute drive and sometimes I probably would have even hit a brick wall. You never know.	I was surprised at how just-- there was someone available. Someone was able to get me in right away. I didn't have to jump through hoops or anything to do it… It was pretty pleasant. I was pretty surprised at how easy and simple it was made for me. I really appreciate that.
Protestors (Jess, 32-year old, Colorado)	A lot of the clinics over there actually do get petitioners and protestors all the time. So a majority of the time when you are going to a Planned Parenthood out there, you are going to run into protestors and things like that. Just having to deal with that makes you feel worse about your decision and makes you feel more guilty about things.	It was nice because you do everything in the comfort of your own home. You don't have to go to a clinic and possibly have protestors there waiting. Saying, "You're going to do X, Y, Z," or objectifying or looking at you any sort of way just because you're seen going into a Planned Parenthood. Everything's at your home. All you have to do is wait for a package. Nobody knows it's from Planned Parenthood… You don't have anybody's views or opinions in the mix of what you're doing. It's basically your own personal business and that's what I liked about it…You're in the comfort of your own home.
Hostile clinic environment (Leanne, 36-year old, Colorado)	I went in there and it was weird because a lot of these [abortion] clinics are lockdown style and bulletproof glass. And I remember the one time like, "Man. This is kind of scary." And I realized it was because they would perform abortions. And so that kind of informed my decision too, just my memory of going into the wrong clinic to try and get birth control and being like, wait, it feels weird.	It was pretty cool, quote that "pretty cool". No, it was just really nice to have this option to be in my home. I could have done a few things better. But at the end of the day, I was just very grateful that I had access to the service.
Traumatic abortion process (Alanah, 18-year old, Hawai'i)	I honestly thought it would just be a terrible process because I had this one friend who was 12, and she got pregnant. But at the time, she was far along, so she had to get surgery. And I don't know, it just seemed like it really changed her. She just got so depressed, and it was such a painful experience. I thought, "I could never put myself through that." She made it seem like it was terrible, which is why I was scared.	It just seemed like I overreacted towards the process, I guess. I thought it was going to be something so heavy, something so scary, but it really wasn't. It was super easy. It was just getting your period and stuff like that. And I just want other girls to know it's not as scary as you think it is. If it's really what you want, it's not scary. It's just like getting your period.

> it for a good reason. And it was a much more pleasant experience. You can tell even from the way that the [TelAbortion website] is worded, they're there to help people and they have that perspective on it instead of it being a nasty business to be associated with. (Jen, 31-year old, New York)

Changing expectations surrounding abortion with participants reporting a good experience has downstream effects. Many participants shared their experience with friends and all said they would recommend TelAbortion if they knew of someone looking for abortion care. Since TelAbortion was highly acceptable to them personally, many felt a need to share with

others, so others would not be in the same situation of expecting a bad experience.

> I hope it [TelAbortion] keeps expanding to be an available product and service, and I really, really hope that it turns to something where people are more accustomed to this being the medical procedure it is… I think the stigma itself comes from the [lack of] availability of [abortion], and the availability of it will lead to the stigma changing. (Megan, 26-year old, Colorado)

Challenges arose when interfacing with the healthcare system outside of TelAbortion

Although communicating with their study team, receiving, and taking the medications generally was easy, participants encountered difficulties when interacting with other healthcare entities, either before finding out about TelAbortion or when obtaining labs or ultrasounds. Some participants were referred directly to TelAbortion from their provider without issues, but many did not feel comfortable talking to their healthcare providers or did not have a primary care provider that they could easily reach. In a few cases, participants were denied a referral and were treated poorly. One participant called her obstetrician's office "to ask if they had any information about it, and they shot me down about it and hung up" (20-year old, Oregon). In another case, a participant saw three different medical providers in-person before finally being referred to TelAbortion.

Most participants had to interact with some healthcare providers outside of their study site to obtain labs or ultrasound or pick up additional medications from a pharmacy. This led to logistical issues with finding nearby facilities, getting appropriate referrals, and having orders misplaced along the way, all of which delayed their abortion.

Interacting with outside providers put participants in the position of having to decide if they would disclose that they were having an abortion. Because of abortion stigma, this decision involved weighing risks.

> Because you had to get a referral for an ultrasound and stuff, and everybody that I talked to, I basically had to explain what I was doing and who it was for because they were just like, "Well, why isn't your OB prescribing this?" So I had to explain to everybody like, "Because I'm getting a fucking abortion." (Aubrey, 26-year old, Minnesota)

Others concealed their pregnancy intentions, due to perceived abortion stigma making them fear judgment. This resulted in uncomfortable situations, compromising trust and honesty in healthcare. Additionally, most outside healthcare workers assumed that a pregnancy would be welcome.

> I didn't feel comfortable talking to the person about what was going on. So of course, they were like, "Oh, congratulations." I'm like, "Yeah." I had to play along with that, and that felt really uncomfortable. (Jeanne 40-year old, Illinois)

Between the scheduling and travel logistics and discomfort with revealing or concealing their planned abortion, obtaining an ultrasound was often the hardest part of the entire abortion process. In some cases, participants went to crisis pregnancy centers (CPCs) for their ultrasound, often not realizing that CPCs are designed to convince patients to not obtain an abortion.

> And I can tell that they're against abortions and everything like that, so even though…I told her that I wasn't going to keep it. And she didn't have a nonchalant attitude about it…But I sucked it up, and all I really needed was the ultrasound, not their opinion…So I just went ahead and got the ultrasound. (Brittney, 24-year old, Georgia)

Other participants were aware of CPCs and purposely avoided them. Even when accessing traditional medical care, they faced judgment.

> I had a woman that was doing my vitals…And she was talking about the baby, and talking about the baby, and asking me questions, if I had a name picked out and all of that. And after I said, "Actually, I'm getting an abortion. I just need this stuff done so that I can get the abortion." And she gave me the meanest look. I told her, I said, "It's my choice." And she told me that there was a special place in hell for people like me. So that's the discrimination that I'm talking about, seeing that people don't know the situation. And they don't know that I'm trying to escape an abusive situation. (Marisa, 26-year old, Illinois)

These instances of enacted abortion stigma stood out as the most difficult parts of the abortion experience for these individuals. Even when prejudice was not explicit, participants explained that it was emotional to see the ultrasound, physically invasive with transvaginal ultrasounds, and added another step.

Multiple participants identified eliminating ultrasound requirements as a way to improve their TelAbortion experience. Many felt confident determining their pregnancy status without an ultrasound. As 27-year-old Rosa from Minnesota explained, "I already did take a pregnancy test, but I feel like I have to take [the ultrasound] with them so they are really sure that I am pregnant. I feel like I did the test more for them than I did it for myself."

Due to practice changes during the early COVID-19 pandemic, eight participants did not have an ultrasound before their abortion. These participants trusted their providers to ensure they did the necessary testing and were relieved to eliminate another step they thought was inconvenient or unnecessary.

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> I didn't see the need of doing bloodwork or having an ultrasound and doing anything like that…If I was like 15 weeks, then okay, but it was only like 8 weeks. And if you don't need it, that's okay. It was convenient that I didn't have to do that. I didn't even have to go see a doctor. I'm like, "I don't want to do that. Just let me get this over with." (Regina, 35-year old, New York)

Each additional step in the process added time, money, and the potential for uncomfortable interactions. Many participants supported streamlining the process and making medication abortion more widely available. "I mean, it would've been easier if I could've just bought it at Target [laughter]. Why can't we find this on Amazon?" (Kelly, 36-year old, Minnesota).

Care provided entirely within the direct-to-patient telemedicine abortion process while eliminating external steps fulfilled participants' needs and minimized opportunities for judgment.

DISCUSSION

Patient experiences demonstrate that TelAbortion is person-centered care, which can be a model for other direct-to-patient telemedicine abortion care. Participants felt safe, supported, and empowered, which often exceeded their expectations for an abortion experience. Challenges participants encountered during their medication abortion through TelAbortion came from external factors, including the outside healthcare system and overarching abortion stigma.

The person-centered outcomes from the PCFRHE are applicable to and met by direct-to-patient telemedicine abortion with TelAbortion. The first theme illustrates how open communication, supportive care, and being at home led participants to feel safe and well supported. With this foundation of support, participants were then able to turn this experience into something comfortable and even empowering as shown in the second theme. With TelAbortion, participants could take control, particularly in terms of who else was involved, affording them privacy and support from others when desired. Participants' expectations about abortion often were negative but their interactions with their TelAbortion teams engendered trust and they felt their decisions were respected.

The impact of telemedicine on abortion care does have unique features since abortion is highly stigmatized, which influenced the support participants both needed and received. Participants assumed that others may have a traumatic abortion experience and need more support, despite their personal experience of having an abortion without emotional distress, which could be an empathetic reflex, but also may demonstrate internalized abortion stigma. Stigma around abortion care contributed to a lack of spaces to talk about abortion, or lack of patient comfort with talking about it, and thus affected the patient's sense of support when completing the abortion remotely.

Abortion stigma presented in three ways with our participants: a sense that abortion would be emotionally traumatic for others, expectations for a judgmental and arduous abortion experience, and discrimination from outside healthcare workers, consistent with internalized, perceived, and enacted abortion stigma.[20] Abortion stigma appropriately is at the highest level of the PCFRHE (Figure 1) as it affected aspects of participants seeking and receiving care and their perception of the quality of care given the change from expectations. Interestingly, there was not much geographic difference noted in experiences of abortion stigma. Those living in states where abortion is less restricted or even legally protected still encountered hostility toward abortion and demonstrated perceived and internalized abortion stigma. In this stigmatized context, having person-centered care was even more impactful, particularly in the domains of privacy, dignity, and trust. Being able to avoid hostile healthcare environments, feel safe at home, and gain autonomy by controlling elements of the process decreased the stigma felt.

The person-centered quality of care not only impacts the outcomes for an individual but also feeds back and changes personal and community level expectations for care, which then influences the decision to access care. We noted this with participants who had a prior abortion experience and were seeking something different with telemedicine abortion. The original PCFRHE emphasizes this bidirectional flow of poor-quality care leading that person and their community to be less likely to seek care or expect high-quality care.[16] Therefore, by providing person-centered care, these participants describe the opposite being true: after receiving high-quality care, they are more likely to tell others about it, and in turn, access to abortion care could increase.

Although responses to TelAbortion were overwhelmingly positive, areas for improvement did emerge. Providing emotional support resources to every patient and routinely asking about mental health at follow up encounters and providing referrals for additional care if needed would enhance the social support, especially when providing stigmatized care where patients are less likely to rely on their typical support networks. This challenge of providing emotional support is not unique to telemedicine abortion and could also be improved for those seeking traditional care.[27] While the abortion itself does not cause long-term adverse mental health outcomes, there can be significant trauma and stress from dealing with an unplanned and undesired pregnancy, so this support is important with any abortion care.[28] Perceived abortion stigma at the time of the abortion has been shown to increase psychological distress years later, so by decreasing stigma with direct-to-patient telemedicine abortion, participants may have better long-term outcomes.[29]

Another area to improve is lessening reliance on outside medical facilities for providing ultrasounds since this was often a challenging experience, whether in traditional healthcare facilities or CPCs. Eliminating pre-abortion ultrasounds where clinically appropriate can facilitate telemedicine and eliminate this burden; however, there still will be cases when ultrasound is required.[7] Educating sonographers on the range of reasons for early pregnancy ultrasounds and provision of non-judgmental care is essential.

A strength of this study is that it captured the experiences of people seeking abortion care before and during the COVID-19 pandemic. During the pandemic, participants were less likely to have other

options, but rather than having decreased satisfaction because options were limited, they appreciated telemedicine from a safety standpoint.[22] Participants' reasons for choosing telemedicine, satisfaction with care, and the person-centeredness of the care were consistent from before to during the pandemic, indicating that the value of direct-to-patient telemedicine abortion existed before, and likely will continue to exist after the current pandemic. Due to changing practices, people who received care during the pandemic were less likely to have had an ultrasound prior to their abortion and were comfortable trusting that their provider would have them do testing if necessary. The convenience of not having to physically attend any appointments and the privacy that afforded was notable in the group who did not have pre-abortion ultrasounds.

This study is limited by the self-selected nature of participants. We only interviewed people who opted to complete a TelAbortion instead of an in-clinic visit and therefore had the appropriate technology to use telemedicine. The perspectives of people who considered but declined TelAbortion are not represented and serve as a reminder that maintaining in-person care is still important for people who cannot access telemedicine or who prefer in-person visits. We anticipated that people with either very good or bad experiences were more likely to participate; subsequently all participants were satisfied with TelAbortion. Participants still provided suggestions to improve TelAbortion even when they were generally content with it. Another limitation is that all participants received their care in a study setting. They paid for their abortion, which simulates a non-study population, but the study staff may have been more attentive or persistent at follow-up than what routine clinical staff could provide in a non-study setting. Given the significance of good communication on patient experience, it is a critical component for any direct-to-patient telemedicine abortion service to provide. Finally, we acknowledge that the findings may not be generalizable outside of the specific TelAbortion model given the heterogeneity of telemedicine models.

Features of the TelAbortion model of direct-to-patient telemedicine abortion may be applied to other types of care. We have identified five ways in which telemedicine can be adopted in a person-centered way based on our participants' experiences: (1) Establish a means of open communication from the first contact with a phone line or messaging service; (2) Use a combination of oral and written patient education materials so that patients can ask questions during the encounter and have instructions to follow after the visit; (3) Offer a variety of times for scheduling and minimize scheduling delays; (4) Minimize reliance on outside healthcare systems when working with stigmatized care like abortion; and (5) Provide supportive care such as pain medications, emotional support resources, and recommendations for when having a support person available may help.

Provision of direct-to-patient telemedicine abortion will likely still be in demand after the current pandemic given its convenience, autonomy, and privacy. As new telemedicine services are developed, these principles can be a guide to emphasize person-centered care. TelAbortion demonstrates that direct-to-patient telemedicine abortion can be person-centered care and provide a high quality, empowering alternative to clinic-based care for people seeking care in a stigmatized abortion landscape.

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CONFLICT OF INTEREST

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Original Research Article

Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models

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ABSTRACT

Objective: To demonstrate the effectiveness of medication abortion with the implementation of telemedicine and a no-test protocol in response to the COVID-19 pandemic.
Study design: This is a retrospective cohort study of patients who had a medication abortion up to 77 days gestation at the University of Hawai'i between April and November 2020. Patients had the option of traditional in clinic care or telemedicine with either in clinic pickup or mailing of medications. During this time, a no-test protocol for medication abortion without prior labs or ultrasound was in place for eligible patients. The primary outcome was the rate of successful medication abortion without surgical intervention. Secondary outcomes included abortion-related complications.
Results: A total of 334 patients were dispensed mifepristone and misoprostol, 149 (44.6%) with telemedicine with in-person pickup of medications, 75 (22.5%) via telemedicine with medications mailed, and 110 (32.9%) via traditional in person visits. The overall rate of complete medication abortion without surgical intervention was 95.8%, with success rates of 96.8, 97.1, and 93.6% for the clinic pickup, mail, and clinic visit groups, respectively. Success for those without an ultrasound performed prior to the procedure was 96.6%, compared to 95.5% for those with ultrasound. We obtained follow-up data for 87.8% of participants.
Conclusions: Medication abortion was safe and effective while offering multiple modes of care delivery including telemedicine visits without an ultrasound performed prior to dispensing medications.
Implications: Incorporating telemedicine and a no-test protocol for medication abortion is safe and has the potential to expand access to abortion care. All care models had low rates of adverse events, which contradicts the idea that the Risk Evaluation and Mitigation Strategyincreases the safety of medication abortion.

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1. Introduction

The COVID-19 pandemic greatly impacted the delivery of healthcare services. Healthcare providers and healthcare systems made rapid shifts from face-to-face medical visits to telemedicine, even for non-COVID positive patients [1]. This rapid increase in the use of telemedicine services since the start of the pandemic has been well accepted, with one retrospective study showing significantly higher patient satisfaction with telemedicine visits compared to in-person visits [2]. Although the body of evidence surrounding the implementation of telemedicine during the pandemic is still growing, early studies have demonstrated its utility in providing safe and satisfactory care to patients.

Prior to the COVID-19 pandemic, several medication abortion delivery models already included telemedicine. Clinic-to-clinic telemedicine models, which incorporate preabortion testing at a clinic remote from where the mifepristone provider is located, a videoconference with the provider, and dispensing abortion medications at a remote site, demonstrated no difference in rates of adverse events, ongoing pregnancy, or blood transfusion compared to in-person visits [3, 4]. Gynuity Health Project's TelAbortion study, in which patients received mifepristone and misoprostol via mail after a telemedicine visit, also demonstrated high abortion completion and low complication rates [5]. In addition, patients and

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providers have found these telemedicine models to be acceptable and satisfactory forms of care delivery [4–6].

Hawai'i has the unique geographic challenge of being comprised of many islands with abortion care only offered on Oahu, Hawai'i Island, and Maui. This challenge was exacerbated by the pandemic, since the prepandemic practice of having patients fly in for a visit now has the added risk of COVID-19 exposure, plus varying limitations and quarantine requirements for interisland travel. In an effort to respond to the COVID-19 pandemic, our clinic expanded use of telemedicine and also adopted a new no-test medication abortion protocol for eligible patients while continuing to offer in person face-to-face visits for medication abortion. The no-test protocol is based on evidence demonstrating that preabortion testing with labs and ultrasound can often be safely omitted for many patients, thus eliminating the need for any in person visit prior to receiving a medication abortion [7]. With appropriate counseling from a clinician, much of the medication abortion process can be managed independently by patients, including confirmation of pregnancy, self-administration of medications, and management of side-effects [8]. Our clinic now offers a variety of models for medication abortion including traditional in-person visits and telemedicine visits with medications dispensed from clinic or by mail, while utilizing a no-test medication abortion protocol for eligible patients. The objective of this study was to describe our experience with these delivery models operating simultaneously.

2. Methods

2.1. Medication abortion protocol

We conducted a retrospective cohort study of patients seen via multiple care models between April 1, 2020 and November 30, 2020 during the COVID-19 pandemic in Hawai'i. Our primary objective was to describe our experience with medication abortion when multiple medication abortion service delivery models were offered to patients. The primary outcome we sought to describe was successful medication abortion, defined as medication abortion completed without any need for surgical intervention. We also described the proportion of patients who had an incomplete abortion (retained gestational sac or tissue without viable pregnancy), ongoing pregnancy (continued viable pregnancy after taking medications), took additional misoprostol beyond what was initially dispensed, received a blood transfusion, or sought care in an emergency room (ER) for an abortion-related concern.

Our family planning clinic is an academic practice with two locations on Oahu and one on Hawai'i Island, with centralized scheduling for abortion care. After April 1, 2020, patients contacting the clinic selected a medication abortion service delivery model depending on their clinical presentation, telemedicine capability, geographic location, and personal preferences, with some limitations. These options are outlined in Table 1. We also continued to offer surgical abortions throughout this time period. Eligibility determination (clinical history, assessment of gestational age) and counseling were conducted either in-person or via telemedicine using synchronous Zoom videoconferencing. Mifepristone consent forms were signed either in person or via telemedicine with an electronic consent. Patients who participated in the TelAbortion Project could have medications mailed to any address in Hawai'i. We also mailed medications to non-study patients under the U.S. District Court for the District of Maryland ruling that temporarily put a hold on the Risk Evaluation and Mitigation Strategy (REMS) in person dispensing requirement during the pandemic.

Patients who had a known last menstrual period (certainty within 1 week) that gave them a gestational age of 11 weeks or less, had regular periods and did not have any risk factors for ectopic pregnancy (prior ectopic pregnancy, tubal surgery, intrauterine contraception use at the time of conception) or symptoms of ectopic pregnancy (vaginal bleeding or pelvic pain in the past week) could forgo an ultrasound. If any of these criteria were not met or the patient desired an ultrasound, we referred the patient for an ultrasound prior to dispensing medications, or performed it while the patient already was in clinic. TelAbortion patients were required to have an ultrasound or pelvic examination performed before being mailed medications.

We provided medication abortion up to 77 days gestation. All patients were dispensed 200 mg mifepristone and 2 doses of 800 mcg misoprostol. We counseled patients to take oral mifepristone followed in 24 to 48 hours by 800 mcg misoprostol, either buccally or vaginally. If they did not start bleeding within 24 hours of their first dose of misoprostol, we advised that they take a second dose of 800 mcg misoprostol. For pregnancies at 63 to 77 days, we instructed patients to take a second dose of 800 mcg misoprostol four hours after the first dose. We required documentation of Rh type for patients above 70 days gestation and administered Rh-immune globulin either at our clinic or a location closer to the patient if more convenient.

Standard follow-up was a telemedicine visit by videoconference or telephone 1 to 2 weeks after ingestion of mifepristone and a high sensitivity urine pregnancy test taken 4 weeks after mifepristone, followed by a phone call from clinic staff. We dispensed urine pregnancy tests with the medications. We also offered patients the option of having an ultrasound at any convenient clinic 1 to 2 weeks after mifepristone ingestion or obtaining serial serum human chorionic gonadotropin (hCG) levels, particularly if they were going to be traveling out of state or desired a long-acting reversible contraceptive method sooner than 4 weeks after the abortion. If the initial telemedicine follow-up visit was concerning for ongoing pregnancy based on provider judgment of the lack of appropriate bleeding or continuation of pregnancy symptoms, we scheduled the patient for an ultrasound. Likewise, if a urine pregnancy test remained positive 4 to 5 weeks after the abortion, patients were advised to have a serum hCG or ultrasound. Patients could contact our on-call physicians at any time with issues or go to their local emergency room.

2.2. Data abstraction and analysis

We performed a retrospective chart review of all patients who initiated a medication abortion visit from April through November 2020. Authorization to perform a chart review was obtained from the Western Institutional Review Board. We excluded patients who were not dispensed the medications.

Researchers independently abstracted de-identified data from patient charts into a secure Qualtrics XM (Qualtrics, Provo, UT) database. We reviewed clinical notes, demographic data, lab results, outside provider notes, and emergency department records. Electronic medical records from the largest health systems in the state were accessible for review when assessing outcomes. We collected data on demographics, payor type, medical history, gestational age, testing done prior to the abortion, medications provided, medications taken, abortion outcome, and complications. If a patient had more than one medication abortion during the time period, we included all encounters. We reported gestational age at the time of dispensing medications based on either ultrasound dating if available or last menstrual period (LMP).

Successful medication abortion was determined by patient history, urine pregnancy tests, serum hCG, and/or ultrasound. Since our last patient included in the database received their medications by November 30, 2020, all patients were followed for at least 8 weeks to confirm abortion outcomes prior to chart abstraction.

Table 1
Service delivery models for medication abortion care at the University of Hawai'i between April and November 2020

Date initiated	Service delivery model	Additional information
April 1, 2020	**In Clinic Visit + Pick Up** – Ultrasound for gestational age dating only if indicated – In-Person Visit Dispensed Mifepristone and Misoprostol from the office during their visit	Was the standard model prior to April 2020 with ultrasound routinely performed
April 1, 2020	**Telemedicine Visit + Pick Up** – Ultrasound for gestational age dating only if indicated – Telemedicine Visit Dispensed Mifepristone and Misoprostol from office on Oahu or Hawai'i Island after their visit	Interaction in person typically lasted less than 5 minutes with a medical assistant dispensing medications.
Program began in 2016, ongoing on April 1, 2020	**Telemedicine + Mail (TelAbortion Project)** – Ultrasound for gestational age dating for all patients – Telemedicine Visit Dispensed Mifepristone and Misoprostol by mail	Only eligible up to 70 days gestation. Details described in previous publication [5].
October 1, 2020	**Telemedicine + Mail** – Ultrasound for gestational age dating only if indicated – Telemedicine Visit Dispensed Mifepristone and Misoprostol by mail	We mailed medications to patients who did not participate in the TelAbortion study under the US District Court ruling. Patients decided on this option if they wished to forgo an ultrasound or did not want to participate in a study.

Descriptive statistics were performed using SPSS Version 27 (IBM, Armonk, NY). We included all patients seen for medication abortion in our practice during the study time period. Pearson's chi-squared tests were used for the primary outcomes but no significant difference in outcomes based on method of dispensing mifepristone or if ultrasound was completed were noted, so they are not displayed.

3. Results

From April through November 2020, we dispensed mifepristone and misoprostol for 334 medication abortions, with a total of 330 unique patients. Patients did not vary demographically based on mode of dispensing medications, except by island where they lived, as shown in Table 2. Four patients (1.2%) had an early pregnancy loss, four (1.2%) stated they were terminating the pregnancy because of maternal health, and one individual stated the pregnancy had resulted from rape.

Figure 1 shows the breakdown of the different methods of receiving care, with two thirds completing a telemedicine visit and one third going to clinic. Of the 223 (66.8%) patients who had an ultrasound performed, 139 (62.3%) were performed prior to presenting to our clinic, 51 (22.9%) were performed for routine gestational dating after presenting to our clinic, 19 (8.5%) were required due to unsure LMP, and 14 (6.3%) due to a history of or symptoms concerning for ectopic pregnancy, 7 of whom had a prior ectopic. Two hundred and thirteen patients (63.8%) had a known Rh type prior to the abortion, either present in their medical records (173, 81.2%), self-reported (24, 11.3%), or ordered specifically for the abortion (16, 7.5%). Patients chose their route of misoprostol administration, with 148 (51.6%) choosing buccal, 93 (32.4%) vaginal, and 46 (16.0%) not reported.

The primary and secondary outcomes are presented in Table 3. Seven patients who were dispensed medications reported that they did not take them and were excluded from analysis of the outcomes. Twelve of 287 patients with follow up data underwent uterine aspiration, giving an overall rate of successful medication abortion of 95.8%. If 100% success is assumed for those without follow up data, 315 out of 327 (96.3%) had a successful medication abortion. If failure is assumed for all those without follow up, 275 out of 327 (84.1%) would have been successful. Of the 12 aspiration procedures done, there were three ongoing pregnancies, four incomplete abortions with a gestational sac present, four procedures for heavy bleeding and/or retained tissue, and one patient who changed her mind after taking mifepristone and desired a surgical abortion rather than taking misoprostol. The subgroups did not have any significant difference in the primary outcome.

Rates of follow up are presented in Table 4, with patient history obtained from over three-quarters of patients, followed by urine pregnancy test results, ultrasound, and serum hCG levels. The mean time from dispensing to taking medications was 1.8 ± 2.6 days and the mean interval from dispensing medications to obtaining the first follow up information was 19.0 ± 12.7 days. There were significant differences in these intervals between the cohorts as expected due to the specifics of each delivery model.

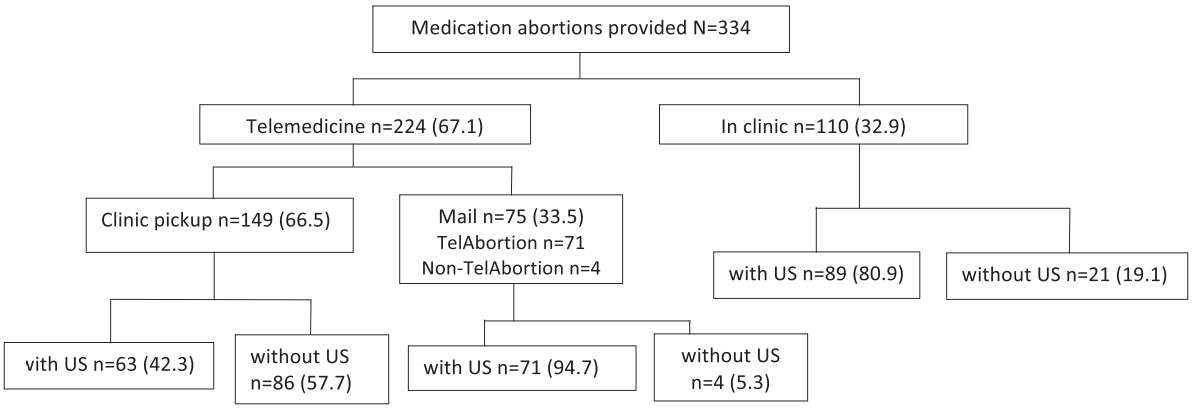

Fig. 1. Methods of providing medication abortion to patients at the University of Hawai'i between April and November 2020. US, ultrasound

Table 2
Demographic characteristics of patients who were dispensed mifepristone and misoprostol for a medication abortion through the University of Hawai'i between April through November 2020. Displayed as n (%) unless otherwise indicated

Characteristics	All Participants (N = 334)	In clinic (n = 110)	Telemedicine + pickup (n = 149)	Telemedicine + mail (n = 75)
Age (y), mean (SD)	27.8 (6.4)	28.1 (7.0)	27.3 (6.3)	28.5 (5.6)
Gravidity, mean (SD)	2.9 (2.0)	2.8 (1.8)	2.8 (1.9)	3.1 (2.3)
Parity, mean (SD)	1.0 (1.3)	1.1 (1.2)	0.9 (1.1)	1.3 (1.6)
Prior abortion	115 (34.4)	36 (32.7)	47 (31.5)	32 (42.7)
Prior medication abortion	44 (13.2)	11 (10.0)	20 (13.4)	13 (17.3)
Race/ethnicity[a]				
Filipino	44 (13.2)	9 (8.3)	18 (12.1)	17 (22.7)
Japanese	27 (8.1)	13 (11.9)	9 (6.0)	5 (6.7)
Other Asian	32 (9.6)	12 (10.9)	10 (6.7)	10 (13.3)
Black	12 (3.6)	6 (5.5)	5 (3.4)	1 (1.3)
Hispanic	29 (8.7)	11 (10.0)	10 (6.8)	8 (10.7)
Native American	7 (2.1)	3 (2.8)	1 (0.7)	3 (4.0)
Native Hawaiian	71 (21.3)	21 (19.3)	27 (18.1)	23 (30.7)
Pacific Islander	15 (4.5)	5 (4.5)	4 (2.7)	6 (8.0)
White	97 (29.0)	30 (27.3)	24 (16.1)	43 (57.3)
Unknown	81 (24.6)	25 (22.9)	56 (37.6)	1 (1.3)
Island[b]				
Oahu	196 (58.7)	87 (79.1)	108 (72.5)	1 (1.3)
Hawai'i	71 (21.3)	21 (19.1)	41 (27.5)	9 (12.0)
Kauai	58 (17.4)	1 (0.9)	0 (0)	57 (76.0)
Lanai	3 (0.9)	0 (0)	0 (0)	3 (4.0)
Maui	4 (1.2)	1 (0.9)	0 (0)	3 (4.0)
Molokai	2 (0.6)	0 (0)	0 (0)	2 (2.7)
Payment method[a]				
Private insurance	128 (38.3)	45 (40.9)	56 (37.6)	27 (36.0)
Medicaid	118 (35.3)	35 (31.8)	48 (32.2)	35 (46.7)
Paid by patient	110 (32.9)	30 (27.3)	47 (31.5)	33 (44.0)
Site abortion fund	8 (2.2)	0 (0)	0 (0)	8 (10.7)
Gestational age when dispensing medications				
Less than 49 d	130 (38.9)	49 (44.5)	51 (34.5)	30 (40.0)
49–62 d	165 (49.4)	55 (50.0)	75 (50.3)	35 (46.7)
63–77 d	39 (11.7)	6 (5.5)	23 (15.4)	10 (13.3)

[a] Multiple options could be selected for these questions so percentages do not equal 100%.
[b] Significant difference of mode of dispensing medications by island ($p < 0.001$)

Table 3
Medication abortion outcomes for patients who obtained a medication abortion via the University of Hawai'i with an in clinic visit or with telemedicine followed by clinic pickup or mailing of medications, with or without ultrasound prior

	n[a]	Gestational age (days, median [IQR])	Follow up data obtained	Medication abortion completion without surgery	Complications		
					Additional misoprostol[b]	Blood transfusion	ER visit[c]
All patients	327	52 [45–58]	287 (87.8)	275 (95.8)	4 (1.4)	2 (0.7)	11 (3.8)
In clinic	110	50 [45–57]	94 (85.5)	88 (93.6)	1 (1.1)	0 (0)	2 (2.1)
Telemedicine + pickup	145	51 [46–59]	124 (85.5)	120 (96.8)	1 (0.8)	2 (1.6)	5 (4.0)
Telemedicine + mail	72	50 [44–59]	69 (95.8)	67 (97.1)	2 (2.9)	0 (0)	4 (5.8)
With ultrasound	219	52 [45–59]	199 (90.9)	190 (95.5)	3 (1.5)	1 (0.5)	9 (4.5)
Without ultrasound	108	48 [44–55]	88 (81.5)	85 (96.6)	1 (1.1)	1 (1.1)	2 (2.3)

[a] Excludes 7 participants who were dispensed the medications but did not take them: 3 who were mailed medications and 4 who picked up the medications from clinic.
[b] Additional misoprostol beyond the 8 tablets dispensed routinely.
[c] ER visit = emergency room visit for any abortion-related concern.

Table 4
Follow-up methods used by 327 patients who received medication abortion care at the University of Hawai'i between April and November 2020

Mode of follow up	Total (n = 327)	In clinic (n = 110)	Telemedicine + pickup (n = 145)	Telemedicine + mail (n = 72)
Patient history	253 (77.4)	85 (77.3)	112 (77.2)	56 (77.8)
Ultrasound	66 (20.2)	28 (25.5)	23 (15.9)	15 (20.8)
Serum hCG	19 (5.8)	5 (4.5)	5 (3.4)	9 (12.5)
Urine pregnancy test	156 (47.7)	40 (36.4)	69 (47.6)	47 (65.3)
No follow up	40 (12.2)	16 (14.5)	21 (14.5)	3 (4.2)

hCG, human chorionic gonadotropin.
Displayed as n (%) with a denominator of the number who were dispensed the medications and did not have evidence that they chose not to take the medications. Patients often followed up by >1 method.

4. Discussion

This retrospective cohort study demonstrates high medication abortion effectiveness amongst people using telemedicine with medications dispensed in clinic or by mail, as well as traditional in person care. The medication abortion success is comparable to previously published data of people dispensed mifepristone in clinic [9, 10]. The 87.8% follow up rate is higher than many prior observational studies of medication abortion [11, 12]. We were able to access the records of the major medical systems in our state so even if the patient did not complete their follow up visit, we were able to obtain information about any visits within those systems. Therefore, it is highly unlikely that the sensitivity analysis scenario where all patients who did not follow up required a surgical procedure is true.

Rates of abortion success are similar for all methods of dispensing mifepristone and misoprostol. They are also similar for those who did and did not have an ultrasound performed prior to the abortion. A limitation of this study is that our patient population was relatively small and unsuccessful medication abortions are rare, so we were underpowered to make groupwise comparisons. No differences between groups were noted for the primary outcome, although the in clinic group trended towards lower success.

Complications were rare with only 2 patients requiring a blood transfusion, 4 who received additional misoprostol and 11 who went to an emergency room. We did not find any hospital admissions, missed ectopic pregnancies, unrecognized ongoing pregnancies, expulsion of a fetus at an advanced gestational age, infections, or hysterectomies. Given that all 3 groups had similar, low rates of adverse events, this does not support that the REMS increases the safety of medication abortion.

Telemedicine is an acceptable option for patients, with 60% of patients living on the islands with all options available using it. Although individuals generally were offered all the options for receiving care, some did not have a choice. Patients reporting an unsure LMP or who needed an interpreter were directed to in person care, whereas individuals living on islands other than Oahu or Hawai'i Island were preferentially offered medication abortion by mail since it would be more complicated for them to arrange a flight to our clinic. Sixty-two patients living on islands without abortion providers were able to have an abortion without flying to a different island. During this pandemic, both spending time at a healthcare facility and traveling puts patients at higher risk of being exposed to COVID-19. Telemedicine with either a quick in clinic pickup or mailing of medications decreases this risk of COVID-19 exposure and transmission.

It is important to highlight that technological barriers to using telemedicine may exacerbate existing health disparities rather than decreasing disparities by increasing access [13, 14]. This can lead to intervention-generated inequalities, widening the gap between those who own a device with videoconferencing capability, are comfortable using that technology, and have access to the internet versus those who do not have these resources. The same people who have access to technology are also likely to be more educated with more social and economic resources, reinforcing the already better health outcomes of this group [15]. In addition, interpreter services may not be as readily available for use in telemedicine, impacting the options available for those with low English proficiency [13]. A third of our patients still came to clinic, demonstrating that it is still important to offer a clinic option for those who have limited technology access, screen in to requiring an ultrasound, or prefer a face-to-face interaction.

This study provides evidence from a practical approach to incorporating telemedicine and eliminating routine testing from medication abortion care. Multimodal care delivery is feasible and did not decrease the safety and effectiveness of medication abortion compared to studies of patients receiving their care in clinic. There remains a role for in clinic care for a certain proportion of patients, such as those who face intervention-generated inequalities. More work should explore ways of reducing technological barriers, such as for our patients on islands with no local abortion provider who would otherwise take on the added burden of flying to a different island. However, our current model demonstrates that using a combination of methods to reach patients is safe and effective and allows us to tailor our care to our patients' specific circumstances and preferences.

Conflict of Interest

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Dr. Kaneshiro receives research support from Contramed Pharmaceuticals (Sebela Pharmaceuticals), Gynuity Health Projects, and the National Institutes of Health. She is a consultant for UpToDate.

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Original Research Article

Mailing abortion pills does not delay care: A cohort study comparing mailed to in-person dispensing of abortion medications in the United States☆,☆☆

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ABSTRACT

Objective: Given the substantial barriers to abortion access in the United States, many clinics now mail patients abortion medications. We examined whether dispensing the medications by mail prolonged time to medication use.

Study design: We analyzed data from no-test medication abortions with medication provided either by mail or in a clinic from 11 United States clinics from February 2020 to January 2021. We examined mean number of days from patients' first contact with the clinic to mifepristone ingestion, its two-component intervals (first contact to medication dispensing and dispensing to mifepristone ingestion), and pregnancy duration at mifepristone ingestion. We used Poisson regression to compare mean outcomes across three dispensing methods: in-person, mailed from the clinic, and mailed from a mail-order pharmacy.

Results: Among the 2600 records, patients took mifepristone on average at 49 days of gestation (95% CI, 47–51) and 7 days (95% CI, 4–10) after first contact. Mean time from first contact to mifepristone ingestion was 6 days when medications were dispensed in-person and 9 days when mailed ($p = 0.38$). While time from first contact to dispensing was similar across methods (6 days in-person, 5 days mailed, $p = 0.77$), more time elapsed from dispensing to mifepristone ingestion when medications were mailed (4 days from clinic, 5 days from mail-order pharmacy) versus dispensed in-person (0.3 days, $p < 0.001$). Time to mifepristone ingestion was shorter with higher pregnancy duration. Pregnancy duration at ingestion was similar across methods (48 days in-person, 50 days mailed).

Conclusions: Mailing medications did not significantly prolong time from patients' first contact with the clinic to mifepristone ingestion or increase pregnancy duration at mifepristone ingestion.

Implications: Abortion providers should offer a range of medication abortion dispensing options, prioritizing patient preference.

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1. Introduction

The approval of mifepristone for medication abortion by the United States (US) Food and Drug Administration in 2000 included a requirement that the drug must be dispensed only in clinics, medical offices, or hospitals. In July 2020, a court order temporarily blocked this requirement, allowing clinicians and mail-order pharmacies to mail the medication directly to patients for the duration of the COVID-19 Public Health Emergency [1]. In 2021, the Food and Drug Administration removed the in-person mandate permanently [2]. This regulatory shift fundamentally changed abortion provision in the US. Many patients do not need an ultrasound or other in-clinic tests for eligibility assessment and can now obtain abortion care from home using telehealth, without any in-person visits to medical facilities. Several recent studies have demonstrated that this fully remote model is safe, effective, and highly satisfactory to patients [3–6].

One concern, however, is that the mailing process could delay treatment, potentially reducing the effectiveness of the medication abortion regimen. Two studies reported that, compared with patients who came to a clinic to obtain both screening ultrasounds and abortion medications, patients who were assessed by videoconference or telephone, had ultrasounds at separate facilities, and then received medications by mail, experienced longer intervals (by 5–7 days) between first contact with the abortion provider and medication use [7,8]. In one of these studies, the pregnancy duration on the day of mifepristone ingestion was also higher among patients who received pills by mail [7]. However, these studies could not determine the extent to which the observed differences were related to the mailing process, delays due to obtaining an ultrasound, or other factors.

No previous US studies have tested whether mailing medication was associated with delays in medication abortion in the context of no-test medication abortions. We sought to examine this issue using data from a large retrospective cohort study of the safety and effectiveness of medication abortion provided without pretreatment ultrasound or pelvic exam. Abortions were provided by multiple diverse clinics in the US between February 1, 2020 and January 31, 2021, preceding and following the July 2020 decision that first allowed for abortion medications to be mailed [4]. In all months, clinics dispensed mifepristone and misoprostol in-person, by mail from the providing clinic, or using a mail-order pharmacy. The objective of the current analysis was to determine whether mailing medications resulted in increased pregnancy duration or time to mifepristone ingestion.

2. Methods

The retrospective parent study collected data from 3779 abortions provided by 14 clinics for predefined time periods between February 2020 and January 2021 [4]. Within the original sample, 425 abortions were provided through the TelAbortion study, a prospective trial [9,10]. Trained clinic staff abstracted data from medical records for medication abortions provided without pretreatment ultrasound. Abstracted data included patient characteristics, abortion medication dispensing method, service dates, and medication administration timing. Abortion medications were provided in-person, by mail from the clinic, or using a mail-order pharmacy. The abortion medication dispensing method was determined by clinic protocol, or patient choice at clinics that offered multiple dispensing methods. Between February and June of 2020, nearly all patients in the sample other than the TelAbortion study obtained medications in-person. After a regulatory change in July 2020, clinics were able to dispense medications by mail outside of the TelAbortion study, either mailed directly from the clinic or from a mail-order pharmacy.

For this secondary analysis, we excluded data from three clinics where the first contact date was known to have been documented as the treatment date, as this would underestimate the intervals of interest. We also excluded abortions in which dates were not credible (e.g., mifepristone ingestion preceded first contact date), pregnancy duration was unknown, the patient took neither mifepristone nor misoprostol, the medications were dispensed in-person to someone other than the patient, or the dates of both mifepristone and misoprostol ingestion were unknown. The study was approved by the Allendale and University of California, San Francisco Institutional Review Boards.

2.1. Measures

The primary exposure was the medication dispensing method: in-person at the clinic, mailed from the clinic, or mailed from a pharmacy. Abortions with medications provided in-person included those with intake visits conducted in-person, without screening ultrasound or pelvic exam, and those with intake visits conducted via telehealth with medications picked up in-person. As a secondary exposure of interest, we examined pregnancy duration on the day of the first contact with the clinic.

The primary outcome was the number of days from the patient's first contact with the clinic to mifepristone ingestion. The date of first contact was defined as the date the patient scheduled the appointment via phone call or online, or otherwise the earliest date in the patient record regarding that abortion. If the date of mifepristone ingestion was missing, we conservatively substituted the date the patient used misoprostol, if available, in lieu of the date the patient used mifepristone, to avoid underestimating the intervals under study. We also assessed two components of this interval: days from first contact to medication dispensing and days from medication dispensing to mifepristone ingestion. The date of medication dispensing was defined as the date the medications were dispensed in-person, the package was mailed to patients, or a prescription was sent to a mail-order pharmacy.

For cases where abortion medications were mailed, we sought to estimate the days between mailing and delivery (the mailing interval) and the days between delivery and mifepristone ingestion. If the date of medication delivery was available, we recorded the days from medication dispensing to delivery as the mailing interval. For cases where the delivery date was not available, we used the mean mailing interval calculated among the cases with known delivery intervals as a proxy, separately for the mailed from clinic and mail-order pharmacy groups. The remainder of the interval from dispensing to mifepristone ingestion was recorded as the time from medication delivery to ingestion.

The secondary outcome was pregnancy duration on the date of mifepristone ingestion. We calculated this variable as the difference between the first date of the patient's last menstrual period and the date of mifepristone ingestion.

2.2. Statistical methods

We first described patient and abortion characteristics, overall and examined differences by medication dispensing group using Student's t-tests, chi-squared tests, and Fisher's exact tests. We compared the characteristics of cases that were missing mifepristone and misoprostol ingestion dates to those where mifepristone or misoprostol dates were known using chi-squared tests.

We used marginal estimates of results from multivariable Poisson regression models to estimate the adjusted number of days from first contact to mifepristone ingestion and to assess differences in the overall interval by medication dispensing method. Multivariable models controlled for patient age at abortion intake, race/ethnicity, pregnancy duration at first contact with the clinic,

Table 1
Characteristics of patients obtaining medication abortion at 11 clinics in the United States from February 2020 to January 2021, by method of medication dispensing (n = 2600)

	Overall	In-person at the clinic	Mailed from the clinic	Mail-order pharmacy	*p* Value
N	2600	1794	514	292	
Treatment date (range)	February 2020–January 2021	February 2020–January 2021	February 2020–January 2021	October 2020–January 2021	
Age (mean + SD)	28+6	28+6	30+6	29+6	< 0.001
White	1096 (42)	681 (38)	275 (54)	140 (48)	< 0.001
Black	668 (26)	430 (24)	139 (27)	99 (34)	
Race/ethnicity					
Latinx/Hispanic	391 (15)	326 (18)	34 (6.6)	31 (11)	
Other	257 (10)	198 (11)	46 (89)	13 (5)	
Unknown	188 (7)	159 (9)	20 (4)	9 (3)	
Residence					
Rural	363 (14)	213 (12)	114 (22)	36 (12)	< 0.001
Urban	2237 (86)	1581 (88)	400 (78)	256 (88)	
Paid out of pocket for abortion					
Did not pay for any portion of abortion out of pocket	1249 (48)	1179 (66)	55 (11)	15 (5)	
Paid for any portion of abortion out of pocket	1351 (52)	615 (34)	459 (89)	277 (95)	< 0.001
Pregnancy duration at the first clinic contact					
< 6 wk	1420 (55)	934 (52)	300 (58)	186 (64)	
6– < 8 wk	942 (36)	681 (38)	176 (34)	85 (29)	< 0.001
8– < 9 wk	167 (6)	117 (7)	34 (7)	16 (6)	
> 9 wk	71 (3)	62 (3)	4 (1)	5 (2)	
TelAbortion study participant					
No	2225 (86)	1793 (100)	140 (27)	292 (100)	< 0.001[a]
Yes	375 (14)	1 (< 1)	374 (73)	0 (0)	

[a] Fisher's exact test.

urban or rural residence, whether the patient paid out of pocket for the abortion, and TelAbortion Study participation. Next, we followed the same procedures to examine whether the two component intervals—first contact to dispensing and dispensing to ingestion—differed by medication dispensing method. Among the mailed cases, we also estimated the share of the dispensing to ingestion interval that was 1) from dispensing to delivery and 2) from delivery to ingestion.

We used Poisson models to estimate pregnancy duration on the day of mifepristone ingestion, overall and compared this interval by medication dispensing method, adjusting for patient age at abortion intake, race/ethnicity, urban or rural residence, whether the patient paid out of pocket for the abortion, and TelAbortion Study participation. In this model, we did not adjust for pregnancy duration at first contact because the outcome was a different measure of pregnancy duration.

To assess whether our findings were influenced by the inclusion of participants in the TelAbortion study, in which clinics had staff time dedicated to mailing medications from clinics, we conducted sensitivity analyses replicating all models excluding all TelAbortion participants. Finally, we tested whether the proportion of abortions where mifepristone was taken over 70 days of pregnancy duration differed by dispensing method using chi-squared tests.

All analyses used abortion as the unit of analysis. Standard error calculations accounted for clustering among abortions provided from the same clinic for all models. We used Stata version 17.0 (College Station, TX) for all analyses.

3. Results

The original study included 3779 abortions. We excluded 178 abortions provided by clinics that reported the intake date as the first contact date, abortions with dates that were not credible, abortions with medications dispensed in-person to someone other than the patient, and those with unknown pregnancy durations. Next, we excluded 1001 abortions because the dates of medication administration were unknown. Patients missing the date of mifepristone and misoprostol administration were first in contact with the clinic at slightly higher gestational ages (44 days among those for whom administration information was missing vs. 41 days), more likely to be white (50% vs. 42%) or to live in a rural area (21% vs. 14%), and less likely to be TelAbortion participants (5% vs. 14%). Those with missing mifepristone and misoprostol administration dates were slightly less likely to have picked up medication in-person (67% vs. 69%). After applying all exclusion criteria, we included 2600 abortions (69%) provided to 2594 patients between February 2020 and January 2021.

Table 1 describes the characteristics of the patients included in our sample. Most (69%) abortion medications in our sample were provided in-person to patients, whereas 20% were mailed to patients, and 11% from a mail-order pharmacy. All patient characteristics differed across dispensing methods. Each clinic contributed between 9 and 882 included abortions, and clinics varied in how many dispensing methods they offered (Appendix Table 1).

In adjusted analyses, the average interval between first contact and mifepristone ingestion was 6.9 days (Table 2). Patients who obtained medications in-person (6.0 days) had shorter intervals than those who received them by mail from the clinic (8.7 days) or from a mail-order pharmacy (9.0 days, $p = 0.38$).

We examined two components of the first contact to mifepristone ingestion interval (Table 3, Fig. 1). The average time from first contact to medication dispensing was 5 days and was similar across dispensing methods. However, the interval from dispensing to mifepristone ingestion differed significantly between the three methods. Time from medication dispensing to mifepristone ingestion was the shortest when the pills were dispensed in-person (< 1 day), 4 days when pills were mailed from the clinic, and 5 days when they were mailed from a pharmacy.

The date that the mailed medications were delivered to the patient was available for 374 of 514 cases (73%) in which medications were mailed from the clinic (all 374 provided through the TelAbortion study), and only 39 of 292 cases (13%) mailed from a pharmacy (all 39 provided from a single clinic). The interval from dispensing to delivery in these 413 cases for which the delivery date was available was on average 2 days in both the mailed from clinic and mail-order pharmacy cases and ranged from 0 – 10 days; 72% were 2 days or fewer,

Table 2
Pregnancy duration in days at mifepristone ingestion and days to mifepristone ingestion among patients obtaining medication abortion at 11 clinics in the United States from February 2020 to January 2021 (n = 2600)

	Days from first contact to mifepristone ingestion	Pregnancy duration in days at mifepristone ingestion
	Estimate [95% confidence interval]	
Overall	6.9 [4.1–9.7]	48.7 [46.9–50.6]
Medication dispensing method		
In-person at clinic *(ref)*	6.0 [2.2–9.9]	48.1 [45.4–50.8]
Mailed from the clinic	8.7 [7.6–9.9]	50.3 [49.5–51.2]
Mail-order pharmacy	9.0 [7.3–10.7]	49.8 [48.4–51.2]
Pregnancy duration at the first contact		
< 6 wk *(ref)*	7.4 [4.5–10.3]	
6– < 8 wk	6.6* [3.9–9.4]	
8–9 wk	5.9* [2.6–9.2]	
> 9 wk	3.4*** [1.1–5.7]	
Residence		
Rural *(ref)*	7.8 [5.6–10.1]	50.7 [49.4–52.1]
Urban	6.8 [3.8–9.7]	48.4** [46.4–50.4]
Race/ethnicity		
White *(ref)*	7.1 [4.1–10.0]	48.6 [46.3–50.9]
Black	7.6 [4.8–10.4]	49.1 [47.8–50.4]
Latinx/Hispanic	5.2 [1.3–9.0]	47.9* [45.6–50.2]
Other[a]	7.8 [6.1–9.6]	50.0 [48.8–51.1]
Unknown	5.5 [2.4–8.6]	47.7 [45.0–50.4]
Paid out of pocket for abortion		
Did not pay for any portion of abortion out of pocket *(ref)*	6.6 [2.8–10.3]	48.9 [46.8–51.0]
Paid for any portion of abortion out of pocket	7.2 [5.0–9.4]	48.5 [46.5–50.6]
TelAbortion study participant		
No *(ref)*	7.1 [4.2–9.9]	48.9 [46.9–50.8]
Yes	6.2 [3.8–8.7]	47.8 [46.0–49.7]

Results are marginal estimates from multivariable Poisson regression models. Models are adjusted for all variables listed in the table as covariates as well as age and standard errors are clustered at the clinic level. The model that examines pregnancy duration at mifepristone is not adjusted for pregnancy duration at first contact.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
[a] Other race/ethnicity: Alaska Native, American Indian, Asian, Asian Indian, Filipino, Guyanian, Guamanian/Chamorro, Japanese, Middle Eastern, Native American, Native Hawaiian, Pacific Islander, and Turkish.

Table 3
Component intervals from first contact to mifepristone ingestion among patients obtaining medication abortion at 11 clinics in the United States from February 2020 to January 2021

	Days from first contact to medication dispensing (n = 2600)	Medication dispensing to mifepristone ingestion (n = 2600)	Among mailed cases (n = 806)	
			Medication dispensing to receipt	Medication receipt to mifepristone ingestion
	Estimate [95% confidence interval]			
Overall	5.4 [2.4–8.4]	1.5 [1.2–1.9]	2.0 [1.7, 2.3]	2.2 [2.0, 2.3]
Medication dispensing method				
In-person at the clinic *(ref)*	5.7 [1.7–9.8]	0.3 [0.0–0.7]		
Mailed from the clinic	4.9 [3.9–5.8]	4.0 [3.2–4.8]***	2.0 [1.6, 2.3]	2.1 [1.4, 2.8]**
Mail-order pharmacy	4.6 [3.4–5.8]	4.6 [3.9–5.3]***,[a]	2.2 [1.9, 2.5]***	2.5 [1.9, 3.1***,[b]
Pregnancy duration at the first contact				
< 6 wk *(ref)*	5.9 [2.8–9.0]	1.5 [1.1–1.8]	2.0 [1.7, 2.3]	0.9 [0.6, 1.1]
6– < 8 wk	5.0 [2.1–8.0]**	1.6 [1.3–2.0]*	2.1 [1.7, 2.4]*	1.0 [0.7, 1.3]*
8– < 9 wk	4.6 [1.3–7.9]*	1.3 [1.0–1.7]	1.9 [1.8, 2.1]	0.7 [0.4, 1.0]
> 9 wk	2.5 [0.2–4.8]***,[c]	1.0 [0.5–1.5]	1.3 [1.0, 1.7]	0.6 [0.2, 1.0]

Results are marginal estimates from multivariable Poisson regression models. Models are adjusted for age, pregnancy duration at first contact, urban/rural residence, race/ethnicity, out-of-pocket payment for the abortion, and participation in the TelAbortion Study, and standard errors are clustered at the clinic level.
Estimates for component intervals do not sum exactly to the estimates for overall intervals because they are modeled separately.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
[a] p Value for comparison of mail-order pharmacy versus mailed from the clinic: $p = 0.01$.
[b] p Value for comparison of mail-order pharmacy to mailed from the clinic: $p < 0.001$.
[c] p Value for comparison of > 9 weeks versus 6– < 8 weeks: $p = 0.03$.

15% were 3–4 days, and 13% were 5–10 days. After assigning the mean mailing intervals for the remaining 393 cases without known delivery dates, we estimated that the mailing interval was similar between mailing methods; however, patients who received medications from a mail-order pharmacy (2.3 days) had a slightly longer delay between receiving and taking the medications than those who were mailed medications from clinics (2.1 days).

Time from first contact with the clinic to mifepristone ingestion was shorter with higher pregnancy duration at first contact, from 7.4 days for those with pregnancy durations less than 6 weeks to 3.4 days for those with pregnancy durations 9 weeks or more (Fig. 2). The time from first contact to medication dispensing was shorter with increasing pregnancy duration at first contact (Table 3). The interval from medication dispensing to mifepristone ingestion was

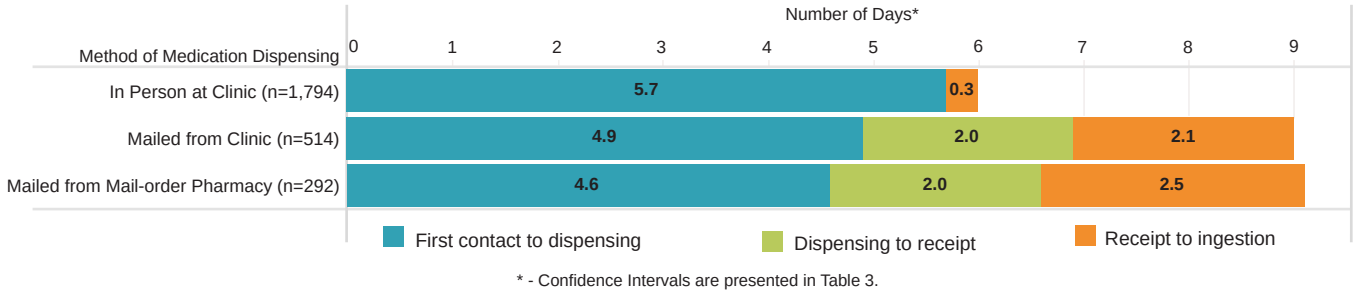

Fig. 1. Mean days from first contact to mifepristone ingestion among medication abortions provided in the US, February 2020–January 2021 (n = 2600).

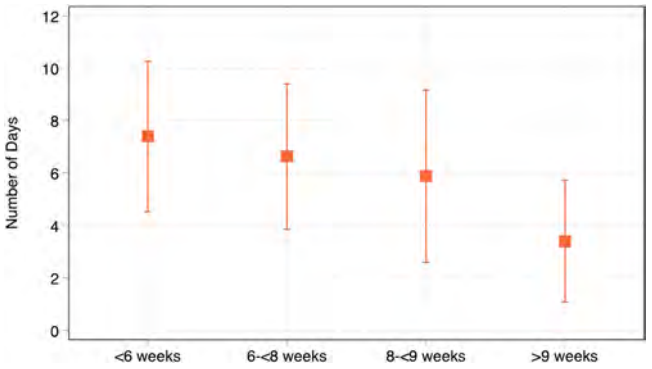

Fig. 2. Days from first contact to mifepristone ingestion among medication abortions provided by 11 clinics in the USA, by pregnancy duration at first contact with the clinic, February 2020–January 2021 (n = 2600).

longer for abortions with pregnancy durations 6 to < 8 weeks compared with those < 6 weeks, and shorter for those > 9 weeks compared with abortions with pregnancy durations 6 to < 8 weeks.

The average pregnancy duration at mifepristone ingestion was 48.7 days and was nearly identical across the dispensing method groups (Table 2). Older patients, those residing in urban areas, and patients who identified as Hispanic/Latinx versus white patients took medications at significantly lower pregnancy durations. The proportion of patients whose pregnancy durations were higher than 70 days on the date of mifepristone ingestion was similar among medication dispensing methods (2.8% for in-person, 1.6% for mailed from the clinic, and 2.4% for mail-order pharmacy, $p = 0.25$). The highest pregnancy duration on the date of mifepristone ingestion was 78 days. Results from sensitivity analyses excluding the 375 TelAbortion study participants yielded similar results (Appendix Table 2).

4. Discussion

In our sample of medication abortions provided without ultrasound or pelvic exam, we found that the average time from patients; first contact with the clinic to ingestion of mifepristone was one week. Time to mifepristone ingestion was 2–3 days longer when the medications were mailed to the patient than when they were dispensed in-person. Data from a sample of our cases suggest that the mailing process itself typically took only 1–2 days, which was consistent with the information on medication shipping times in 2020–2021 provided to us by Honeybee Pharmacy, one of several mail-order pharmacies that filled mifepristone prescriptions in the US during those years (email communication, April 2022). We estimate that patients who receive their medication by mail tend to take the pills on average 2 days after they were received. Additionally, our estimation of delivery dates was consistent with another of abortion medications dispensed from mail-order pharmacies, which found that 82% received the medications within three days [13]. In contrast, while it took somewhat longer to get an in-person appointment, most patients who obtained the medications in-person took the mifepristone that same day. However, a 3-day difference is unlikely to affect either safety or effectiveness of the treatment. The difference may reflect patient preference for taking the medications at the most convenient time once they are received by mail. Notably, the medication dispensing method had no apparent effect on the average pregnancy duration at mifepristone ingestion. The medication dispensing method also did not impact the proportion of patients who took the medications at more than 70 days of pregnancy duration.

The interval between first contact and mifepristone ingestion was shorter in patients whose first contact was later in pregnancy, due primarily to a shorter interval between first contact and medication dispensing. This finding may reflect both clinicians' and patients' desire to expedite treatment when patients are at later pregnancy durations. Medication abortion care provided earlier is consistent with patient-centered care, results in fewer side effects, and is more effective [11,12].

Our analysis has several limitations. We included only records where the patient provided medication administration dates, which may have biased our findings. Several important characteristics differed between patients whose medication administration dates were and were not known, which may have influenced time to mifepristone ingestion. Because some clinics do not maintain detailed records about when patients schedule appointments, the date of first contact for some records may have reflected a subsequent interaction, resulting in an underestimation of several intervals in our analysis. Similarly, the date of medication dispensing for the patients who received medications by mail could have reflected the date the clinician approved the medication for the patient or the date the package was mailed, which were not necessarily the same day for all patients although this would not impact overall time to mifepristone ingestion, the main outcome. Delivery dates were missing for most cases, which impaired our ability to investigate the dynamics of the post-dispensing interval among the cases where medications were mailed. Within the group that received abortion medications in-person, we were unable to distinguish between cases where the intake visit was conducted via telehealth or in-person. This may have obscured differences in the length of the interval between first contact and medication dispensing within this group, and underestimated differences in this interval between abortions with medications provided in-person and by mail. Finally, our data did not enable us to estimate the time from the patient's decision to terminate the pregnancy to treatment, which may be more salient to patients than the intervals we examined in this study.

Patients should be able to start their abortions at a time that is most convenient to them and decide whether they want to pick up the abortion medications at the clinic or receive them by mail. Patients should be informed about the small delay associated with obtaining medications by mail. In January 2023, the Food and Drug

Administration allowed for retail pharmacies to dispense mifepristone; however, important restrictions remain in place that limit access. Our findings support regulatory shifts to expand pharmacy access to the medication abortion regimen by demonstrating that patients take the abortion medications at a clinically acceptable time and early in pregnancy, regardless of how they receive the medications.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.contraception.2023.109962.

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Patient Acceptability of Telehealth Medication Abortion Care in the United States, 2021–2022: A Cohort Study

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See also Munson and Hall, p. 152.

Objectives. Despite the recent expansion of direct-to-patient telehealth abortion care in the United States, patient experiences with the service are not well understood.

Methods. We described care experiences of 1600 telehealth abortion patients in 2021 to 2022 and used logistic regression to explore differences by race or ethnicity and between synchronous (phone or video) and asynchronous (secure messaging) telehealth abortion care.

Results. Most patients trusted the provider (98%), felt telehealth was the right decision (96%), felt cared for (92%), and were very satisfied (89%). Patients most commonly cited privacy (76%), timeliness (74%), and staying at home (71%) as benefits. The most commonly reported drawback was initial uncertainty about whether the service was legitimate (38%). Asian patients were less likely to be very satisfied than White patients (79% vs 90%; $P = .008$). Acceptability was high for both synchronous and asynchronous care.

Conclusions. Telehealth abortion care is highly acceptable, and benefits include privacy and expediency.

Public Health Implications. Telehealth abortion can expand abortion access in an increasingly restricted landscape while maintaining patient-centered care. (*Am J Public Health*. 2024;114(2):241–250. https://doi.org/10.2105/AJPH.2023.307437)

In the wake of the June 2022 *Dobbs v Jackson* Supreme Court decision that allowed states to ban abortion, telehealth medication abortion has played a vital role in abortion provision and access in the United States. Telehealth can help mitigate surges in demand for abortion care in states where it remains legal.[1,2] For patients in states with abortion bans, telehealth services can also increase abortion access through methods like mail forwarding and mailing medications to a postal address or post office box in neighboring states over the border, minimizing the amount of travel required.

Medication abortion has emerged as the leading abortion method both within[3] and outside of[4] the health care system in the United States in recent years. Concurrently, there has been a rise in medication abortion provided via telehealth, facilitated by regulatory changes that allowed abortion medications to be mailed beginning in the COVID-19 pandemic.[5] Before the pandemic, telehealth abortion models were primarily "site-to-site," requiring patients to travel to abortion clinics, where they received ultrasonography and other in-person tests and then remotely consulted with a clinician who was at another location.[6,7]

Direct-to-patient telehealth abortion care first became widely available in the United States in 2020 and has been found to be safe and effective.[8–10] Since then, virtual clinics—online-only abortion providers—began providing this model of telehealth abortion care in states where it is legally permitted.[11–13] Patients are screened for eligibility

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remotely by a clinician, receiving an ultrasound only if desired or medically indicated, and subsequently receive medications from a mail-order pharmacy.[14] In all medication abortion care models, patients typically take the medications, pass the pregnancy, and complete follow-up at home.[15] Patient–provider communication is either entirely over secure text messaging (asynchronous care) or with a videoconference or phone call (synchronous care).[16]

As of November 2023, telehealth for abortion was legally permitted in 24 states and Washington, DC (Figure A, available as a supplement to the online version of this article at https://ajph.org).[17] Between April 2022 and June 2023, the number of abortions provided by virtual clinics nearly doubled, accounting for almost 1 in 10 US abortions by June 2023.[2]

Despite the critical role that telehealth plays in maintaining access to abortion across an increasingly restricted landscape, the acceptability of direct-to-patient telehealth for abortion in the United States is not well understood. Evidence from the TelAbortion study has demonstrated US patients' positive experiences with synchronous telehealth abortion care within a clinical study.[9,18–20] No studies have examined differences in patient experiences between synchronous and asynchronous care. Telehealth medication abortion care models are less medicalized compared with in-clinic care, and differences in experiences by patient sociodemographic characteristics have not been documented. As ongoing legal cases threaten to curtail access to telehealth abortion, it is critical to understand how patients experience these models of care. Therefore, we aimed to explore the real-world acceptability of novel direct-to-patient abortion services provided by US virtual clinics and to examine differences in abortion care experiences between synchronous and asynchronous models and patient sociodemographic characteristics.

METHODS

We used data from the California Home Abortion by Telehealth (CHAT) Study, which evaluates the safety, effectiveness, and acceptability of telehealth abortion care provided by 3 United States–based virtual clinics. The CHAT Study began in California and increased in scope as virtual clinics expanded to provide care in 20 states and Washington, DC. The study collected electronic clinical data from all abortions provided by the participating clinics for a defined period between April 2021 and January 2022. During clinic intake, patients consented to share anonymized data with our research team. Patients approved for care between June 2021 and January 2022 were also invited to participate in a series of 3 surveys: 1 at abortion intake, another in the week after intake, and a final survey 4 weeks after intake. The baseline survey assessed patient sociodemographic characteristics and initial reasons for choosing telehealth. The first follow-up survey assessed medication administration and additional medical care received. The final survey assessed additional medical care received and experiences with the telehealth model including open-ended and closed-ended questions. Surveys were administered until all 3 surveys were completed by approximately 400 participants from each clinic. Participants received $50 as remuneration after the completion of all 3 surveys.

One clinic used synchronous communication with a phone or video call to screen patients for eligibility. The other 2 screened patients through asynchronous communication, which involved an online consultation form and subsequent communication via secure written messages. One of the clinics that screened patients through asynchronous communication by default also offered the option to request a synchronous intake appointment. Abortion costs from the 3 virtual clinics ranged from $199 to $239. During the study period, virtual clinics did not accept health insurance; however, each clinic offered financial assistance for the cost of the abortion via abortion funds.

Measures

We used several indicators of patient acceptability as the main outcome measures (Table A, available as a supplement to the online version of this article at https://ajph.org). We examined participants' reasons for choosing telehealth reported in the baseline survey; participants could select all reasons that applied. The remaining outcome measures were asked in the 4-week follow-up survey. We assessed overall satisfaction, with Likert scale response options categorized into "very satisfied" versus other responses. We assessed whether participants could trust the virtual clinic with their care, whether they felt cared for throughout the abortion process, and whether telehealth was the right decision for them using individual dichotomous items ("yes" vs "no" or "don't know"). Open-ended questions modeled the closed-ended items, assessing reasons for choosing telehealth, benefits of telehealth abortion, why they did or did not feel cared for,

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and how they felt like they could or could not trust the virtual clinic.

The baseline survey asked participants to identify the benefits and drawbacks of the telehealth abortion model in 2 select-all-that-apply items, with the option to write in other responses. Other responses were coded into closed-ended responses, the most common of which are represented in the results.

Our primary key predictor was whether patient acceptability outcomes differed between those who received synchronous and asynchronous abortion care. Our secondary key predictor was the participant's race or ethnicity. Covariates included categorized measures of participant age at abortion intake, pregnancy duration on the day of abortion intake, education level, and health insurance coverage. We included binary measures reflecting experiences of food insecurity in the past month, previous medication abortion, whether the participant was born outside of the United States, and whether their zip code corresponded to an urban, or a suburban or rural area.

Statistical Analysis

We reported sample characteristics using descriptive statistics and used the χ^2 and Fisher exact test to examine differences between the groups that received synchronous and asynchronous care. We used multivariable logistic regression to examine associations between participant and abortion model characteristics, and each patient acceptability indicator. Patient age (< 25 years; 25–29 years; 30–34 years; ≥ 35 years), pregnancy duration (< 35 days; 35–49 days; ≥ 50 days), and race or ethnicity categories (White; Black; Hispanic or Latinx; Asian, Native Hawaiian, or Pacific Islander; American Indian or Alaska Native, Middle Eastern or North African, or multiracial) were collapsed in the regression analyses to facilitate model convergence. We used predictive margins to calculate adjusted rates of each patient acceptability indicator.

Open-Text Responses

To illustrate meaning and provide context for the quantitative results, we purposively selected from the open-ended survey responses. L. R. K. and U. D. U. identified candidate quotes that corresponded to each patient acceptability indicator, among which L. R. K. selected final quotes for inclusion.

RESULTS

Originally, 1632 participants enrolled in the longitudinal surveys (32% of invited patients). Among those, we excluded 32 participants who took neither mifepristone nor misoprostol, resulting in an initial sample of 1600 survey participants in 20 states and Washington, DC. Ultimately, 1312 (82%) completed the 4-week follow-up survey.

We described sample characteristics in Table 1. At abortion intake, mean participant age was 29 years and mean pregnancy duration was 40 days (< 7 weeks). Across the sample, 53% identified as White; 14% as multiple races or ethnicities; 13% as Hispanic or Latinx; 9% as Black; 6% as Asian, Native Hawaiian, or Pacific Islander; 1% as American Indian, Native American, or Alaska Native; and 1% as Middle Eastern or North African. Nearly half (42%) had completed college or more education, and 21% experienced running out of food in the past month. Most (89%) participants were born in the United States and resided in urban areas (91%). More than half (56%) resided in the US West, 20% in the Northeast, and smaller proportions in the Midwest (12%) and South (12%). One third (29%) had a previous medication abortion and 59% had private health insurance. One third (31%) had a video or phone call during abortion intake (synchronous care). At the clinic that provided asynchronous care but offered the option to request synchronous care, 1% received synchronous care.

Motivations for and Benefits of Telehealth

We examined participants' reasons for choosing telehealth at baseline (Figure 1). The most common reasons for choosing telehealth were feeling more comfortable at home (75%) and privacy (59%). Participants explained the importance of these features in open-ended responses:

> I felt more comfortable and less anxious about the whole process from being able to be home. I really appreciate having the opportunity to be in the comfort of my own home for the abortion and with my spouse for the entire duration and not in a cold room with strangers to have an uncomfortable procedure. –Age 26 years, Georgia, synchronous care

More than half (58%) identified lower costs relative to in-clinic care as a reason for using telehealth, a theme that participants expanded on in open-ended responses:

> I couldn't afford a surgical or medical abortion from the clinic. [Telehealth care] is half the price of abortions where I live. –Age 21 years, Oregon, synchronous care

More than half (55%) of respondents endorsed a desire to have the abortion

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TABLE 1— Characteristics of the Sample: United States, 2021–2022

Characteristic	Overall (n = 1600), No. (%)	Synchronous (n = 503), No. (%)	Asynchronous (n = 1097), No. (%)	P
Patient age at abortion intake, y				.07
16–17	8 (< 1)	0 (0)	8 (1)	
18–19	67 (4)	14 (3)	53 (5)	
20–24	381 (24)	111 (22)	270 (25)	
25–29	418 (26)	138 (27)	280 (26)	
30–34	405 (25)	140 (28)	265 (24)	
≥ 35	321 (20)	100 (20)	221 (20)	
Pregnancy duration at abortion intake, d				< .001
< 35	448 (28)	161 (32)	287 (26)	
35–49	885 (55)	294 (58)	591 (54)	
50–62	229 (14)	46 (9)	183 (17)	
≥ 63	38 (2)	2 (< 1)	36 (3)	
Race or ethnicity				< .001
Non-Hispanic White	841 (53)	285 (57)	556 (51)	
Non-Hispanic Black or African American	148 (9)	68 (14)	80 (7)	
Hispanic or Latinx	203 (13)	46 (9)	157 (14)	
American Indian, Alaska Native, Middle Eastern, North African, or multiracial	237 (15)	60 (12)	177 (16)	
Asian, Native Hawaiian, or Pacific Islander	105 (7)	19 (4)	86 (8)	
Unknown	66 (4)	25 (5)	41 (4)	
Food did not last, last month				< .001
No	1207 (75)	393 (78)	814 (74)	
Yes	340 (21)	82 (16)	258 (24)	
Unknown	53 (3)	28 (6)	25 (2)	
Previous medication abortion				.61
No	1136 (71)	349 (69)	787 (72)	
Yes	457 (29)	152 (30)	305 (28)	
Unknown	7 (< 1)	2 (< 1)	5 (< 1)	
US region				< .001
West	896 (56)	177 (35)	719 (66)	
Northeast	313 (20)	99 (20)	214 (20)	
South	195 (12)	181 (36)	14 (1)	
Midwest	196 (12)	46 (9)	150 (14)	
Highest level of education achieved				< .001
High school or less	274 (17)	62 (12)	212 (19)	
Some college or technical school	659 (41)	200 (40)	459 (42)	
Completed 4-y degree or more	667 (42)	241 (48)	426 (39)	
Health insurance coverage				.019
Private insurance	941 (59)	315 (63)	626 (57)	
No insurance	317 (20)	83 (17)	234 (21)	
Medicaid	293 (18)	96 (19)	197 (18)	
Unknown	49 (3)	9 (2)	40 (4)	
Nativity				< .001
Born in the United States	1430 (89)	435 (86)	995 (91)	

Continued

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TABLE 1— Continued

Characteristic	Overall (n = 1600), No. (%)	Synchronous (n = 503), No. (%)	Asynchronous (n = 1097), No. (%)	*P*
Born outside the United States	138 (9)	44 (9)	94 (9)	
Unknown	32 (2)	24 (5)	8 (1)	
Residence				.59
Suburban or rural	146 (9)	43 (9)	103 (9)	
Urban	1454 (91)	460 (91)	994 (91)	
Completion of 4-wk follow-up survey				< .001
Did not complete survey	288 (18)	27 (5)	261 (24)	
Completed survey	1312 (82)	476 (95)	836 (76)	

Note. The sample size was 1600.

as soon as possible, and many cited long waiting times at abortion clinics as a reason for choosing telehealth in open-ended fields:

> The biggest thing was time. [Clinics were] booked out for weeks, and I didn't want to wait weeks. –Age 32 years, Oregon, synchronous care

Meanwhile, 44% were motivated to use telehealth because it allowed them to take care of their own treatment. One participant explained,

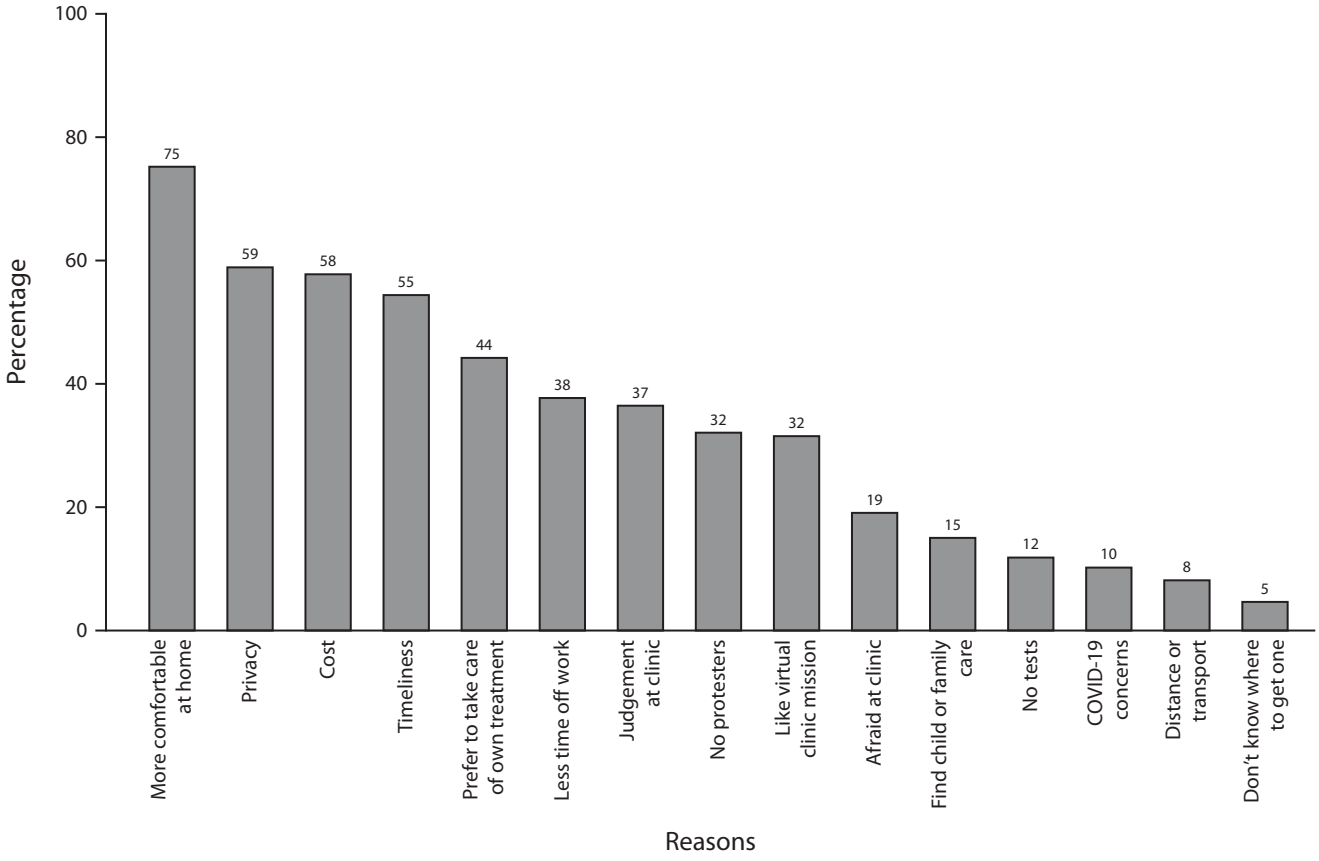

FIGURE 1— Reasons for Choosing Telehealth: United States, 2021–2022

Note. The sample size was 1600.

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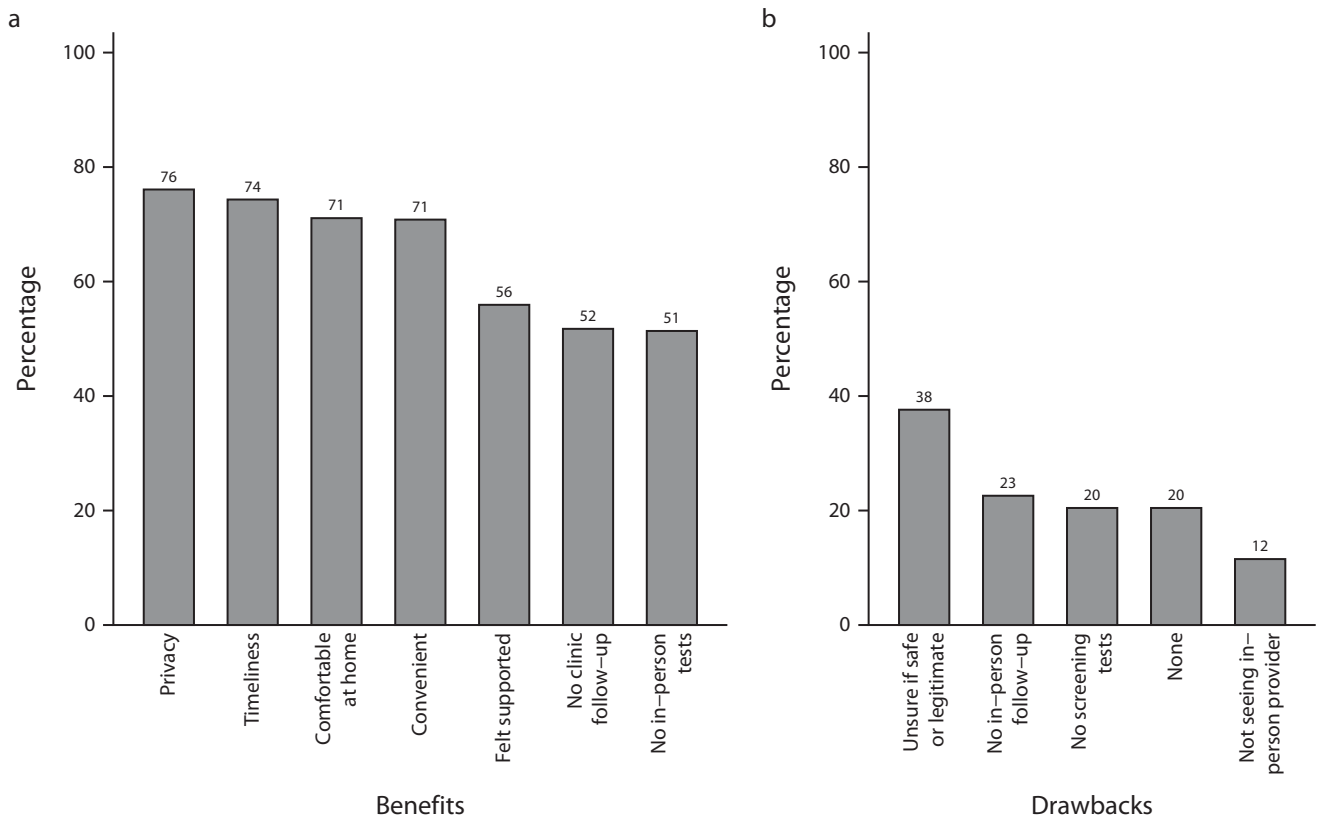

FIGURE 2— Telehealth Abortion (a) Benefits and (b) Drawbacks: United States, 2021–2022

Note. The sample size was 1312.

> I appreciate this experience of having the autonomy to be able to manage my own care with adequate support from a nurse practitioner. –Age 32 years, Illinois, asynchronous care

Similarly, another participant wrote,

> I felt more safe or secure, more empowered doing it my own way. –Age 26 years, California, asynchronous care

At the 4-week follow-up survey, the most common benefits of telehealth that participants cited were privacy (76%), expediency (74%), being more comfortable at home (71%), and convenience (71%; Figure 2). Overall, 56% of participants endorsed feeling supported as a benefit, and half cited not needing to go to the clinic for in-person screening tests (51%) or for follow-up (52%). One participant described their preference to have their abortion without ultrasound:

> At a stressful time, I don't want to be subjected to a vaginal ultrasound and blood work. If I know when I got pregnant, I don't need an ultrasound. –Age 36 years, Illinois, asynchronous care

Drawbacks of Telehealth

When asked about the drawbacks of telehealth, the most common response was uncertainty about whether the service was safe or legitimate (38%). Some participants described deciding to place their trust in the virtual clinic as a leap of faith:

> Not having any other option made me trust the service. There were times I doubted it could possibly be this easy or straightforward without there being some horrible catch. –Age 36 years, New Jersey, synchronous care

Overall, 20% reported no drawbacks. About one fifth cited not having screening (20%) and follow-up (23%) tests as drawbacks of their telehealth abortion experience. One participant stated,

> I would have liked confirmation that it was complete via ultrasound. –Age 29 years, New York, asynchronous care

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TABLE 2— Associations Between Patient and Abortion Characteristic and Acceptability Indicators: United States, 2021–2022

	Very Satisfied, PPR (95% CI)	Right Decision, PPR (95% CI)	Trust Provider, PPR (95% CI)	Cared for, PPR (95% CI)
Overall	89.7 (88.0, 91.4)	95.6 (94.4, 96.7)	98.0 (97.1, 98.8)	91.9 (90.4, 93.4)
Model of care				
Synchronous (n = 476; Ref)	90.4 (87.7, 93.2)	97.1 (95.6, 98.6)	97.3 (95.8, 98.8)	88.5 (85.5, 91.4)
Asynchronous (n = 836)	88.7 (86.5, 90.9)	94.7 (93.1, 96.2)	98.3 (97.5, 99.2)	93.4 (91.7, 95.1)**
Race or ethnicity				
Non-Hispanic White (n = 689; Ref)	89.5 (87.2, 91.8)	95.4 (93.7, 97.0)	97.9 (96.7, 99.1)	92.7 (90.7, 94.6)
Non-Hispanic Black or African American (n = 121)	91.4 (86.3, 96.5)	95.1 (91.3, 99.0)	97.9 (95.4, 100.0)	88.6 (83.0, 94.3)
Hispanic or Latinx[a] (n = 166)	90.7 (86.1, 95.2)	97.3 (94.9, 99.7)	98.8 (97.5, 100.0)	95.1 (91.5, 98.7)
American Indian, Alaska Native, Middle Eastern, North African, or multiracial (n = 194)	91.1 (87.2, 95.0)	97.1 (94.8, 99.4)	96.8 (94.3, 99.3)	89.6 (85.4, 93.9)
Asian, Native Hawaiian, or Pacific Islander[a] (n = 87)	78.5 (69.0, 87.9)**	91.5 (85.4, 97.7)	98.8 (97.5, 100.0)	87.7 (79.9, 95.6)

Note. CI = confidence interval; PPR = predicted prevalence rate. The sample size was n = 1312. Estimates are PPRs that draw from marginal estimates of multivariable logistic regression models. *P* values compare each category to the reference group in the multivariable logistic regression models. Multivariable models are adjusted for synchronous versus asynchronous care, patient age at abortion intake, pregnancy duration at abortion intake, food insecurity in the past month, race or ethnicity, previous medication abortion, education level, health insurance coverage, US nativity, and urban residence.

[a]Variable for race or ethnicity combined Hispanic or Latinx with Asian, Native Hawaiian, or Pacific Islander for the "trust provider" model.
*$P < .05$; **$P < .01$; ***$P < .001$.

A smaller proportion (12%) listed not seeing a provider in person as a drawback of the telehealth model. In the open-ended responses, some participants also described being unable to reach the virtual clinic at times:

> I took my pills on the weekend, so I had nobody to contact, which was unfortunate because I really wasn't sure if the severity of what I was experiencing was normal. –Age 24 years, California, asynchronous care

Overall Rates of Acceptability Indicators

We next examined the adjusted proportion of participants who reported each of the 4 patient acceptability indicators of interest: trust, right decision, cared for, and satisfied (Table 2). Overall, 98% trusted the virtual clinic, 96% felt telehealth was the right decision, 92% felt cared for, and 90% of participants were very satisfied with the telehealth model of care. Full regression output is presented in Table B (available as a supplement to the online version of this article at https://ajph.org).

Differences in Patient Acceptability by Participant Characteristics

Finally, we assessed differences in adjusted prevalence rates of each patient acceptability indicator by participant characteristics (Table 2). Asian, Native Hawaiian, and Pacific Islander participants were less likely than White participants to be very satisfied (79% vs 90%; $P = .008$). Similar proportions of patients who received synchronous and asynchronous care were very satisfied, felt telehealth was the right decision, and felt cared for by the telehealth provider. However, participants who had asynchronous care were slightly more likely to feel cared for (93% vs 89%; $P = .004$).

In the open-ended responses, we found that some participants stated clear preferences for synchronous care, while others clearly preferred asynchronous care. One participant explained their preference for asynchronous care because it facilitated anonymity:

> Everything was very professional and never pressed for any information. There was no pressure to do an appointment showing who I was. Privacy was well respected, and the ball was in my court to decide how much care I wish to receive (ex. seeing the doctor or nurse). –Age 29 years, California, asynchronous care

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However, some participants who received asynchronous care described how asynchronous communication could feel impersonal. One participant wrote,

> Since I talked to a nurse through chat, it didn't feel personable, and I wasn't sure if I was getting an automated message or if I was chatting with an actual person. –Age 27 years, California, asynchronous care

Another participant described how their synchronous care facilitated trust in the virtual clinic, despite initial reluctance about a video call:

> It was the video call! It proved it was a real service and that it was their focus at [the virtual clinic]. As much as I didn't want to do a video call, it helped solidify the legitimacy of the service. –Age 41 years, California, asynchronous care

One participant explained how being offered options for both synchronous and asynchronous services was important to their care:

> I knew it was legitimate because they were considering all the right things: the 24/7 hotline, video calls if we want but also that they aren't necessary. You can make it into the right abortion care for you. I personally didn't make any calls or message much, but I trust the service because I know I can get whatever help I need. –Age 23 years, Washington, asynchronous care

Another participant stated,

> They gave me a number to call if I needed, texted multiple times, and always said to text (which I love because I hate talking on the phone), or to call if I needed anything or had questions. –Age 43 years, California, asynchronous care

DISCUSSION

In this study, we found high acceptability of telehealth for abortion, whether it involved synchronous or asynchronous services. Nearly all participants were very satisfied with telehealth abortion. Telehealth abortion care is a new service and, thus, it was previously unknown whether this less medicalized model that eliminates in-person patient–provider interaction would negatively impact patient acceptability. Of course, telehealth abortion care is not for everyone, including individuals who are seeking abortion care later in pregnancy, those who prefer procedural abortions, and those who prefer to have screening and follow-up tests as a part of their medication abortion care. Thus, while access to in-person abortion care remains critical, this study indicates that telehealth is an important addition to the abortion landscape and offers substantial benefits over in-person care for some patients.

The most common reason for choosing telehealth was that patients felt more comfortable at home. Most patients also reported choosing telehealth for greater privacy, lower cost, expediency, and more agency in managing their abortion care. Thus, telehealth abortion appears to help mitigate some barriers patients face in accessing care from an abortion clinic. Beyond its role in increasing access to abortion care and addressing the surges abortion facilities face as patients travel in wake of *Dobbs*, telehealth can promote patient-centered care for some people seeking an abortion.[18,21]

We found few differences in acceptability between synchronous or asynchronous telehealth abortion care: patients were equally likely to be highly satisfied, trust the virtual clinic, and feel telehealth was the right decision. These findings suggest that both synchronous and asynchronous models are highly acceptable to patients. We found slightly higher rates of feeling cared for among participants who received asynchronous services. When patients from one clinic were offered asynchronous telehealth abortion services by default with an additional option for synchronous communication, almost no patients opted for synchronous care. While our results were largely similar for the 2 models, there may be different benefits and drawbacks of synchronous and asynchronous care with implications for providers and administrators. Services without real-time communication are presumed to feel less personable, but messaging can facilitate more frequent and responsive communication, which may contribute to patients feeling cared for. In addition, asynchronous models can require less time to provide, making them more cost-effective.[22,23] Our results demonstrate that asynchronous services can be provided while maintaining high levels of patient acceptability.

Nearly 40% of the sample was initially uncertain whether the virtual clinic services were safe or legitimate. At the time of the study, telehealth abortion services and virtual clinics were newly available within the formal US health care system. We expect that skepticism about legitimacy will decrease over time as public awareness about the safety and effectiveness of telehealth abortion increases. While these data draw from a time when interest in telehealth was very high because of the COVID-19 pandemic, use of telehealth abortion has continued to expand as barriers to access abortion care mount.[2]

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We found few differences in acceptability of telehealth abortion care by race or ethnicity in this sample, apart from finding lower rates of satisfaction among Asian versus White participants. Asian Americans are underrepresented among abortion patients, which could contribute to stigma and help to explain these findings.[24] Research has found lower levels of broader telehealth adoption among Asian individuals despite high levels of digital connectedness, which may be explained by discrimination in medical settings.[25]

Limitations

This analysis has several limitations. First, all participants self-selected into telehealth care. Participants in our study were disproportionately older, White, and more financially secure than the national population of abortion patients,[24] although our sample may be more representative of the 24 states where telehealth abortion is legal. In addition, virtual clinic abortion services were available only in English and required a credit or debit card. These factors may limit the generalizability of our findings, leading us to find higher acceptability than we would have seen if patients had been more representative of the general abortion patient population. While our follow-up rate was high compared with other medication abortion studies, 18% of the sample was lost to follow-up, which may have introduced selection bias. This could have overestimated patient acceptability if those less satisfied dropped out of the study at higher rates or underestimated acceptability if participants for whom privacy was very important were more likely to be lost to follow-up. Finally, our study had limited variation in synchronous and asynchronous care among the 3 included clinics and an insufficient number of clusters to calculate clustered standard errors within each virtual clinic. Therefore, our study may have overestimated differences in acceptability of care if the observed differences between synchronous and asynchronous are truly attributable to differences in acceptability across the virtual clinics. However, each virtual clinic had multiple clinicians, bolstering the validity of the differences we detected.

Public Health Implications

In a post-Roe world, telehealth is taking on a greater role in the US abortion care landscape. Therefore, medication abortion, and telehealth medication abortion specifically, has become a focus of abortion restrictions. The high patient satisfaction with telehealth abortion found in this study combined with documentation of the safety and effectiveness of this service delivery modality[8,26] supports its continued availability.

Although this study found very high patient satisfaction with telehealth abortion, it is critical to understand abortion service delivery preferences and lower levels of acceptability among Asian patients. Our data suggest that telehealth is disproportionately accessible to patient populations who face fewer barriers to in-clinic abortion care. Policy and service changes that facilitate patients' use of Medicaid and insurance to pay for the abortion, offer services in multiple languages, and increase minors' access to care are critical to ensuring a range of accessible and acceptable telehealth abortion models.[21] Given increasing barriers to abortion across the United States, it is essential to further develop innovative models of care and ensure that all people who need abortion care will have access to a service delivery model that is right for them. AJPH

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CONTRIBUTORS

L. R. Koenig conceptualized the analysis, conducted the data analysis, drafted the article, interpreted the data, and coordinated subsequent revisions. J. Ko provided administrative support for the study, interpreted the data, reviewed drafts of the article, and revised the article. E. S. Valladares, F. M. Coeytaux, E. Wells, and C. R. Lyles interpreted the data, reviewed drafts of the article, and provided substantive input on its content. U. D. Upadhyay obtained funding, supervised data analysis, drafted the article, interpreted the data, and revised the article.

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CONFLICTS OF INTEREST

C. R. Lyles receives contract funding from AppliedVR, InquisitHealth, and Somnology and was a visiting researcher at Google in 2022–2023.

HUMAN PARTICIPANT PROTECTION

The study was approved by the University of California, San Francisco's institutional review board (20-32951).

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Original Paper

The Role of Telehealth in Promoting Equitable Abortion Access in the United States: Spatial Analysis

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Abstract

Background: Even preceding the Supreme Court's 2022 *Dobbs v. Jackson Women's Health Organization* decision, patients in the United States faced exceptional barriers to reach abortion providers. Abortion restrictions disproportionately limited abortion access among people of color, young people, and those living on low incomes. Presently, clinics in states where abortion remains legal are experiencing an influx of out-of-state patients and wait times for in-person appointments are increasing. Direct-to-patient telehealth for abortion care has expanded since its introduction in the United States in 2020. However, the role of this telehealth model in addressing geographic barriers to and inequities in abortion access remains unclear.

Objective: We sought to examine the amount of travel that patients averted by using telehealth for abortion care, and the role of telehealth in mitigating inequities in abortion access by race or ethnicity, age, pregnancy duration, socioeconomic status, rural residence, and distance to a facility.

Methods: We used geospatial analyses and data from patients in the California Home Abortion by Telehealth Study, residing in 31 states and Washington DC, who obtained telehealth abortion care at 1 of 3 virtual abortion clinics. We used patients' residential ZIP code data and data from US abortion facility locations to document the round-trip driving distance in miles, driving time, and public transit time to the nearest abortion facility that patients averted by using telehealth abortion services from April 2021 to January 2022, before the *Dobbs* decision. We used binomial regression to assess whether patients reported that telehealth was more likely to make it possible to access a timely abortion among patients of color, those experiencing food insecurity, younger patients, those with longer pregnancy durations, rural patients, and those residing further from their closest abortion facility.

Results: The 6027 patients averted a median of 10 (IQR 5-26) miles and 25 (IQR 14-46) minutes of round-trip driving, and 1 hour 25 minutes (IQR 46 minutes to 2 hours 30 minutes) of round-trip public transit time. Among a subsample of 1586 patients surveyed, 43% (n=683) reported that telehealth made it possible to obtain timely abortion care. Telehealth was most likely to make it possible to have a timely abortion for younger patients (prevalence ratio [PR] 1.4, 95% CI 1.2-1.6) for patients younger than 25 years of age compared to those 35 years of age or older), rural patients (PR 1.4, 95% CI 1.2-1.6), those experiencing food insecurity (PR 1.3, 95% CI 1.1-1.4), and those who averted over 100 miles of driving to their closest abortion facility (PR 1.6, 95% CI 1.3-1.9).

Conclusions: These findings support the role of telehealth in reducing abortion-related travel barriers in states where abortion remains legal, especially among patient populations who already face structural barriers to abortion care. Restrictions on telehealth abortion threaten health equity.

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(JMIR Public Health Surveill 2023;9:e45671) doi: 10.2196/45671

KEYWORDS

telehealth; abortion; spatial analysis; health equity; barriers; abortion access; legal; health equity; young people; remote; rural

Introduction

Distance has long been understood to be a key barrier to abortion access in the United States. The distance that patients must travel to the nearest abortion provider has increased substantially in the wake of the July 2022 US Supreme Court's *Dobbs v. Jackson Women's Health Services* decision, which has led to abortion being banned in at least 14 states [1,2]. As a result, providers in protected access states—states where abortion care remains legally available—have experienced an influx of out-of-state patients, which is increasing wait times to care, and may force abortion seekers to travel farther than they would if they could obtain care at the facility closest to their home [3].

Prior studies have found that the further a patient must travel to a provider, the less likely they are to obtain a desired abortion [4,5]. National data indicate that longer travel distances to care due to a spike in antiabortion restrictions in the United States in recent years have contributed to the decreased abortion rate [6]. As of 2019, 20% of people who can get pregnant in the United States lived 43 or more miles from an abortion provider [7] and as of 2018, the United States had 27 "abortion deserts," that is, major cities with no abortion provider within 100 miles [8]. These geographic barriers to abortion facilities exist even within states where abortion is legal [9].

Research has also demonstrated that the impacts of state abortion bans are experienced unequally. Increased distance poses particular challenges for low-income patients due to the lower likelihood of car ownership, loss of wages from the time needed off work, transportation costs for gas or transit fare, as well as the cost of lodging and childcare [10]. People living in rural areas, the South, Midwest, and Mountain West; Black and Hispanic individuals; and minors face greater distances to reach an abortion provider [11,12]. Since the *Dobbs* decision, travel times to abortion facilities have increased disproportionately for Black and Indigenous populations [2].

However, direct-to-patient telehealth abortion may greatly mitigate existing geospatial inequities in abortion access [10,13], despite only being legal in 24 states and Washington, DC as of September 2023 (although more states permit abortion care but prohibit telehealth) [14,15]. In direct-to-patient telehealth abortion, a clinician can interact with patients remotely through videoconferencing or secure messaging and dispense abortion medications via mail-order pharmacies. Prior to 2020, telehealth for abortion was limited to clinic-to-clinic models with remote patient-provider interactions that took place at medical facilities with ultrasonography and other in-person tests [16-20]. Early in the COVID-19 pandemic, professional organizations including The American College of Obstetricians and Gynecologists endorsed a telehealth abortion model [21]. Recent studies have demonstrated the safety and effectiveness of this model of abortion care that can take place without any visits to a clinic or medical facility [22-25]. However, existing research has not captured the travel averted due to telehealth access.

In addition to the potential benefits of direct-to-patient telehealth (subsequently referred to as telehealth) in reducing abortion-related travel, the role of these models in enabling people to obtain a wanted, timely abortion is not well understood. A study conducted in the Pacific Northwest found that patients who used telehealth abortion services resided further from an abortion facility than those who accessed in-clinic care and that some patients chose telehealth even when a clinic is geographically convenient, indicating a preference for telehealth among some patients who obtained an abortion [26]. It is critical to understand who benefits most from abortion models that allow patients to carry out the entire abortion process from home. Few studies have examined the extent to which patients choose telehealth abortion when they have access to in-clinic abortion or whether telehealth is making an otherwise inaccessible abortion possible, therefore reducing barriers to access.

Therefore, we aimed to estimate the amount of travel patients avert by using a telehealth service for medication abortion among a sample of patients who obtained abortions who overwhelmingly resided in states that allow telehealth for abortion care. We also aimed to understand the role that telehealth plays in enabling people to obtain a timely abortion, especially for those who face the greatest barriers to in-clinic care.

Methods

Overview

We used data from the California Home Abortion by Telehealth (CHAT) Study, a study that examines medication abortions provided via telehealth from 3 US virtual clinics, defined as telehealth abortion clinics without brick-and-mortar facilities: Choix, Hey Jane, and Abortion on Demand. While the study was initiated in California, it expanded as the virtual clinics expanded their services to 20 states and Washington, DC. We obtained anonymized clinical chart data from patients who obtained abortion care from these clinics for a defined period between April 2021 and January 2022. At the time of consent to care with the virtual clinic, patients provided permission for the telehealth provider to share their anonymized clinical records with researchers in accordance with each clinic's privacy policy. All clinical data received were deidentified apart from ZIP code (United States postal codes) and dates of service.

In addition, each virtual clinic invited patients who were approved for abortion care during a defined period between June 2021 and January 2022 to participate in a series of 3 surveys on the abortion provider's telehealth platform. Directly following the abortion intake, patients were directed to a page containing detailed information about the study and, if interested, patients provided electronic informed consent prior

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to their participation. The first survey was administered directly following abortion intake, after obtaining informed consent. Two follow-up surveys were administered within 4 weeks after abortion intake. All surveys were completed on the virtual clinics' telehealth platforms to maximize continuity and survey completion and minimize disruption for participants. Virtual clinics continued to invite patients to complete surveys until approximately 400 patients from each completed all 3 surveys. These participant surveys were linked with their clinical records, and all data were standardized and stored on a secure Research Electronic Data Capture (REDCap; Vanderbilt University) server [27]. We excluded records for abortions where the patient did not take the abortion medications, surveys that were not matched to a clinical chart, and patients with invalid ZIP codes.

Measures

Our key independent variables of interest reflected the amount of travel to the nearest abortion provider averted by using telehealth abortion services. Patient's ZIP codes were recorded in both the clinical chart data and in the surveys. For cases where the clinical chart ZIP code (used for mailing the medications) differed from the ZIP code reported in the survey, we retained the survey ZIP codes with the rationale that some patients may use addresses besides their home addresses for medication delivery. Using ArcGIS (Esri), we first calculated the centroid—the center point of all coordinate points inside the ZIP code polygon—of each unique ZIP code of patients' residences. Next, we used the Advancing New Standards in Reproductive Health 2021 Abortion Facility Database to establish the coordinates of publicly advertising US abortion facilities [28]. We used the ArcGIS Find Nearest feature to calculate the driving distance between the coordinates of the centroid of each patient's ZIP code and the coordinates of the closest abortion facility in miles. We doubled the calculation of 1-way driving distance in miles to calculate the total round-trip driving distance averted in miles. This ArcGIS calculation also generated 1-way travel time in minutes without traffic, which we doubled to develop estimates of round-trip travel time averted and converted to hours. We calculated public transit travel time in hours between patients' ZIP codes and abortion providers' geographic coordinates using the gmapsdistance package in R (R Core Team) [29].

Our outcome of interest was a measure that reflected whether telehealth made it possible to access an abortion in a timely manner (Multimedia Appendix 1). The original item was phrased: "If you didn't have an abortion through telehealth, what would have happened?" Response options were: "I would have gotten an abortion at a clinic soon;" "I would have gotten an abortion at a clinic, but it would have been a while;" "I would have continued the pregnancy;" "I don't know what would have happened;" or "something else." If the patient responded with "something else," they could provide free-text responses. These free-text responses included the following themes: patients would have attempted to self-manage their abortion (primarily seeking abortion pills through other channels), traveled out of state, or sought abortion care at a clinic without a specified time frame. We dichotomized this variable to reflect whether the patient perceived that telehealth made it possible to have an abortion in a timely manner ("I would have gotten an abortion at a clinic, but it would have been a while;" "I would have continued the pregnancy;" "I don't know what would have happened;" or "something else"), versus not ("I would have gotten an abortion at a clinic soon").

We also examined patient characteristics including: patient age at the time of abortion screening (younger than 18, 18-24, 25-29, 30-34, and ≥35 years); pregnancy duration (<35, 35-49, 50-62, and ≥63 days); self-reported race or ethnicity (Asian, Native Hawaiian, or Pacific Islander; Black; Hispanic or Latinx; White; multiracial, Native American, American Indian, or Alaska Native; Middle Eastern or North African; or unknown); urban versus suburban or rural residence based on the rural-urban commuting area codes corresponding to the patient's ZIP code [30]; and the round-trip driving distance to the nearest abortion facility (<5, 5-24, 25-49, 50-99, and ≥100 miles). In regression analyses, we collapsed patient age (younger than 24, 25-29, 30-34, ≥35 years) due to small cell sizes.

Data Analysis

We first described the median, IQR, and total amounts of round-trip driving distance, driving time, and public transit time averted using telehealth for abortion across the clinical chart sample. Next, we calculated median driving distances by the patient characteristic examined and tested for differences in driving distances by each characteristic using Kruskal-Wallis tests.

We used bivariate binomial regression to estimate prevalence ratios (PRs). We then calculated marginal estimates from these binomial regression models to estimate the proportion of participants within each category for whom telehealth made it possible to have an abortion in a timely manner as prevalence percentages (PPs). Analyses were conducted using ArcGIS Online, Stata (version 17.0; StataCorp), and RStudio (version 2022.10.0; Posit, PBC).

Ethical Considerations

This study was approved by the University of California, San Francisco institutional review board (20-32951). Clinical chart data that were deidentified except for patients' ZIP codes and dates of service were obtained from participating virtual clinics in accordance with their privacy policies. The subsample of patients who participated in detailed surveys provided electronic informed consent for their participation and were remunerated with a US $50 electronic debit card after the completion of the final survey. Clinical chart and survey data from participating virtual clinics were standardized and stored on a secure REDCap server [27].

Results

Overview

We obtained records for 6154 abortions provided by the virtual clinics between April 2021 and January 2022. Of those, 120 did not take medications, and 7 patients listed ZIP codes from which driving and transit distances could not be calculated, leaving 6027 records included overall. Among these, 1600 patients also participated in CHAT Study baseline surveys. The

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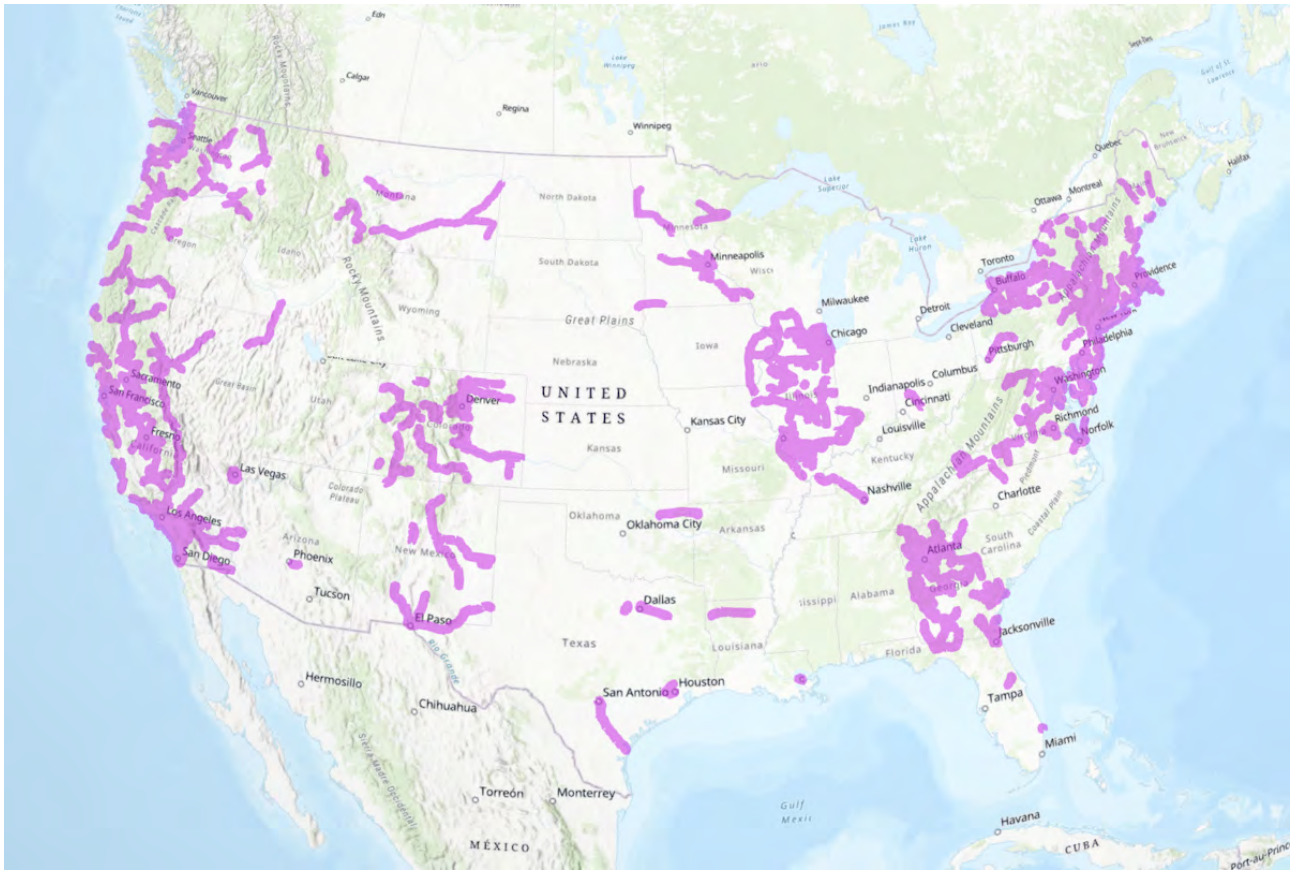
ZIP codes in the dataset corresponded to 31 states and Washington, DC.

Travel Averted

The 6027 patients in this analysis averted a median of 10 (IQR 4.5-26.0, range 0.13-566) miles of round-trip driving travel and 25 minutes (IQR 14.1-46.1 minutes, range <1 minute-9 hours) of driving time each. Driving routes averted are depicted in Figure 1 and illustrate the vast distances averted and the distribution of these routes by region. This corresponded to a total of 162,663 miles and 4195 hours of driving averted across the sample (Multimedia Appendix 2). Next, we examined the total public transit time averted for the 5116 (85%) patients for whom public transit routes were available between patients' home ZIP codes and the nearest abortion facility. Patients in the sample averted a median of 1 hour 25 minutes (IQR 45.6 minutes-2 hours 30 minutes, range 2 minutes-48 hours) and a total of 11,720 hours of public transit time. Among the subsample of 1600 patients who completed surveys, patients averted a median of 10 (IQR 4.5-24.6) miles and 25 (IQR 14.3-44.1) minutes of driving, and 1 hour 26 minutes (IQR 46.5 minutes-2 hours 26 minutes) of public transit time. In total, this group of survey participants averted 41,746 miles and 1096 hours of driving, and 3070 hours of public transit time.

Figure 1. Driving routes to the closest abortion facility averted through telehealth (N=6027).



Sample Description

Characteristics of the clinical chart sample and of the survey participants are presented in Table 1. Among the survey subsample, most patients were 25-34 (51%, n=823) years of age and had pregnancy durations between 5 and 7 weeks (55%, n=885). Over half (53%, n=841) identified as White and in the remaining sample 13% (n=203) identified as Hispanic or Latinx; 9% (n=148) identified as Black; 7% (n=105) as Asian, Native Hawaiian, or Pacific Islander; and 19% (n=303) reported more than 1 race or ethnicity, another race or ethnicity, or their race or ethnicity was unknown. In total, 91% (n=1454) of the sample resided in an urban area.

Next, we examined whether patients perceived that telehealth made it possible to have an abortion in a timely manner. Approximately one-fourth (23%, n=371) thought they would have had an abortion at a clinic, but it would have taken some time. Meanwhile, 17% (n=268) did not know what would have happened, and 2% (n=29) said they would have continued the pregnancy. The other 57% (n=903) of the sample thought they would have gotten an abortion at a clinic soon.

We then evaluated differences in travel averted by patient characteristics (Table 2). White patients averted the most driving to the nearest abortion facility (median 12, IQR 5-30 miles), while Asian, Native Hawaiian, or Pacific Islander patients averted the least (median 8, IQR 3-16 miles). Urban residents averted a median of 9 (IQR 4-19) miles of driving time, while those living in rural areas averted a median of 83 (IQR 47-141) miles. The driving miles patients averted did not differ by age, pregnancy duration, or food insecurity.

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Table 1. Description of the clinical chart sample and survey subsample.

Factor	Clinical chart sample (n=6027), n (%)	Survey subsample (n=1600), n (%)
Age (years)		
<18	30 (0.5)	8 (0.5)
18-24	1458 (24.2)	448 (28.0)
25-34	3088 (41.2)	823 (51.4)
≥35	1451 (24.1)	321 (20.1)
Pregnancy duration at abortion intake (days)		
<35	1736 (28.8)	448 (28.0)
35-49	3333 (55.3)	885 (55.3)
50-62	825 (13.7)	229 (14.3)
≥63	128 (2.1)	38 (2.4)
Race or ethnicity		
Asian, Native Hawaiian, or Pacific Islander	270 (4.5)	105 (6.6)
Black	413 (6.9)	148 (9.2)
Hispanic or Latinx	339 (5.6)	203 (12.7)
White	2488 (41.3)	841 (52.6)
Multiracial, Native American, American Indian, or Alaska Native; Middle Eastern or North African; or unknown	2517 (41.8)	303 (18.9)
Food insecurity in past month		
No	—[a]	1148 (72.8)
Yes	—	428 (27.2)
Residence		
Suburban or rural	593 (9.8)	146 (9.1)
Urban	5434 (90.2)	1454 (90.9)
Round-trip driving miles averted (miles)		
<5	1705 (28.3)	437 (27.3)
5-24	2765 (45.9)	775 (48.4)
25-49	698 (11.6)	165 (10.3)
50-99	467 (7.8)	120 (7.5)
≥100	392 (6.5)	103 (6.4)
If you didn't have an abortion through telehealth, what would have happened?		
I would have gotten an abortion at a clinic soon	—	903 (56.9)
I would have gotten an abortion at a clinic, but it would have been a while	—	371 (23.4)
I would have continued the pregnancy	—	29 (1.8)
Something else	—	15 (0.9)
I don't know what would have happened	—	268 (16.9)

[a]—: not available.

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Table 2. Round-trip driving distance averted, by patient characteristics (N=1600).

	Driving miles averted	
	Median (IQR)	*P* value
Age (years)		.54
<18	14.5 (5.1-46.2)	
18-24	9.5 (4.0-24.3)	
25-34	10.2 (4.4-24.0)	
≥35	11.4 (5.1-25.6)	
Pregnancy duration at abortion intake (day)		.12
<35	11.1 (4.7-25.0)	
35-49	10.3 (4.6-23.4)	
50-62	8.8 (3.7-24.5)	
≥63	16.0 (6.3-57.5)	
Race or ethnicity		.001
Asian, Native Hawaiian, or Pacific Islander	7.7 (3.4-15.6)	
Black	9.8 (4.9-21.5)	
Hispanic or Latinx	8.3 (5.0-19.3)	
White	12.0 (4.7-30.2)	
Multiracial, Native American, American Indian, Alaska Native, Middle Eastern or North African, or unknown	9.2 (4.4-19.4)	
Food insecurity in past month		.96
No	10.3 (4.6-23.6)	
Yes	10.2 (4.5-25.5)	
Residence		<.001
Urban	9.3 (4.3-19.4)	
Suburban or rural	82.6 (47.2-140.7)	

The Role of Telehealth in Abortion Access

Next, we examined the differences in whether telehealth made it possible to obtain an abortion in a timely manner by patient characteristics and by the amount of travel averted (Table 3 and Figure 2). Compared to patients who were 35 years of age or older (PP 35.2%), telehealth was more likely to make abortion possible for patients 24 years of age or younger (PP 48.3%, PR 1.4, 95% CI 1.2-1.6) and for those of 25-29 years of age (PP 47.6%, PR 1.4, 95% CI 1.1-1.6). Patients who experienced food insecurity in the past month were more likely than those who had not experienced food insecurity to have reported that telehealth made a timely abortion possible (PP 51.2% vs 40.2%, PR 1.3, 95% CI 1.1-1.4). When we examined differences by race or ethnicity, patients who were Asian, Native Hawaiian, or Pacific Islander were less likely to report that telehealth made it possible to obtain a timely abortion than White patients (PP 30.5% vs 41.5%, PR 0.7, 95% CI 0.5-1.0). For patients who lived in rural areas, telehealth was more likely to make timely abortion care possible than those who resided in urban areas (PP 56.9% vs 41.7%, PR 1.4, 95% CI 1.2-1.6). Compared to those who averted 5-25 miles of driving to reach an abortion provider (PP 39.3%), those who averted less than 5 miles of round-trip driving (PP 47.7%, PR 1.2, 95% CI 1.1-1.4) or more than 100 miles of round-trip driving (PP 62.4%, PR 1.6, 95% CI 1.3-1.9) were more likely to perceive that telehealth made a timely abortion possible than those that averted less travel. The proportion of patients for whom telehealth made it possible to have an abortion soon was similar across pregnancy duration categories.

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Table 3. Associations between patient characteristics and whether telehealth made it possible to obtain a timely abortion (N=1586).

Overall	Prevalence ratio (95% CI)	Marginal prevalence estimates (95% CI)
Patient age (years) at abortion intake		
<25	1.4 (1.2-1.6)	48.3 (43.7-52.9)
25-29	1.4 (1.1-1.6)	47.6 (42.8-52.4)
30-34	1.1 (0.9-1.3)	38.8 (34.0-43.5)
>34	Reference category	35.2 (30.0-40.4)
Pregnancy duration at abortion intake (days)		
<35	Reference category	44.5 (39.9-49.1)
35-49	0.9 (0.8-1.0)	40.6 (37.4-43.9)
50-62	1.1 (0.9-1.3)	48.5 (42.0-55.0)
≥63	1.1 (0.8-1.6)	50.0 (34.1-65.9)
Food did not last in the last month		
No	Reference category	40.2 (37.4-42.9)
Yes	1.3 (1.1-1.4)	51.2 (45.9-56.5)
Race or ethnicity		
Asian, Native Hawaiian, or Pacific Islander	0.7 (0.5-1.0)	30.5 (21.7-39.3)
Black	1.0 (0.9-1.3)	43.8 (35.8-51.9)
Hispanic or Latinx	1.2 (1.0-1.4)	48.8 (41.9-55.6)
White	Reference category	41.9 (38.6-45.3)
Multiracial, other, or unknown	1.1 (1.0-1.3)	46.3 (40.7-52.0)
Rural residence		
Urban	Reference category	41.7 (39.1-44.2)
Suburban or rural	1.4 (1.2-1.6)	56.9 (48.9-65.0)
Round-trip driving miles averted (miles)		
<5	1.2 (1.1-1.4)	47.7 (43.0-52.4)
5-24	Reference category	39.3 (35.8-42.8)
25-49	1.1 (0.9-1.3)	42.3 (34.7-49.9)
50-99	0.9 (0.7-1.2)	35.0 (26.5-43.5)
≥100	1.6 (1.3-1.9)	62.4 (52.9-71.8)

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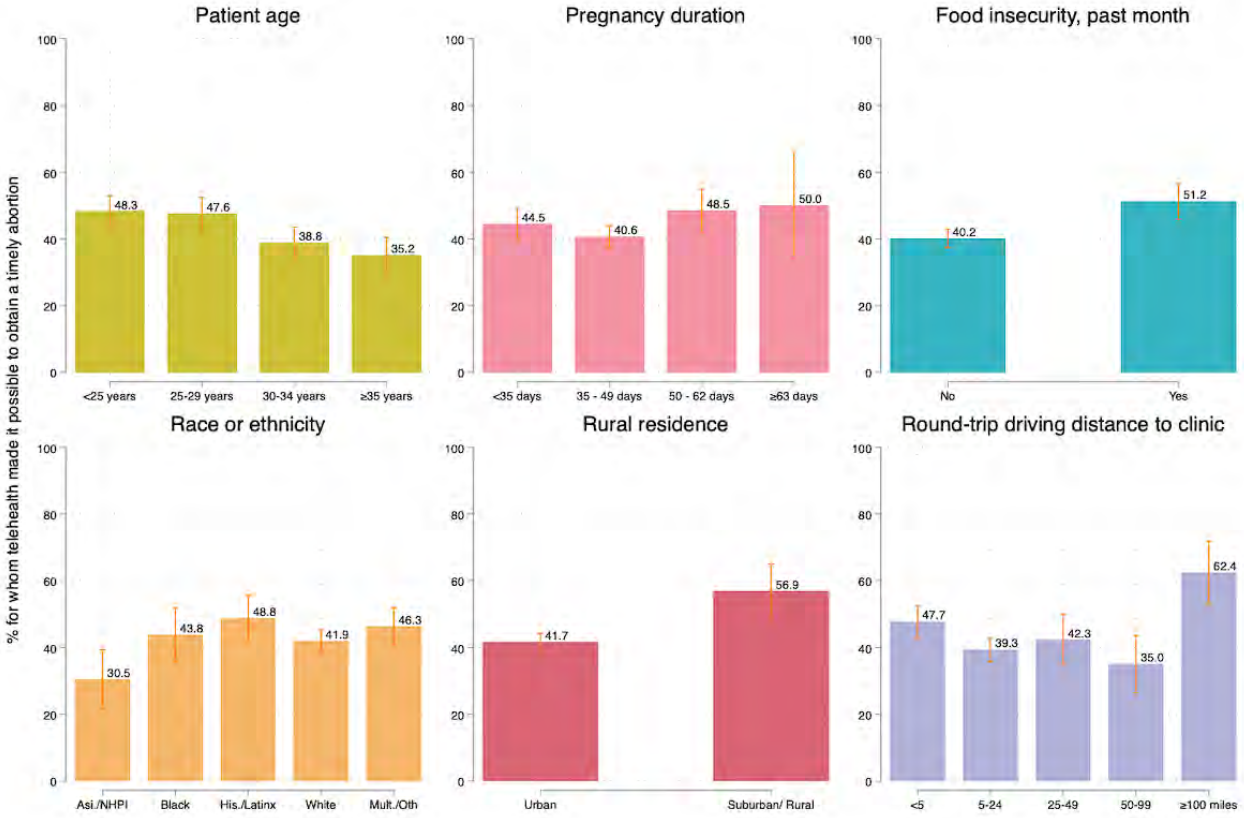
Figure 2. Marginal estimates of the proportion for whom telehealth made it possible to obtain a timely abortion, by patient characteristics, calculated from multivariable binomial regression (N=1586). NHPI: Native Hawaiian or Pacific Islander.



Discussion

Principal Findings

In this study, we found that direct-to-patient telehealth can be an important tool to overcome disparities in abortion access. While the expansion of telehealth is key to improving health equity broadly, abortion care is largely siloed to abortion facilities, which are few and far between and are now closing in record numbers [31]. Therefore, the impact of telehealth on improving equitable abortion access is even greater than for other health care services.

We found that using a telehealth abortion model can avert substantial driving distance and time for those with access to a car and travel time for those who would have used public transit. Our sample drew overwhelmingly from urban areas and from protected access states. Even so, while most of our sample resided close to an abortion facility, 15% lived 25 miles or further, and 7% lived 50 miles or further. Therefore, telehealth can expand the geographic reach of abortion services in states where abortion remains legal.

Telehealth abortion fits within an environmental justice framework, which views telehealth as a means of reducing the carbon footprint of health care services and space as a key component of health disparities [32,33]. Marginalized communities disproportionately bear the brunt of both unequal health policies and the unequal impacts of climate change. This analysis elucidates the connection between environmental justice and reproductive justice by examining abortion access within this framework of geospatial and environmental inequality.

These results suggest that telehealth abortion is poised to address health equity concerns across age, socioeconomic status, and geospatial location. Young people face unique logistical and privacy challenges, many of which can be alleviated by using telehealth, which allows patients to maintain privacy and avoid travel [34]. For low-income patients, the cost of abortion is often a substantial barrier to care, which is only exacerbated when coupled with the costs of associated travel [35]. Telehealth abortion has the potential to address geographic inequities in access to care for those living in abortion deserts or rural areas within protected access states. These findings on telehealth abortion fit within a broader literature that views telehealth as beneficial for reducing health care costs [36], serving underserved and rural patients [37,38], and easing the convenience and comfort of health care provision [39,40].

Compared to the national population of patients who obtained abortions during the same time period, patients in our sample who obtained abortions by telehealth were more likely to be older, White, and have higher socioeconomic statuses [41]. Thus, telehealth abortion may be reaching a subset of patients who are more resourced or have higher technology literacy. However, when patients were asked what would have happened had they not obtained the telehealth abortion, we found that for nearly half, telehealth made it possible to obtain timely abortion care. Telehealth was more likely to play this instrumental role in obtaining an abortion among patient populations who are known to face the most structural barriers to abortion care, such

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as younger people, those experiencing food insecurity, those residing in rural areas, and those who resided far from an abortion facility [2,42]. Telehealth was less likely to make timely abortion care possible for Asian patients than White patients, perhaps due to urban residence and proximity to abortion providers. Given that telehealth abortion care is situated within a highly unequal health care landscape, there is interest in its role in mitigating inequities in abortion access [43,44]. Our results suggest that telehealth is playing different roles among different demographic groups within our sample. More specifically, while currently, White, urban patients might prefer telehealth due to its convenience or privacy, many patients from groups facing structural barriers to abortion care, such as people of color, those living on lower incomes, those who are younger, and those residing in rural areas, face greater distances to abortion facilities and thus may rely on telehealth for abortion access. These findings suggest that telehealth is key to promoting equitable access to abortion care in the United States, and expanding access to telehealth would be key for these groups.

We found that for patients who resided more than 100 miles from an abortion facility, telehealth was more likely to make it possible to access timely abortion care. This finding echoes prior research that has documented that geospatial barriers can determine whether patients obtain wanted abortions [4,5]. These results bolster the need for alternatives to in-clinic abortion care, especially as geographic access to abortion facilities grows increasingly unequal.

Limitations

This paper has several limitations. Our use of ZIP codes as the location of patient residences reduces the accuracy of the travel distances and travel times we calculated. This likely resulted in overestimated distances and times for some patients and underestimated distances and times for others; however, the net misclassification remains unknown [45]. Only one-fourth of patients elected to participate in the surveys, which may have introduced selection bias and limited the generalizability of these findings to the broader population of virtual clinic patients. Some patients from restricted access states who traveled for abortion care or used various mail-forwarding techniques may have chosen not to disclose their true home ZIP codes. Further, this analysis was conducted on data collected prior to the *Dobbs* decision in June 2022, after which 14 states have banned abortion care. Given the increased wait times for abortion care that have resulted from widespread abortion restrictions, many patients who seek in-person abortion care may need to travel further than their closest abortion facility. Therefore, our analysis may have underestimated the travel averted that we documented in this study. The overwhelming majority of patients in our sample resided in states that allow telehealth for abortion care. Most other states have laws that prohibit telehealth for abortion [15]. Our analysis, therefore, does not capture the full range of travel that could be averted if telehealth abortion care were available across the country. While we did not find that telehealth was more likely to make a critical difference in obtaining an abortion for people of color, this finding may be limited by the racial composition of our sample, in which Black and Hispanic patients, who face the greatest barriers to abortion care, were greatly underrepresented compared to the population of US patients who obtained abortions [41]. Despite these limitations, this study highlights the benefits of telehealth services by being among the first to use geospatial analysis to examine the travel averted, across both driving and public transit transportation, from using a telehealth model for abortion care.

Conclusions

This paper makes important contributions to a growing body of work on telehealth abortion and the broader literature on telehealth. Our findings support the role of telehealth abortion in reducing travel distance, time, and costs, which in turn mitigates the inequities embedded in abortion provision based on geospatial location, socioeconomic status, and local abortion policy. We found that telehealth can play a key role in accessing an otherwise unobtainable or delayed abortion, especially for marginalized patient populations. Future research should examine how telehealth abortion services can be tailored to improve health equity and digital inclusion. These findings may help direct future policy on expanding access to telehealth abortion, especially in the wake of the *Dobbs* decision, which is continuing to exacerbate longstanding inequities in abortion access. While states that ban abortion are unlikely to support telehealth for abortion, there are 6 states that permit abortion but restrict telehealth abortion care [14]. States invested in health equity that want to safeguard access in an increasingly restricted abortion landscape should legalize telehealth abortion. There is a need for federal actions to protect patients who seek and providers who dispense telehealth abortion care across state lines.

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Data Availability

The data sets generated and analyzed during this study are not publicly available due to privacy concerns of patients who obtained abortions and the changing legal status of abortion care but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Definition of primary outcome measure.
[PNG File , 165 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Density plot of travel averted by using telehealth.
[PNG File , 230 KB-Multimedia Appendix 2]

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Abbreviations

CHAT: California Home Abortion by Telehealth Study
PP: prevalence percentage
PR: prevalence ratio
REDCap: Research Electronic Data Capture

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Acceptability and feasibility of mifepristone medical abortion in the early first trimester in Azerbaijan

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ABSTRACT

Objective To examine the acceptability and feasibility of early medical abortion using mifepristone and misoprostol in Azerbaijan.

Methods A total of 863 women in Baku and two regions of Azerbaijan who sought termination of gestations up to 63 days were enrolled in the study. In the capital, women swallowed 200 mg mifepristone in the clinic and were given the option of taking 800 μg misoprostol buccally either at the clinic or at home 24–48 hours later. In the regions, women were given the option of taking both drugs at home. Follow-up visits were to take place two weeks after mifepristone administration to determine abortion status.

Results Seventy-four percent of women in the regions chose home administration of mifepristone, and 92% of women from all locations selected misoprostol home administration. Ninety-seven percent of women had complete abortions, and 97% were satisfied or very satisfied with the method. The vast majority of participants preferred medical abortion for a future procedure (96%). Nearly all women (98%) would recommend medical abortion for pregnancy termination to a friend.

Conclusion Mifepristone-misoprostol medical abortion with the option of home administration of both drugs is an acceptable and feasible option for women in Azerbaijan.

KEYWORDS Azerbaijan; First trimester pregnancy; Medical abortion; Mifepristone; Misoprostol

INTRODUCTION

The Republic of Azerbaijan, with a population of 9.4 million, is the largest country in the Caucasus region. Like in many of its neighbouring countries, abortion is a major and often resorted to method of fertility regulation[1,2]. The 2006 Demographic and Health Survey (DHS) reported a total abortion rate of 0.77 per woman year for the three-year period preceding the survey, with no difference between urban or rural residence[3]. The proportion of pregnancies that end in induced abortions increases dramatically with pregnancy order. The desire for small-sized families, early completion of childbearing, and continued reliance on traditional methods of contraception, contribute to persistently high rates of unwanted pregnancy and abortion[3,4].

Abortion has been legal for more than 50 years in Azerbaijan and, under the current law, abortion services

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are available without restriction during the first 12 weeks of gestation. From 13 to 22 weeks of pregnancy, abortion is available only on select socioeconomic and broad medical grounds. Induced abortion can be performed by obstetrician/gynaecologists by either vacuum aspiration or sharp curettage under local or general anaesthesia depending on the woman's choice. Abortion procedures are permitted in private and public medical facilities. Women's consultation clinics can perform induced abortion only by electric or manual vacuum aspiration for pregnancies up to 6 weeks' gestation[5]. At the time these studies were conducted, mifepristone was not registered, and formal medical abortion services were not available in Azerbaijan.

Establishing mifepristone-misoprostol medical abortion in Azerbaijan would provide women with an alternative to surgical abortion and potentially increase access to safe abortion services. The World Health Organization recommends the use of 800 μg vaginal, buccal or sublingual misoprostol following 200 mg oral mifepristone for early medical abortion through 63 days since the last menstrual period (LMP)[6]. All three routes of misoprostol administration are highly effective, though some women prefer non-vaginal routes of administration and find in-the-mouth routes more private, comfortable and easy to administer[7–10]. This clinical trial examines the acceptability and feasibility of introducing the medical abortion regimen of 800 μg buccal misoprostol after 200 mg mifepristone up to 63 days' LMP in Azerbaijan. The study regimen also gave women the option to take the mifepristone at home, in addition to the misoprostol, which would afford them greater privacy, and allow them to schedule their bleeding around their other responsibilities.

METHODS

The first round of the study was conducted from October 2008 through March 2010 at two clinical sites in the capital city of Baku (Scientific Research Institute of Obstetrics and Gynaecology, and Family Planning Centre). The second round was conducted from November 2010 through November 2011 at three clinical sites in two north-western regions of Azerbaijan (Antenatal Clinic, Ganja; Family Planning Centre, Ganja; and Central Regional Hospital, Zakatala). All clinics provided surgical abortion services prior to this study. Clinicians at all five sites were trained in mifepristone-misoprostol medical abortion provision as well as in the study procedures. The Allendale Investigational Review Board reviewed and approved the study protocol. All participants gave written informed consent to participate in the study.

Women who presented for termination of a gestation up to 63 days' LMP were recruited to participate in the study. Exclusion criteria were suspicion of ectopic pregnancy, concurrent anticoagulant therapy, history of haemorrhagic disorders, concurrent long-term corticosteroid therapy, adrenal insufficiency, inherited porphyria, and known allergy to mifepristone or misoprostol. Gestational age was determined using one or more standard methods, including: menstrual history, physical examination, and ultrasound. In addition, women had to be 18 years or older, were expected to live or work within one hour of the study site, and had to be willing to return for a follow-up visit two weeks later.

In the first round of the study, women swallowed one 200 mg mifepristone pill (Pencrofton®; Pencroft Pharma, Russia) in the clinic and were given the option of taking misoprostol (Cytotec®; Pfizer, USA) either at the clinic or at home. During the second round of the study, women were given the option to take both the mifepristone and the misoprostol at home. For both rounds, women were instructed to take the misoprostol 24 to 48 hours after they had ingested the mifepristone.

Women opting for home administration of misoprostol were given four 200 μg pills of misoprostol to take at home. They were informed that they could return to the clinic to take the pills if they changed their minds. Participants were instructed to place two tablets of misoprostol between their cheek and gums on each side and to hold them there, letting the pills dissolve for 30 minutes, after which they were to swallow any remaining fragments. Participants choosing in-clinic misoprostol administration were given an appointment one to two days later to take the second set of pills in the presence of study staff. Women were given pain medication to use at their discretion. All participants were given a home study card with detailed instructions on misoprostol administration. Women in the capital were asked to note the date and time of misoprostol administration, the level of bleeding and any side effects experienced in the two weeks following mifepristone administration. Women in the region were asked to note the date and time of mifepristone

and misoprostol administration, and the number of missed days of work and/or school and hours of childcare needed due to the abortion. Participants were instructed to call the clinic if they had any questions and advised to return to the clinic if heavy or prolonged bleeding occurred, or if they experienced fever lasting six hours or more.

At the follow-up visit two weeks after mifepristone administration, providers used clinical examination and ultrasound as needed to determine the status of the abortion. Women with ongoing, viable pregnancies were offered a surgical abortion; those with incomplete abortions were given the option of a surgical completion or waiting another week, with or without an additional dose of 800 μg buccal misoprostol. If symptoms of incomplete abortion persisted after the additional week, a surgical completion was scheduled. Participants could request a surgical completion at any time during the study. If the abortion was determined to be complete, women were interviewed and discharged from the study.

This study assessed the acceptability and feasibility of mifepristone-misoprostol medical abortion, a new method of abortion in the country. The sample size (500 in the first round and 363 in the second) was selected to allow staff to gain expertise in this new method. Based on previous reports[11], we expected an efficacy rate of about 96%. All data were entered into SPSS version 13.0 at Gynuity Health Projects in Tbilisi and sent to Gynuity Health Projects in New York for analysis in SPSS version 15.0, using descriptive statistics. Analyses included all women who enrolled and provided any follow-up data.

RESULTS

Between October 2008 and November 2011, the study sites enrolled 863 women in total, 500 (58%) in the capital and 363 (42%) in the regions. None were lost to follow-up. Aside from one woman who did not take misoprostol after ingesting mifepristone and opted for surgical completion of the abortion instead, all participants followed the medical abortion protocol.

The median age of the women was 29 years, and more than half had completed a university education (Table 1). Nearly all participants were married and 90% had at least one live birth. More than two-thirds of them reported having had a previous abortion. Demographic characteristics were similar across the study sites, except that women from Baku were more educated than those from the regions.

Table 1 Characteristics of study participants ($N = 863$).

Age, years; median (range)	29 (17–48)
Highest level of education completed, %*	
High school or less	39
University	61
Married, %**	93
Gravidity; median (range)	4.0 (1–22)
Nulliparity, %	10
Previous abortion, %	70
Gestational age, days; median (range)	45.0 (30–63)

*$n = 858$; five women did not answer the question
**$n = 860$; three women did not answer the question

Ninety-seven percent of cases were successful (95% confidence interval [CI]: 96.2%, 98.4%), defined as complete abortions that did not require surgical completion at any point (Table 2). At the initial follow-up visit, 28 women presented with incomplete abortions with ten electing to have a surgical completion. The 16 subjects who received an additional dose of misoprostol and the two who chose expectant management all had complete abortions by their extended follow-up visit. There was no significant difference in success rates between participants who took the mifepristone at home and those who took it in the clinic. Success rates remained high as gestational age increased, with 96% of women with pregnancies of 57 to 63 days' LMP having a successful abortion. Twenty-three women received a surgical intervention to complete the abortion, seven of whom were diagnosed with

Table 2 Outcome of medical abortion ($N = 863$).

Success, %*	97
Success by gestational age category, % (*n*)*	
up to 49 days' LMP	97 (608/627)
50–56 days' LMP	99 (152/153)
57–63 days' LMP	96 (80/83)
Failure, % (*n*)	3 (23)
Ongoing pregnancy	0.8 (7)
Incomplete abortion	0.6 (5)
Surgery due to heavy bleeding	0.5 (4)
Surgery at patient request	0.8 (7)

*Success defined as complete abortion without recourse to surgical evacuation at any point during the study period.

Table 3 Top reasons for choice of mifepristone location among women in the region, % (*n*)*.

	Home administration (n = 267)		*Clinic administration (n = 96)*	
1	Presence of partner	49 (130)	Like staff presence	82 (74)
2	More private experience	35 (94)	Less anxiety	72 (65)
3	Compatible with duties	32 (84)	More comfortable	21 (19)
4	More comfortable	32 (84)	More private experience	14 (13)
5	Easier to plan childcare	27 (73)	Flexibility with schedule	11 (10)

*Women were allowed to choose more than one answer.

ongoing pregnancies. Ultrasound was used at the follow-up visit to determine abortion status for one-third of participants in the region and 86% of participants in Baku.

Overall, three quarters (74%) of women given the option chose to take the mifepristone at home rather than in the clinic. Almost half made this choice because they wanted their partner present, and more than one-third wanted a more private experience (Table 3). Of women who chose to take the mifepristone in the clinic, 82% liked the presence of clinic staff, and many stated that being in the clinic would make them less anxious about the procedure. All of the women in the home user group took mifepristone at the scheduled time (defined as within a window of ± 6 hours of the time they had selected with the provider) (Table 4). Only two of the 267 women selecting home mifepristone chose to take the pill a day or more after their initial visit with the doctor.

Home administration of misoprostol was offered to all participants, both in the capital and in the regions, and over 90% of them selected this option. All home mifepristone users and 88% of clinic mifepristone users chose to take the misoprostol at home. Among home misoprostol users, 96% took the drug within the therapeutic range of 24 to 48 hours after mifepristone. Only one woman deviated from her scheduled time of administration (defined as within a window of ± 6 hours of the selected time), taking the misoprostol 13 hours earlier than planned.

Participants in both groups were asked about the side effects they experienced during the abortion (Table 5). Women from the capital were instructed to document them daily on the home study card, while those from the region were asked to recall side effects at their follow-up visit. More than half of the subjects from Baku reported nausea, which was also the most frequently reported side effect among women from Zakatala and Ganja. Other commonly reported side effects included fever/chills and vomiting. Eighty-five percent of participants found the side effects acceptable or very acceptable.

Table 4 Timing of mifepristone and misoprostol administration.

Mifepristone administration among women in the region, % (n)		
Chose home mifepristone	74 (267/363)	
Zakatala	77 (118/153)	
Ganja	71 (149/210)	
Took home mifepristone at scheduled time*	100 (267/267)	
Took home mifepristone the same day as initial visit	99 (265/267)	
Home misoprostol administration by location of mifepristone administration	*Home mifepristone n = 267*	*Clinic mifepristone n = 525*
Took home misoprostol at scheduled time, % (*n*)*	99.6 (266)	100 (525)
Median mifepristone-misoprostol interval, h (range)	48 (25–52)	47 (26–54)

*Women who took the drug ± 6 hours of the scheduled time were considered to have taken the drug on time.

Table 5 Reported side effects of medical abortion, %.

	*Capital (n = 500)**	*Region (n = 360)***
Nausea	53	38
Fever/chills	23	15
Diarrhoea	1	3
Vomiting	25	13
Other***	1	0.3

*Women from the capital reported side effects on the home study card.
**Women in the regions reported side effects at their exit interview.
***Other reported side effects included weakness, drowsiness, headache, syncope.

For the most part, women in the regions did not report that the abortion interfered with their work responsibilities. A little more than one third of the participants worked outside of the home, and only three reported that the medical abortion caused them to miss work. Additionally, the medical abortion interfered with the ability to fulfil childcare responsibilities for only less than 1% of participants.

At the follow-up exit interview, participants were asked about their experience and acceptability of the medical abortion (Table 6). Nearly all (96%) were satisfied or very satisfied with the method. Ninety-six percent of them would prefer medical over surgical abortion in the future, and 98% would recommend the medical method to a friend. Almost all women were satisfied with the counselling they received from their provider, reporting that they felt prepared for the amount of bleeding and pain, and the duration of the entire medical abortion procedure. In the regions, almost all participants (99%) who chose home administration for mifepristone would prefer home use again, while a third of clinic mifepristone users would switch to home use in the future. Women at all sites were very satisfied with taking the misoprostol at home, with 93% preferring home use in the future.

Women were asked to report the best and worst features of the abortion. The most commonly cited best feature was avoiding surgery and anaesthesia, followed by having a successful abortion without complications. More than half of participants felt that pain/cramps were the worst feature, with those from the capital reporting it with much higher frequency than regional residents (83% vs. 28%). Few women reported that there were no best or worst features of the abortion, 2% and 5%, respectively.

Table 6 Women's reported experience with and acceptability of medical abortion, % (*n*).

Very satisfied/satisfied with method	97 (828/858)
Side effects very acceptable/acceptable	85 (723/855)
Prefer medical abortion as method of next abortion	96 (820/859)
Prefer home as next place of misoprostol administration	93 (794/856)
Would recommend to a friend	98 (839/859)
Best features*	
Avoided surgery/anaesthesia	66 (569/859)
Successful, no complications	57 (485/859)
Home administration of misoprostol	28 (242/859)
Easy, quick, simple treatment	21 (179/859)
Private, confidential	13 (114/859)
No best feature	2 (19/859)
Worst features*	
Pain, cramps	60 (517/860)
Anxiety	39 (334/860)
Bleeding	33 (287/860)
Nausea, vomiting	29 (246/860)
Duration of procedure	18 (153/860)
No worst feature	5 (43/860)

*Women could choose more than one answer.

Providers at all sites were satisfied with the method; overall, only 6% of women made an unscheduled visit or call to the clinic with concerns about the abortion. Regardless of where participants chose to take the mifepristone, the providers in the region would recommend home administration of mifepristone for almost every patient if she was to have another abortion in the future.

DISCUSSION

Findings and interpretation

The study shows that medical abortion is highly feasible and acceptable in Azerbaijan. High success rates were achieved in the capital city, Baku, as well as in the regions. Almost all women enrolled in the study were either very satisfied or satisfied with the method, and stated that they would choose this method if termination of an unwanted pregnancy is needed in the future. The majority of participants would opt for home

administration of mifepristone as well as misoprostol, and nearly all would recommend medical abortion method to a friend.

Women who take mifepristone at home may be better able to schedule their bleeding around their work and family responsibilities, and previous research has shown that this option is safe and acceptable to women and providers[11]. This study confirmed the desirability of this option, evidenced by the high proportion of participants (74%) who opted for home administration of mifepristone. However, the opportunity to time the bleeding so that it did not conflict with daily activities did not seem to be the prime motivation of women's wish to use the mifepristone at home, contrary to what we believed, as most in the home group did not delay mifepristone administration after seeing the doctor, even if their appointments were earlier in the week.

Misoprostol home administration is a widespread practice in many countries[12] and appeared to be similarly preferable for women in Azerbaijan. The study demonstrated that women were able to take mifepristone and misoprostol on their own without increasing the burden on clinic staff through extra calls and visits, and providers were confident in their patients' abilities to take the mifepristone and misoprostol independently as well.

Reports of side effects were higher in Baku than in the regions, which may be due to differences in the method of data collection between the rounds. Women from Baku were told to record side effects on the home study card each day, while women in the regions were asked to recall them during the exit interview at the follow-up visit. However, previous research that collected side effects information from the same women through both means of data collection found differences of less than 10%[13]. Regardless of the data source, nausea was by far the most commonly reported side effect.

Despite widely varying ultrasound rates at the follow-up visit, success rates across all sites were 97 to 98%. Because medical abortion was a new method, some doctors were reluctant not to use this diagnostic tool. Yet, reducing the unnecessary use of ultrasound could decrease the cost of the procedure and make the method more accessible to women.

For the purposes of the study, all participants were encouraged to return to the clinic for follow-up in order to provide information on the outcome of their abortion. However, WHO's most recent recommendations state that there is no medical need for a routine follow-up visit following an uncomplicated medical abortion[6]. In the future, providers as well as women in Azerbaijan should be advised that follow-up can occur by phone in most cases, saving women time and costs associated with travel, and reducing the burden on clinics.

Strengths and weaknesses of the study

Our study was conducted in both the capital of Azerbaijan and in regional areas of the country. Having information on women residing in other parts of the country allows us to generalise the results to the majority of women in Azerbaijan.

One weakness of our study is that women were interviewed by study doctors to ascertain their satisfaction and acceptability of the medical abortion method, which may have led to over-reporting due to social desirability bias. Additionally, more women in the capital are likely to work outside of the home but because we did not offer them the option of taking mifepristone outside of the clinic, we were unable to assess the acceptability of this option among those who may find it more beneficial to schedule their bleeding for convenience than women living in the regions.

Differences in results and conclusions in relation to other studies

The success rate of 97% of complete abortions and an ongoing pregnancy rate of 0.8% are comparable to the rates our team reported earlier for the use of the same regimen (800 μg buccal misoprostol 24 to 48 h after 200 mg mifepristone)[13,14]. In addition, the high levels of satisfaction among women were similar to those from trials conducted in other countries of the former Soviet Union[15–17].

Compared to earlier research, the home mifepristone option was even more popular in this setting (with 74% choosing this option, compared to 46% in a US population)[11]. In some settings like Moldova where the drugs can be purchased at the pharmacy with a prescription, home use of mifepristone may be the norm (Bracken H., Personal communication, 12 May 2014). Whereas American women primarily chose home mifepristone because it afforded them flexibility in their schedule, participants in this study

strongly valued having their partner present. This may reflect the higher proportions who were working and/or in school in the US study.

Relevance of the findings: Implications for clinicians and policymakers

Our results provide evidence to support the use of medical abortion in Azerbaijan. At the time of study implementation, only surgical abortion services were available in the country. The success of this study convinced health officials that medical abortion services should be established and triggered negotiations with pharmaceutical companies to register mifepristone in the country, with the drug receiving approval in July 2013. In addition, local experts developed national guidelines for medical abortion in the early first trimester, which will be used to foster the process of institutionalising medical abortion services country-wide now that mifepristone is registered and becoming available.

More broadly, the results of this study contribute to the evidence and can help build confidence among clinicians everywhere that this step in increasing convenience and autonomy for women is a feasible and important one to take.

Unanswered questions and future research

This study identified a need to train providers on when ultrasound use is warranted. Additional research on alternatives to in-person follow-up would be helpful to demonstrate the safety of relaxing this requirement, which would be especially pertinent to those who travel long distances to seek care.

CONCLUSION

This study, conducted in the capital as well as in regional cities in Azerbaijan, provides strong evidence that mifepristone-misoprostol medical abortion is a highly effective, safe and acceptable option to women which can be expanded nationwide. Offering a simplified, non-surgical method for pregnancy termination will be a beneficial and important step in improving the quality of reproductive health care for women in the country.

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CLINICAL ARTICLE

Simplified medical abortion using a semi-quantitative pregnancy test for home-based follow-up

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ABSTRACT

Objective: To simplify follow-up after medical abortion by examining whether women could use a semi-quantitative pregnancy test at home to screen for ongoing pregnancy. *Methods:* Three hundred women seeking medical abortion at a tertiary hospital in Vietnam participated in the study. Participants used a semi-quantitative pregnancy test at the hospital to estimate baseline human chorionic gonadotropin (hCG) levels and administered another test at home 2 weeks later for comparison. Women interpreted the test result at home and then returned to hospital for follow-up care. At this visit, self-assessment was verified. To assess further the feasibility of the test as a follow-up tool in service delivery, 200 additional women completed a user comprehension survey. *Results:* The tests identified all 11 ongoing pregnancies among study participants (100% sensitivity; 89.7% specificity). Women reported that the test was easy to use (255/292 [87.3%]) and that provider instructions helped them to use the test (291/292 [99.7%]). *Conclusion:* Semi-quantitative pregnancy tests offer high sensitivity and negative predictive value. If user instructions can be further simplified, the tests could be used in lieu of transvaginal ultrasound and/or serum hCG at clinic-based follow-up or by women themselves for home-based follow-up.

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1. Introduction

Common practice for medical abortion includes clinic-based follow-up and clinical assessment, including transvaginal ultrasound, to determine abortion status. This follow-up visit can be costly and time consuming for both the healthcare system and the woman [1,2]. As medical abortion becomes more widely used, many women simply do not return to the clinic to receive clinician confirmation of complete abortion. Providing women with a safe, effective, and affordable at-home diagnostic tool to confirm whether a pregnancy is ongoing after administration of mifepristone and misoprostol could reduce costs and simplify the procedure by limiting the number of clinic visits and costly exams, and reducing waiting time. Ideally, during her initial clinic visit, a woman would receive misoprostol, a pregnancy test, and counseling on how to manage her abortion at home. With these tools, the majority of women could manage their abortion at home on their own. With this objective in mind, providers and researchers have explored ways to simplify medical abortion follow-up with serial human chorionic gonadotropin (hCG) testing, high- and low-sensitivity pregnancy tests, and telephone or other virtual follow-up [3–7].

Quantitative serum hCG testing to confirm abortion completion is commonly used in the USA and Europe. Previous research has documented change in hCG level after medical abortion [6,8–10]. Since 2005, Planned Parenthood Federation of America has waived the follow-up visit if it poses undue hardships owing to distances from abortion facilities or other reasons, and women manage their follow-up with serial hCG testing [11]. This method of follow-up has proven effective because ongoing pregnancies exhibit increasing hCG levels (hCG levels that do not increase in the 2 weeks after mifepristone administration indicate that no viable pregnancy is present). In general, in the event of a successful medical abortion, the hCG level decreases by at least half of its pretreatment level within a week of mifepristone administration [12]. Service delivery programs seeking to integrate serum hCG testing into medical abortion follow-up services must confirm that it is acceptable and affordable to women and compatible with the infrastructure and human resources available. In some instances, laboratory confirmation of hCG results can be delayed for hours or days, depending on the location of the laboratory and the volume of specimens processed. This delay might be incompatible with efficient service delivery.

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Serum hCG testing can also be very expensive. Furthermore, in some low-resource settings, serum hCG testing is not yet widely available.

Urine pregnancy tests offer another way to measure hCG level. Several studies have documented that urine hCG level is highly correlated with serum hCG level in confirming pregnancy status [3,4,13]. Other research has modeled various algorithms to confirm abortion success using patient symptoms and a low-sensitivity urine pregnancy test [14]. Grossman et al. [7] reviewed published studies examining alternatives to follow-up, including serial hCG testing, urine pregnancy tests, and telephone interview. The authors concluded that alternative follow-up modalities could successfully identify ongoing pregnancy and proposed that further research examine service delivery options that include both at-home urine pregnancy tests and self- or clinician assessment.

In an effort to offer something potentially less costly and less invasive than serum hCG testing or sonography but more informative than a simple low-sensitivity pregnancy test, the aim of the present study was to investigate the feasibility of Vietnamese women performing a semi-quantitative pregnancy test at home, on their own, to determine their abortion status.

2. Materials and methods

From September 14, 2009, to April 2, 2010, 300 women presenting for medical abortion with pregnancies dated up to 63 days since last menstrual period were recruited at a large tertiary facility in Ho Chi Minh City, Vietnam. Additional inclusion criteria were intrauterine pregnancy; no known contraindications to abortion with mifepristone and/or misoprostol; general good health; ability to provide informed consent; and willingness to return for follow-up.

Study clinical staff identified potential participants and offered them enrollment. After the consent and screening process was completed, study staff taught participants how to perform the urine-based semi-quantitative pregnancy test. The result of this initial test, carried out prior to mifepristone administration, located the range of each participant's hCG level before abortion. A 5-bracketed semi-quantitative immunochromatographic assay panel (dBest hCG Panel Test; Ameritek, Seattle, WA, USA) was used (Fig. 1). The test operates as both a high-sensitivity (at least 25-mIU/mL reading) and a low-sensitivity (at least 2000-mIU/mL and at least 10 000-mIU/mL reading) test, in addition to providing readings at 2 other ranges (>100 mIU/mL and >500 mIU/mL). The test offers a technical improvement compared with other pregnancy tests because it provides greater precision to help minimize the likelihood of false-negative results and, uniquely, provides information about the trend in hCG level, which can be compared with the pre-abortion level for each woman. Tests were conducted by dipping the test strip into a urine cup and stirring the strips for at least 10 seconds to saturate the test thoroughly. Training emphasized the need to stir and soak the panel to achieve saturation. The tests were then placed face-up on a flat surface and read 15 minutes later.

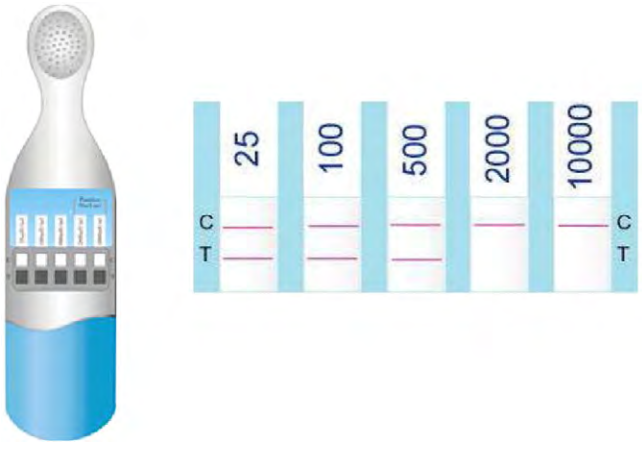

Fig. 1. The dBest (Ameritek, Seattle, WA, USA) semi-quantitative pregnancy test showing a reading of 500 mIU/mL of human chorionic gonadotropin (hCG). C denotes control line. A control line indicates that the test strip has been properly saturated with urine. A control line must appear in all 5 columns for the test to be considered valid. T denotes test line. A test line indicates a positive test result. A column with 1 line (a C line but not a T line) is indicative of a negative test reading. A column consisting of 2 lines (a C line and a T line) indicates a positive test reading for the specific level of hCG.

Each woman was provided with misoprostol for home administration, a second semi-quantitative pregnancy test, a urine sample cup, an instruction sheet, and a questionnaire to take home. Participants administered misoprostol at home 1–2 days later. Women were instructed to take the test and complete the form on the morning of their follow-up visit, which was approximately 2 weeks after mifepristone administration. Either first morning urine or random urine could be used. Emphasis was placed on the importance of saturating all 5 paper strips and waiting at least 15 minutes before reading the tests. The instruction sheet included information on how to read the test and pictorial images of each possible result, as well as a list of commonly asked questions with responses.

Regardless of the results of the pregnancy test conducted at home, each participant was scheduled for clinic-based follow-up. Participants were asked to bring their completed pregnancy tests and study questionnaires with them to this visit. Clinicians then documented the result of the at-home pregnancy tests and assessed each participant's abortion status using standard clinical means, including physical examination and/or transvaginal ultrasound. The results of this standard clinic-based examination were used to determine whether additional care was needed. Women who forgot to complete the at-home pregnancy test or for whom the at-home test showed an inconclusive result were given an additional test to perform at the clinic.

A user comprehension survey was also conducted among 200 additional women of any age from the patient waiting area to ascertain whether potential users understood how to use and interpret the test. Participants were randomly provided with a sample semi-quantitative pregnancy test that indicated 1 of the 5 possible results, the instruction sheet, and a questionnaire. Women were asked to use the instruction sheet to interpret the test results and to complete the questionnaire.

The primary outcome of the clinical study was the feasibility of using the test as part of follow-up for medical abortion. To that end, we documented whether the tests identified all ongoing pregnancies (the main outcome of interest) and whether participants were able to interpret the test correctly. Clinician assessment, via pregnancy test or ultrasound/clinical examination, determined abortion status; semi-quantitative pregnancy test results were evaluated in comparison with this assessment. The primary outcomes of the user comprehension study were the ability to both understand and interpret the test. Data entry and analysis were performed using SPSS version 15 (IBM, Armonk, NY, USA) and STATA version 11 (StataCorp, College Station, TX, USA). Sensitivity/specificity and positive/negative predictive values were calculated to assess the accuracy of the pregnancy test in identifying ongoing pregnancies. Because the main outcome of interest—identification of ongoing pregnancy—would be rare following early medical abortion with mifepristone and misoprostol, it was determined that 300 participants for the clinical study and 200 participants for the user comprehension study would be sufficient for assessing the feasibility of the test in medical abortion care. Ethics approval was provided by Hung Vuong Hospital, Ho Chi Minh City.

3. Results

On average, participants were 29 years of age and most had a secondary education or higher (Table 1). Medical abortion was successful

Table 1
Clinical participant characteristics (n = 300).[a]

Characteristic	Value
Age, y	29 ± 6 (18–44)
Education completed	
Primary school (1–5 years)	10 (3.3)
Secondary school (6–12 years)	232 (77.3)
University level or higher	58 (19.3)
Gestational age, d	42.4 ± 5.9 (30–64)
Medical abortion outcome[b]	
Complete abortion	275 (93.9)
Surgical intervention	18 (6.1)
Ongoing pregnancy	11 (3.8)
Medically indicated (persistent/heavy bleeding)	2 (0.7)
Persistent non-viable pregnancy or sac	4 (1.4)
Provider or woman's preference	1 (0.3)
Participant thought she was still pregnant (or was unsure) prior to taking at-home test[c]	54 (18.5)
Participant had complete medical abortion	41 (75.9)
Participant had surgical intervention	13 (24.1)

[a] Values are given as mean ± SD (range) or number (percentage).
[b] Data do not include 4 women who were lost to follow-up and 3 women who left the study early.
[c] Data do not include 4 women who were lost to follow-up, 3 women who left the study early, and 1 woman with successful medical abortion who did not return her home questionnaire.

for 275 of 293 (93.9%) participants. Eighteen women underwent surgical intervention owing to: ongoing pregnancy (11 [3.8%]); bleeding (2 [0.7%]); persistent non-viable pregnancy or sac (4 [1.4%]); or provider or woman's preference (1 [0.3%]). Fig. 2 shows the trial profile.

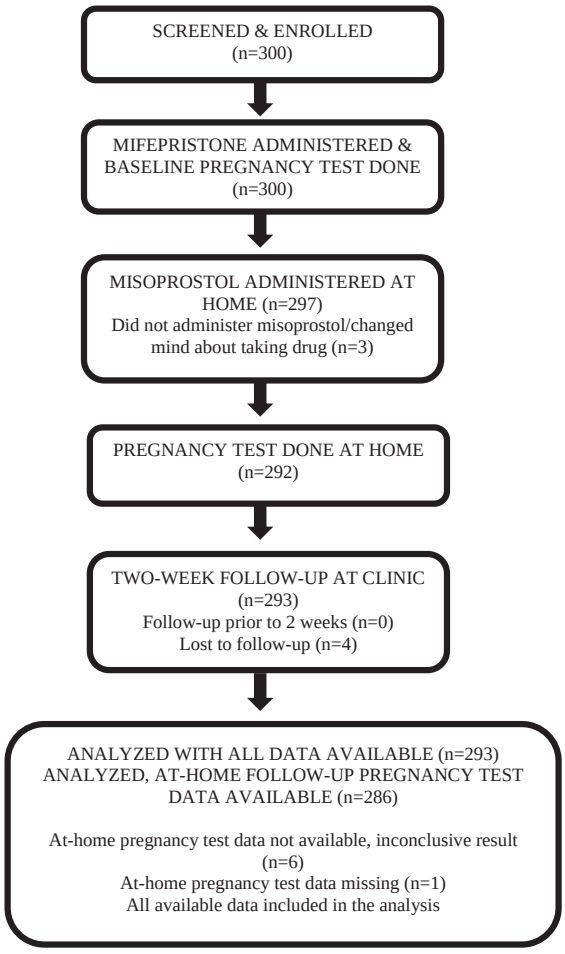

Fig. 2. Clinical trial profile.

Table 2
Sensitivity/specificity and positive/negative predictive values of SQPT to detect ongoing pregnancy versus all other outcomes based on user reading in the clinical study.[a]

	Ongoing pregnancy	All other outcomes
Test indicated steady or increasing hCG level, or test inconclusive[b]	100.0% (11/11)	10.3% (29/281)
Test indicated decreasing hCG level	0.0% (0/11)	89.7% (252/281)
Sensitivity: 100.0%		Specificity: 89.7%
Positive predictive value: 27.5%		Negative predictive value: 100.0%

Abbreviations: hCG, human chorionic gonadotropin; SQPT, semi-quantitative pregnancy test.
[a] User reading unavailable for 1 woman for whom home pregnancy test data were not available.
[b] All 6 women with inconclusive test results had successful medical abortions with no additional intervention.

On the morning of the follow-up visit, participants used the semi-quantitative pregnancy test at home and recorded their interpretation of the result. Fifty-four of 292 (18.5%) participants reported that they thought they were still pregnant prior to using the at-home test (Table 1). The test identified all 11 ongoing pregnancies, with 100% sensitivity (11/11) and 89.7% specificity (252/281) (Table 2). In addition to identifying all of the ongoing pregnancies, the test did not show a decrease in hCG level for an additional 29 women (Table 3). Of these, 24 received no intervention at follow-up and 5 underwent treatment for persistent non-viable pregnancy or sac. None of the participants whose tests showed a decrease in hCG level from baseline to follow-up was later identified as having an ongoing pregnancy. Four of 252 (1.6%) women who showed a reduction in hCG level received interventions at the follow-up visit (Table 3).

Among the 11 women for whom the test identified an ongoing pregnancy, 10 (90.9%) understood that an additional clinic visit was needed. Of the 252 women whose test indicated that clinic-based follow-up was not needed, 147 (58.3%) understood that no additional visit was necessary. Most participants (255/292 [87.3%]) reported that the test was “very easy” or “easy” to use. Nearly all participants (291/292 [99.7%]) felt that the information given by providers helped them use the test.

Results from the user comprehension survey are shown in Table 4. Participants had similar profiles to women participating in the clinical study. When given a test with a pre-configured result and shown an illustration of the 5 possible test outcomes, 195 (97.5%) women correctly matched the test they had been given with the correlating illustrated result. Education level did not impact the capacity of survey participants to interpret the test correctly. In total, 190 of 195 (97.4%) women understood the numeric value of the test. Only 7 (3.5 %) women felt that the test was difficult to use. Overall, 196 (98.0%) participants felt that they could use the test on their own in the future; this perception was not impacted by education level.

4. Discussion

The present results complement previous findings that urine hCG testing can be used as part of early medical abortion follow-up [3–5]. The use of a semi-quantitative test instead of universal clinic-based follow-up could significantly impact medical abortion service delivery because the test could be used as at-home follow-up for women living away from abortion facilities who may wish to avoid a follow-up visit if not required. For women undergoing clinic-based follow-up, the test could provide an alternative to transvaginal ultrasound (often repeated several times for each woman) as the primary means for confirming a complete medical abortion. A tool such as the semi-quantitative pregnancy test could reduce the proportion of women paying for and receiving ultrasound. It would also free-up

Table 3
Effectiveness and acceptability of SQPT in assessing medical abortion outcomes.

	No. (%)
Intervention at follow-up among women whose at-home pregnancy test showed steady or increasing hCG level, or test was inconclusive (n = 40)[a]	
No intervention	24 (60.0)
Intervention performed	16 (40.0)
Ongoing pregnancy managed surgically	11 (27.5)
Persistent non-viable pregnancy or sac managed surgically or with additional dose of misoprostol	5 (12.5)
Intervention at follow-up among women whose at-home pregnancy test showed decreasing hCG level (n = 252) [a]	
No intervention	248 (98.4)
Intervention performed	4 (1.6)
Ongoing pregnancy managed surgically	0 (0.0)
Persistent non-viable pregnancy or sac managed surgically or with additional dose of misoprostol	1 (0.4)
Medically indicated (persistent/heavy bleeding)	2 (0.8)
Provider or woman's preference	1 (0.4)
SQPT reading identified ongoing pregnancy	11/11 (100.0)
Participant understood that this result meant that an additional clinic visit was needed	10 (90.9)
Participant did not understand that an additional clinic visit was needed	1 (9.1)
SQPT reading indicated that clinic-based follow-up was not needed	252/281 (89.7)
Participant understood that this result meant that no additional clinic visit was needed	147 (58.3)
Participant did not understand that no additional clinic visit was needed	105 (41.7)
Participant report on ease of use of test (n = 292)	
Test was neither easy nor difficult	37 (12.7)
Test was "easy" to use	143 (49.0)
Test was "very easy" to use	112 (38.4)
Participant felt that the information given by providers helped them use the test (n = 292)	291 (99.7)

Abbreviations: hCG, human chorionic gonadotropin; SQPT, semi-quantitative pregnancy test.
[a] Includes 14 of the 18 women who underwent surgical intervention (all 11 with ongoing pregnancies and 3 with persistent non-viable pregnancy or sac); the other 4 had pregnancy tests indicating a decrease in hCG level.

provider time for other services and may reduce the number of unnecessary surgical completions for retained products of conception. Such effects may be especially beneficial in resource-poor countries, where clinics may be overcrowded and understaffed, with limited access to serum hCG testing and ultrasound.

The semi-quantitative pregnancy test, with its 5-bracketed ranges, enabled ongoing pregnancy to be ruled out earlier than in previous studies using high- or low-sensitivity pregnancy tests. For instance, Perriera et al. [5] investigated the at-home use of a high-sensitivity pregnancy test 4 weeks after mifepristone administration as part of a telephone follow-up study. Nearly three-quarters of participants were able to avoid clinic-based follow-up; however, they had to wait 4 weeks to confirm that their abortion was complete [5]. In the present study, women were able to confirm their abortion outcome 2 weeks after mifepristone administration. In another study using the same semi-quantitative pregnancy test, women in the USA obtained results using the test just 1 week after mifepristone administration [15]. The semi-quantitative pregnancy test enables women to find out their abortion status sooner, thereby shortening the duration of the procedure. Furthermore, in the rare event of a continued ongoing pregnancy after early medical abortion, diagnosis of a growing embryo 1 to 2 weeks after mifepristone administration facilitates earlier clinical action.

Table 4
Results of user comprehension survey (n = 200).[a,b]

Characteristic	Value
Age, y	31 ± 8 (18–55)
Education completed	
Primary school (1–5 years)	26 (13.0)
Secondary school (6–12 years)	130 (65.0)
University level or higher	44 (22.0)
Pregnancy test was matched with correct corresponding image	195 (97.5)
Among women with less than college degree	151/156 (96.8)
Among women with college degree or higher	44/44 (100.0)
Understood numeric value of test	190/195 (97.4)
Among women with less than college degree	147/151 (97.4)
Among women with college degree or higher	43/44 (97.7)
Instruction sheet helped with interpreting pregnancy test results	198/199 (99.5)
Test was easy to use	
Very easy/easy	100 (50.0)
Neither easy nor difficult	93 (46.5)
Difficult/very difficult	7 (3.5)
Woman believed she could use test on her own in the future to determine pregnancy status	196 (98.0)
Among women with less than college degree	153/156 (98.1)
Among women with college degree or higher	43/44 (97.7)

[a] Values are given as mean ± SD (range) or number (percentage).
[b] Participants in the user comprehension survey were not the same women as in the clinical study.

The potential feasibility of using this test in resource-poor settings is underscored by the fact that nearly all of the participants in both the clinical study and the user comprehension survey reported that the test was easy to use. It should be noted, however, that most of the participants in the present study had completed at least secondary-school education. Despite the nearly unanimous responses that the test was easy to use, when asked to interpret their own test results, nearly half of the women with a decrease in hCG level were not sure whether they needed clinic-based follow-up. Interestingly, an increase or no change in hCG level seemed to be more easily understandable for participants: nearly all (90.9%) of those with ongoing pregnancy correctly interpreted their results. Future simplifications of the instructions sheet should help to improve user comprehension in this regard. Upon discussion with the study investigators, we hypothesize that the design of the study protocol—stipulating that all women must return for follow-up—may have confused women when asked to respond to the question of whether they felt they "needed" to return for follow-up.

The present study was limited by its small sample size and geographic specificity to a single hospital in 1 country, with results that may not be generalizable to other settings. The small sample size meant that potential differences in the cohort could not be examined; instead, the feasibility of this potential service delivery innovation was examined and information was collected from which larger prospective studies could be conducted.

Future research should document how post-abortion contraception can be integrated into medical abortion services with at-home follow-up protocols. More operational research to document "virtual" reporting of at-home follow-up using cellular phones and/or the Internet could also reveal the benefits of this type of service delivery in a range of settings.

Allowing women the option to use semi-quantitative pregnancy tests as at-home tools in lieu of clinic-based follow-up with ultrasound has potential for significant cost-savings for both the healthcare system and women. Yet, for this to be realized, the test must be widely available and at a low cost. Currently, only 1 manufacturer produces the semi-quantitative pregnancy test, meaning that wide availability is inhibited. Future efforts should seek to increase access to this promising technology.

Acknowledgments

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Conflict of interest

The authors have no conflicts of interest.

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FDA U.S. FOOD & DRUG ADMINISTRATION

June 2, 2025

The Honorable Josh Hawley
United States Senate
Washington, D.C. 20510

Dear Senator Hawley:

Thank you for your letter to the Food and Drug Administration (FDA or the Agency) regarding the safety of mifepristone for the medical termination of early pregnancy. I appreciate your continued interest in this topic.

FDA is committed to safeguarding public health by ensuring the safety, efficacy, and quality of the products it regulates. The Agency carefully evaluates the scientific data, leveraging rigorous science to make informed decisions. As with all drugs, FDA continues to closely monitor the postmarketing safety data on mifepristone for the medical termination of early pregnancy. As the Commissioner of Food and Drugs, I am committed to conducting a review of mifepristone and working with the professional career scientists at the Agency who review this data.

Mifepristone for medical termination of early pregnancy is the subject of pending litigation. FDA generally does not comment on matters that are the subject of pending litigation and therefore is unable to provide further information on this topic at this time.

Thank you again for contacting the Agency regarding this matter. Please do not hesitate to reach out if there are any additional questions.

Sincerely,

Martin A. Makary, M.D., M.P.H.
Commissioner of Food and Drugs

U.S. Food & Drug Administration
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GenBioPro

GenBioPro, Inc.
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Las Vegas, NV 89103

The Honorable Robert M. Califf, MD
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Building 32, Room 2346
Silver Spring, MD 20993-0002

March 1, 2023

Dear Commissioner Califf:

GenBioPro, Inc. ("GBP") is dedicated to ensuring that people have access to evidence-based, essential medications and, to that end, markets a generic version of Mifeprex (mifepristone) 200 mg consistent with FDA's regulatory regime. Given the external environment, I write to request prompt confirmation that any withdrawal of the approval of GBP's abbreviated new drug application ("ANDA") for mifepristone—whether by court order or otherwise—will follow all applicable procedures afforded by law and regulation to GBP as the ANDA holder and that FDA will permit GBP to continue marketing and selling mifepristone until those procedures have been completed.

GBP's ANDA (No. 091178) was approved by FDA on April 11, 2019, following almost a decade of efforts by GBP to bring the first and only generic version of Mifeprex (mifepristone) 200mg tablet to market. As you know, mifepristone 200 mg tablet is the first drug in a two-drug regimen approved by FDA for medication abortion. FDA's approval of GBP's ANDA reflects its judgment that this drug is safe and effective and was based on a robust review of vast amounts of data and hundreds of medical studies over more than two decades, including data submitted by GBP to support approval of its ANDA. FDA's decisions regarding mifepristone have twice been found to be legally and factually valid by the U.S. Government Accountability Office. *See* U.S. Gov't Accountability Off., *Approval and Oversight of the Drug Mifeprex* (Aug. 2008); U.S. Gov't Accountability Off., *Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts* (Mar. 2018).

Moreover, in the 2007 enactment of the Food and Drug Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823, Congress specified that, for 16 drugs that FDA had approved previously with "elements to assure safe use," Congress deemed them to have an effective Risk Evaluation and Mitigation Strategy (REMS) in effect. As to the set of drugs, including mifepristone, that have a REMS with elements to assure safe use, Congress mandated that any elements provide "safe access" for patients for the drug, and not be "unduly burdensome on patient access to the drug." 21 U.S.C. § 355-1(f). FDA thus regulates mifepristone under this congressional mandate, which requires safe access for patients. FDA most recently revised the REMS for mifepristone on January 3, 2023, after an extensive review of updated research and data.

Despite mifepristone's longstanding congressional and regulatory approval and despite widespread acknowledgment of the public health benefits of access to mifepristone, in the aftermath of the Supreme Court's decision last year in *Dobbs*, FDA's approvals have come under challenge and efforts are

underway to seek withdrawal of the approval for mifepristone. These ill-advised and unfounded attacks on FDA's decisions pursuant to its congressional mandate are of grave concern to GBP, which has invested considerable effort and expense in reliance on FDA's past regulatory actions with respect to mifepristone, as well as on FDA's well-established regulatory process for the withdrawal of existing drug approvals. Withdrawal of the mifepristone ANDA approval would threaten irreparable harm to both GBP as a company and the public interest, as expressed in the 2007 Amendments, in continued access to the medication.

As you are aware, in addition to mandating that FDA ensure safe access to mifepristone, Congress also granted FDA, and FDA alone, the authority to oversee the withdrawal of an approved drug application. See 21 U.S.C. § 355(e). Withdrawal requires a finding by FDA that one of the relevant statutory criteria has been met, as well as "due notice and opportunity for hearing to the applicant." Under the Food Drug and Cosmetic Act ("FDCA"), and as relevant here, the Secretary of HHS shall withdraw approval of an application if the Secretary finds that:

> clinical or other experience, tests or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved . . . [or] on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling thereof.

21 U.S.C. § 355(e)(1), (3).

The Secretary, in turn, has delegated the responsibility for making such a finding to the FDA Commissioner. *See* FDA Staff Medical Guides, Staff Manual Guides 1410.10, *Delegations of Authority to the Commissioner of Food and Drugs* 1.A(1) (Nov. 29, 2022) (all functions vested in the Secretary under the FDCA are delegated to the Commissioner). Any withdrawal of a drug approval on safety or efficacy grounds therefore mandates that the Commissioner find that the evidence demonstrates that the drug's benefit-risk balance requires withdrawal. As the Supreme Court has emphasized, the statute does "not provide any mechanism other than the Commissioner's suspension authority under [section 355(e)], whereby an NDA once effective could cease to be effective." *See Weinberger v. Hynson, Wescott & Dunning, Inc.*, 412 U.S. 609, 633 (1973).

The regulations that implement section 355(e)'s requirements of notice and opportunity to be heard set out specific and detailed procedures the Agency must follow when analyzing withdrawal of a drug approval. In addition to notice and the opportunity for a hearing on a proposal to withdraw a drug, those regulations also expressly permit the applicant to submit studies, data and other information. *See* 21 C.F.R. §§ 314.150, 314.200, 314.530. Specifically with regard to the holder of an ANDA, like GBP, the regulations require an opportunity to submit written comments and, if a hearing is granted, the opportunity to participate and to submit written objections to an initial decision. *See* 21 C.F.R. §

314.151. The due process protections embodied within these statutory and regulatory procedures are constitutionally necessary for the protection of GBP's property interest in its mifepristone ANDA.[1]

Accordingly, GBP respectfully requests FDA's confirmation that for any FDA withdrawal of GBP's ANDA approval, including in response to a court order, FDA will initiate the statutory and regulatory procedures and apply the substantive criteria set forth above and that GBP would be permitted to continue to market and sell mifepristone in the United States while the established process for withdrawal of any approval for a drug process runs its lawful course.

Thank you for your consideration of this matter of pressing public importance. In light of the exigency of this matter, we respectfully request FDA's response as soon as practicable, but, in any event, no later than March 15, 2023. If you or your staff have questions, please do not hesitate to reach out.

Sincerely,

Evan Masingill
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CC:
Hon. Xavier Becerra
Secretary
Department of Health and Human Services
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Brian D. Netter
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U.S. Department of Justice-Civil Division
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[1] Moreover, and importantly, if the reference drug in GBP's ANDA is required to be withdrawn for reasons *other than FDA's determination that the reference drug is unsafe or ineffective for use under the conditions set forth in its application*, that should have no impact on GBP's ANDA for mifepristone. *See* 21 U.S.C § 355(j)(6).

GenBioPro

GenBioPro, Inc.
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April 9, 2023

The Honorable Robert M. Califf, M.D.
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Building 32, Room 2346
Silver Spring, MD 20993-0002

Re: ANDA #A091178 (GenBioPro / Mifepristone)

Dear Commissioner Califf:

I am writing regarding GenBioPro's ("GBP") abbreviated new drug application ("ANDA") for mifepristone (No. 091178), GBP's March 1, 2023 Letter to FDA ("March 1 Letter"), and FDA's March 24, 2023 Letter from Center for Drug Evaluation and Research Director Patrizia Cavazzoni, MD ("March 24 Letter") responding to our March 1 Letter. On April 7, 2023, two separate federal district courts issued rulings relating to mifepristone and FDA's approval of GBP's ANDA. In view of these two rulings, the issues raised in our prior correspondence have taken on even greater and more pressing importance. GBP respectfully submits that those issues require FDA's immediate attention and action.

As explained in the March 1 Letter, GBP is dedicated to ensuring that people have access to evidence-based, essential medications and, to that end, GBP markets a generic version of Mifeprex® (mifepristone) 200 mg consistent with FDA's regulatory framework. In the March 1 Letter, we wrote to request confirmation that any withdrawal or suspension of the approval of GBP's ANDA for mifepristone—whether by court order or otherwise—would follow all applicable procedures afforded by law and regulation to GBP as the ANDA holder, and that FDA would permit GBP to continue marketing and selling mifepristone unless and until those procedures have been completed.

In the March 24 Letter, FDA declined to confirm that it would follow all applicable rules and procedures for any withdrawal or suspension of GBP's ANDA. Indicating the reason for its response, FDA referenced the litigation in *Alliance for Hippocratic Medicine v. FDA* ("*AHM*"), No. 2:22-CV-00223-Z (N.D. Tex.), in which the plaintiffs had argued that "'the Court, on its own accord, can order the FDA to withdraw or suspend the approval of the drug,' rather than 'order the FDA to begin a suspension or withdrawal' process under 21 U.S.C. § 355(e)." March 24 Letter (quoting Arg. Tr. at 145-46). The March 24 Letter then stated that FDA would "need to review the Court's opinion and order before determining what steps may be necessary to comply with it."

On April 7, the *AHM* court issued an order that dramatically increased the legal importance of the March 24 Letter. Mem. Op. and Order, *All. for Hippocratic Med.*, No. 2:22-CV-00223-Z (N.D. Tex. Apr. 7, 2023), ECF No. 137 ("*AHM* Order"). The *AHM* Order purported to "stay" the effective

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date of a number of FDA actions, including FDA's approval of GBP's ANDA for mifepristone, under 5 U.S.C. § 705. *Id.* at 65-67.

On the same day as the *AHM* Order, a federal court in Washington state issued a separate ruling enjoining FDA from "altering the status quo and rights as it relates to the availability of Mifepristone under the current operative January 2023 Risk Evaluation and Mitigation Strategy under 21 U.S.C. § 355-1 in" 17 states and the District of Columbia. *Washington v. FDA*, No. 1:23-CV-3026-TOR (E.D. Wash. Apr. 7, 2023), ECF No. 80 ("*Washington* Order") at 30.

In light of these two conflicting orders—and particularly the *AHM* Order, which purports to alter the validity of FDA's approval of GBP's ANDA—GBP respectfully requests the following:

First, FDA should immediately commit that it will not withdraw, suspend, or otherwise take action that would impair GBP's ANDA approval and associated rights. In particular, but without limitation, FDA should not make any changes to GBP's registration or product listing with the agency, and it should not remove GBP's ANDA from the Orange Book. The *AHM* Order does not order FDA to take any of these actions, and FDA should not interpret the *AHM* Order to require them. Disrupting the status quo—and upending more than 22 years of mifepristone access—is premature at this stage and would have devastating public health consequences.

As detailed in the March 1 Letter, GBP's ANDA was approved by FDA on April 11, 2019, following almost a decade of efforts by GBP to bring the first and only generic version of Mifeprex (mifepristone) 200mg tablet to market. As you know, mifepristone 200 mg tablet is the first drug in a two-drug regimen approved by FDA for medication abortion. FDA's approval of mifepristone reflected its judgment that this medication is safe and effective and was based on a robust review of vast amounts of data and hundreds of medical studies over more than two decades, including data submitted by GBP to support approval of its ANDA. FDA's decisions regarding mifepristone have twice been found to be legally and factually valid by the U.S. Government Accountability Office. *See* U.S. Gov't Accountability Off., *Approval and Oversight of the Drug Mifeprex* (Aug. 2008); U.S. Gov't Accountability Off., *Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts* (Mar. 2018).

Congress has recognized the public health benefits of mifepristone as well. As the March 1 Letter explained, in enacting the Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823, Congress specified that 16 drugs that FDA had approved previously with "elements to assure safe use" would be deemed by statute to have an effective Risk Evaluation and Mitigation Strategy (REMS) in place. As to the set of drugs, including mifepristone, that have a REMS with elements to assure safe use, Congress mandated that any elements provide "safe access" for patients to the drug, and not be "unduly burdensome on patient access to the drug." 21 U.S.C. § 355-1(f). FDA thus regulates mifepristone under this congressional mandate, which requires safe access for patients. FDA most recently revised the REMS for mifepristone on January 3, 2023, after an extensive review of updated research and data. The *Washington* Order commands FDA to maintain the REMS as currently in effect with respect to the 17 plaintiff states and the District of Columbia in that lawsuit. *Washington* Order at 30.

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The *AHM* Order, in contrast, purports to order a "stay" of, among other things, the 2000 Mifeprex approval and the 2019 approval of GBP's ANDA. *AHM* Order at 67. But in recognition of the public and private reliance on FDA's approval of drugs as safe and effective, Congress vested the authority to stay or suspend an approved drug application *exclusively* in the Secretary of Health and Human Services; Congress also restricted that authority to be used only in extraordinary circumstances. *See* 21 U.S.C. § 355(e). Specifically, under the Federal Food, Drug, and Cosmetic Act ("FDCA"), if the Secretary "finds that there is an imminent hazard to the public health, he may suspend the approval of [an NDA] immediately." 21 U.S.C. § 355(e).[1]

Contrary to the *AHM* Order's suggestion that a federal court is permitted to "second-guess FDA's decision-making," *AHM* Order at 57, Congress expressly directed that the Secretary's suspension authority "shall not be delegated" to anyone, 21 U.S.C. § 355(e). Rather, as the Supreme Court has explained, "an NDA remains effective unless it is suspended" pursuant to the authority vested exclusively in the Secretary by 21 U.S.C. § 355(e). *See Weinberger v. Hynson, Wescott & Dunning, Inc.*, 412 U.S. 609, 633 (1973). Moreover, in the extreme circumstances in which the Secretary finds an "imminent hazard" and orders the immediate suspension of an application approval, the approval holder is entitled to immediate procedural protections, including "prompt notice," and "an expedited hearing." 21 U.S.C. § 355(e); *see* 21 C.F.R. § 314.150(a)(1).

Secretary Becerra has made no "imminent hazard" finding with respect to mifepristone. Under Supreme Court precedent, therefore, all mifepristone approvals "remain[] effective." *See Weinberger*, 412 U.S. at 633.[2]

Second, FDA should immediately commit that, in the event the *AHM* Order is deemed to alter the validity of FDA's Mifeprex approval, FDA nonetheless will not withdraw, suspend, or otherwise take action that would impair GBP's ANDA approval and associated rights. As the *AHM* Order itself recognizes, "[i]f FDA withdraws the listed drug on which the ANDA-approved generic drug is based, the agency is *generally* required to withdraw the generic drug as well." *AHM* Order at 60 (emphasis added). Though it recognizes that rule as "general[]," the *AHM* Order ignores the actual criteria for any such withdrawal. *See id.* (declaring the court is "inclined to agree with Plaintiffs" based solely on analysis of the Mifeprex NDA without analyzing the generic drug withdrawal provisions at 21 U.S.C. § 355(j)). Those legal criteria do not apply here.

Specifically, FDA regulations provide that, if the reference drug in GBP's ANDA is required to be withdrawn for reasons other than *FDA's determination* that the reference drug is unsafe or ineffective for use under the conditions set forth in its application, then its withdrawal has no impact on GBP's ANDA for mifepristone. *See* 21 U.S.C § 355(j)(6); 21 C.F.R. § 314.151. Here, FDA has made no determination that the reference drug is not safe or effective. Instead, a court has purported to "stay" the effective date of approval of the approved reference drug. While the

[1] The *AHM* Order appears to equate a judicially ordered "stay" with the Secretary's suspension authority, noting that the court considered ordering FDA to "suspend the chemical abortion approval" as an alternative to its "stay." *See AHM* Order at 67.

[2] The FDCA also allows for the withdrawal of an approved drug application under specified circumstances. 21 U.S.C. § 355(e). Withdrawal requires a finding by FDA that one of the relevant statutory criteria has been met. *Id.* It also requires extensive procedures before a withdrawal may occur. *Id.*; *see* 21 C.F.R. §§ 314.150, 314.200, 314.530.

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effect of that "stay" on Mifeprex is also without legal basis, at a minimum, the Mifeprex "stay" can have no legal effect on approval of GBP's ANDA under section 355(j) and its implementing regulations. Moreover, GBP is not a party to the *AHM* litigation and, as the Supreme Court has held, "[i]t is a violation of due process for a judgment to be binding on a litigant who was not a party or a privy and therefore has never had an opportunity to be heard." *Parklane Hosiery Co. v. Shore*, 439 U.S. 322, 327 n.7 (1979).

Third, regardless of any other action FDA takes in response to the *AHM* Order, FDA should immediately issue a non-enforcement order declaring that it will not, under any circumstances, take any enforcement action against GBP or its distributors, customers, and partners based on the *AHM* Order's purported "stay" of GBP's ANDA. This includes, but is not limited to, any enforcement action pursuant to 21 U.S.C. §§ 355(a), 331(d), 333(a), and 334(a). FDA is authorized to issue such a non-enforcement order based on its wide discretion to develop enforcement priorities and to articulate the exercise of that discretion to regulated entities. *See Heckler v. Chaney*, 470 U.S. 821, 832 (1985).

A non-enforcement order is particularly appropriate here because there is a direct conflict between two federal courts. *See Nat'l Env't Dev. Assoc.'s Clean Air Project v. EPA*, 891 F.3d 1041, 1045 (D.C. Cir. 2018) (upholding agency's adoption of "permissible and sensible solutions to issues emanating from intercircuit conflicts and agency nonacquiescence"). The *AHM* Order "stays the effective date" of FDA's approval of Mifeprex and GBP's ANDA. *AHM* Order at 67. At the same time, the *Washington* Order prohibits FDA from "altering the status quo and rights as it relates to the availability of Mifepristone under the current operative" REMS in 17 states. *Washington* Order at 30. These two rulings cannot be reconciled, and distributors, doctors, patients, and manufacturers all require guidance.

Fourth, FDA should issue an interim final rule with immediate effect, declaring that FDA's approval of GBP's ANDA shall remain effective pending public comments and any further judicial review of the *AHM* Order. Such a rule is authorized by the FDCA, 21 U.S.C. § 371(a) ("The authority to promulgate regulations for the efficient enforcement of this chapter, except as otherwise provided in this section, is vested in the Secretary"), and the Administrative Procedure Act, 5 U.S.C. § 553(b)(B) (notice-and-comment procedures not required when they are "impracticable, unnecessary, or contrary to the public interest").[3] With an interim rule in effect, FDA can then accept public comments to address, among other things, how it should reconcile the conflicts between the *Washington* Order and the *AHM* Order, including but not limited to the relevant geographic scope of the *AHM* Order.

Even aside from the conflicting judicial orders, good cause exists to issue an interim rule here. *See* 5 U.S.C. § 553(b). The potential nationwide unavailability of mifepristone due to court action presents a grave threat to public health. FDA should accordingly issue an interim final rule to affirm all mifepristone approvals and open a comment period to gather public input.

[3] FDA commonly issues interim final rules with subsequent comment periods, including for issues surrounding drugs. *See, e.g., Applications for Food and Drug Administration Approval To Market a New Drug; Revision of Postmarketing Reporting Requirements—Discontinuance*, 76 Fed. Reg. 78,530 (Dec. 19, 2011).

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Thank you for your consideration of this matter of pressing public importance. In light of the exigency of this matter, we respectfully request FDA's response as immediately as practicable. If you or your staff have questions, please do not hesitate to reach out.

Sincerely,

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April 13, 2023

The Honorable Robert M. Califf, M.D.
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Building 32, Room 2346
Silver Spring, MD 20993-0002

Re: ANDA #A091178 (GenBioPro / Mifepristone)

Dear Commissioner Califf:

I am writing regarding GenBioPro's ("GBP") abbreviated new drug application ("ANDA") for mifepristone (No. 091178) and following up on GBP's March 1, 2023 Letter to FDA ("March 1 Letter"), FDA's March 24, 2023 Letter from Center for Drug Evaluation and Research Director Patrizia Cavazzoni, MD ("March 24 Letter") and GBP's April 9, 2023 Letter to FDA ("April 9 Letter").

As you are aware, just before midnight last night, the U.S. Court of Appeals for the Fifth Circuit issued an unpublished order granting in part and denying in part Defendants' Emergency Motion for a Stay Pending Appeal in *Alliance for Hippocratic Medicine v. FDA* ("*AHM*"), No. 2:23-10362 ("*AHM* Fifth Circuit Order"). The *AHM* Fifth Circuit Order granted Defendant's requested stay only as to the district court's "stay" of the 2000 Approval of Mifeprex and denied the stay as to the district court's "stay" of "all subsequent actions," including FDA's approval of GBP's ANDA for mifepristone.

As you are aware, a federal court in Washington state has also enjoined FDA from "altering the status quo and rights as it relates to the availability of Mifepristone under the current operative January 2023 Risk Evaluation and Mitigation Strategy under 21 U.S.C. § 355-1 in" 17 states and the District of Columbia. *Washington v. FDA*, No. 1:23-CV-3026-TOR (E.D. Wash. Apr. 7, 2023), ECF No. 80 ("*Washington* Order") at 30.

Given the conflicts between these orders, GBP urgently requests that FDA confirm it will follow all applicable rules and procedures afforded by law and regulation to GBP as the ANDA holder, and that GBP is permitted to continue marketing and selling mifepristone under its 2019 approval and subsequent approved supplements and the operative 2023 REMs. As you know, GBP is not a party to the *AHM* litigation and is thus not bound by the orders in that case. Instead, FDA is the

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regulatory agency that exercises authority over GBP and GBP is seeking much needed clarity from FDA regarding the status of its ANDA and related regulatory approvals.

GBP once again seeks immediate confirmation from FDA of the following requests:

First, please confirm that GBP's ANDA approval remains in effect as currently approved, particularly given that the reference drug upon which GBP's ANDA is based remains approved pursuant to the *AHM* Fifth Circuit Order reversing the district court's stay. Given that the reference drug has not been withdrawn for safety or efficacy reasons—and indeed, remains fully approved—GBP's ANDA must also remain approved. 21 U.S.C. § 355(j)(6); 21 C.F.R. § 314.151.

Second, please commit that FDA will not withdraw, suspend, or otherwise take action that would impair GBP's ANDA approval and associated rights. Congress vested the authority to stay or suspend an approved drug application *exclusively* in the Secretary of Health and Human Services; Congress also restricted that authority to be used only in extraordinary circumstances. *See* 21 U.S.C. § 355(e). Specifically, under the Federal Food, Drug, and Cosmetic Act ("FDCA"), if the Secretary "finds that there is an imminent hazard to the public health, he may suspend the approval of [an NDA] immediately." 21 U.S.C. § 355(e). Secretary Becerra has made no "imminent hazard" finding with respect to mifepristone.

Third, please confirm that FDA will issue a non-enforcement order declaring that it will not, under any circumstances, take any enforcement action against GBP or its distributors, customers, and partners based on the *AHM* Order's purported "stay" of GBP's ANDA. This includes, but is not limited to, any enforcement action pursuant to 21 U.S.C. §§ 355(a), 331(d), 333(a), and 334(a). A non-enforcement order is particularly appropriate here because there is a direct conflict between two federal courts. *See AHM* District Court Order at 67 ("stay[ing] the effective date" of FDA's approval of GBP's ANDA); *Washington* Order at 30 (enjoining FDA from "altering the status quo and rights as it relates to the availability of Mifepristone under the current operative" REMS in 17 states). These rulings cannot be reconciled, and distributors, doctors, patients, and manufacturers all require guidance.

Fourth, the *AHM* Fifth Circuit Order refused to stay the district court's order relating to several subsequent regulatory decisions related to the REMs that apply to mifepristone. GBP requests immediate guidance from FDA confirming that mifepristone may continue to be sold under the existing 2023 REMs, which reapproved the safety and efficacy of the drug, until further guidance. Any other outcome creates an untenable situation where mifepristone will become unavailable to the public and thus presents a grave threat to public health.

Fifth, as GBP previously proposed, an immediate remedy for the existing conflict between the two federal court orders is for FDA to issue an interim final rule with immediate effect, declaring that FDA's approval of GBP's ANDA shall remain effective pending public comments and any further judicial review of the *AHM* Order. Such a rule is authorized by the FDCA and the APA. *See* 21 U.S.C. § 371(a); 5 U.S.C. § 553(b)(B).

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Thank you for your consideration of this matter of pressing public importance. In light of the exigency here, we respectfully request FDA's response by 10:00 a.m. EDT on Friday, April 14, 2023. If you or your staff have questions, please do not hesitate to reach out.

Sincerely,

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The role of nurses and midwives in the provision of abortion care: A scoping review

Article *in* Journal of Clinical Nursing · February 2020

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REVIEW

Journal of Clinical Nursing WILEY

The role of nurses and midwives in the provision of abortion care: A scoping review

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Funding information
The primary author is an Australian PhD candidate funded through the Australian Government Research Training Program (RTP).

Abstract

Aims and objectives: To define the role and scope of the nurse and midwife within the global context of abortion.

Background: An estimated 56 million women seek abortions each year; nurses and midwives are commonly involved in their care (Singh et al., 2018, https://www.guttmacher.org/sites/default/files/report_pdf/abortion-worldwide-2017.pdf). As new models of abortion care emerge, there is a pressing need to develop a baseline understanding of the role and scope of nurses and midwives who care for women seeking abortions.

Design: The review design was Arksey and O'Malley's five-stage methodological framework. The review follows the PRISMA-ScR checklist.

Methods: MEDLINE, CINAHL, Scopus and ScienceDirect were used to identify original research, commentaries and reports, published between 2008–2019, from which we selected 74 publications reporting on the nursing or midwifery role in abortion care.

Results: Nurses and midwives provide abortion care in a variety of practice. Three themes emerged from the literature: the regulated role; providing psychosocial care; and the expanding scope of practice.

Conclusions: The literature on nursing and midwifery practice in abortion care is broad. Abortion-related practices are potentially over-regulated. Appropriately trained nurses and midwives can provide abortions as safely as physicians. The preparation of nurses and midwives to provide abortion care requires further research. Also, healthcare organisations should explore person-centred models of abortion care.

Relevance to clinical practice: Abortion care is a common procedure performed across many healthcare settings. Nurses and midwives provide technical and psychosocial care to women who seek abortions. Governments and regulatory bodies could safely extend their scope of practice to increase women's access to safe abortions. Introduction of education programmes, as well as embedding practice in person-centred models of care, may improve outcomes for women seeking abortions.

KEYWORDS

abortion, nurse's role, nursing, scoping review

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GBP-PET00454

Case 6:25-cv-01491-DCJ-DJA Document 231-6 Filed 02/24/26 Page 114 of 239 PageID #: 7327

1 | INTRODUCTION

Access to safe abortion is considered a human right and has directly contributed to a steep decrease in maternal mortality and morbidity worldwide (Erdman, Depiñeres, & Kismödi, 2013). Still, women seek unsafe abortions in places where safe and legal abortion is inaccessible. For every 100,000 unsafe abortions performed in developed areas, 30 women will die from complications. In developing regions, this number rises to between 220–520 deaths per 100,000 (Ganatra et al., 2017). Estimates from a decade ago put the global economic impact of treating the complications of unsafe abortion at $US553 million per year (Vlassoff, Shearer, Walker, & Lucas, 2008).

This paper reports on a systematic scoping review of research on nursing or midwifery abortion care to define the role and scope of the nurse and midwife within the global context of abortion.

Nurses and midwives together form the largest group of professionals employed in healthcare services and potentially play an important role in abortion care worldwide (Levi, Simmonds, & Taylor, 2009; Singh, 2018; Sutherland, Fontenot, & Fantasia, 2014). The activities undertaken by individual nurses and midwives are regulated and standardised according to their scope of practice, which is determined by education and law (Nursing & Midwifery Board of Australia, 2016). Scope of practice is influenced by the context of practice, the nurse or midwife's confidence and competence, the health needs of the people and the policy requirements of the health service (Nursing & Midwifery Board of Australia, 2016). Internationally, there has been a call to enhance the reproductive rights of women by integrating self-managed medical abortions (m-tops) into the current abortion service model (Jelinska & Yanow, 2018) as well expand the scope of nurses and midwives to provide medical and surgical abortions (s-top) (Renner, Brahmi, & Kapp, 2013). Improved research is needed to inform the nurse/midwives' scope in emerging abortion care frameworks to improve practice, streamline service provision and improve the health and reproductive autonomy of women. Ultimately, this may increase the availability, access and affordability of abortion services. The first step in this process is to identify the main types and sources of evidence available to develop future research priorities.

2 | AIMS

This scoping review is part of a larger doctoral study exploring the experiences of nurses managing the care of women seeking abortions in the context of violence. This review aims to define the role and scope of the nurse/midwife within the global context of abortion care.

The review addressed the following overarching question:

1. What is the nurse or midwife's role and scope of practice within abortion care?

What does this paper contribute to the wider global clinical community?

- This review consolidates the literature regarding the nurse and midwife's role in abortion care. In doing so it highlights research and practice gaps.
- This review demonstrates that nurses and midwives are essential to the delivery of abortion care. However, there are political and educational barriers that prevent nurses and midwives from working to an extended scope of practice. Further research is required to determine the extent of evidence-based abortion practice taught across nursing and midwifery curricula.
- This review demonstrates that nurses and midwives can improve access to women in rural and remote areas. Further inquiry is needed to ensure that care is provided within a person-centred model of care.

3 | METHODS

3.1 | Protocol registration

This scoping literature review is not registered and is not associated with a pre-existing protocol. The authors did not find any published systematic review protocols on this topic in Prospero, OSF Registries, Joanna Briggs Institute or Research Registry. Nor did the database search unearth published reviews of a similar nature.

3.2 | Study design

We have employed Arksey and O'Malley's (2005) systematic five-stage methodological framework for scoping reviews to identify, analyse and synthesise the literature. The five stages are (a) identify the search question (outlined above), (b) identify relevant studies, (c) study selection, (d) charting the data and (e) collating, summarising and report the results. The review follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Extension for Scoping Reviews (Tricco et al., 2018; Appendix S1).

3.3 | Eligibility criteria

To identify relevant studies (stage one), we selected the initial search terms using the SPIDER tool (Sample, Phenomenon of Interest, Design, Evaluation and Research type). While other search tools may have been appropriate, SPIDER is purported to be more efficient than other search strategy tools with qualitative and mixed-method research questions (Cooke, Smith, & Booth, 2012).

Sample—nurses or midwives
Phenomenon of Interest—abortion care
Design—any
Evaluation—nursing or midwifery practice
Research Type—qualitative, quantitative and mixed methods

Search terms were tested and modified iteratively to find relevant articles. We restricted abortion to elective abortions and not those conducted for foetal abnormalities. We deemed studies eligible if they were published from 2008 onwards, citing both qualitative and quantitative original research data and published in English. We also included discussion papers and reports where they directly related to the role of the nurse or midwife (refer to Table 1 for inclusions/exclusions).

3.4 | Information sources and data collection process

LM searched MEDLINE, CINAHL, Scopus and ScienceDirect databases from 2008–December 2019 to identify relevant articles. LM drafted the search strategy and further refined through team discussion. The MEDLINE search strategy is demonstrated below.

3.5 | Search

The final search strategy for MEDLINE can be found in Table 2.

3.6 | Selection of sources of evidence

The articles collected in the previous step were imported into EndNote and screened for duplicates. To select the studies (stage three), LM performed title and abstract screening on the articles collected in the previous step and tracked this process in an Excel spreadsheet. These results were discussed with CO. LM then read the full-text articles and assessed them against inclusion and exclusion criteria to confirm their eligibility in the scoping review. Study relevance and validity were evaluated by considering how helpful each article was in answering the overarching scoping review question. The reviewers did not conduct a critical appraisal of individual articles; this is not a requirement for scoping reviews (Arksey & O'Malley, 2005; Pham et al., 2014).

3.7 | Data charting process (stage four)

LM charted data from eligible studies using a standardised data abstraction tool designed for this study. We abstracted data on nursing or midwifery care and charted the article characteristics including author, study population, methodology and outcomes. This information is presented in Appendix S2.

4 | RESULTS

4.1 | Selection of sources of evidence

A total of 140 records were identified using the outlined search strategy. Citations were imported to EndNote and screened for duplicates. Thirty articles were removed. Next, titles and abstracts were scrutinised against the inclusion and exclusion criteria. Twenty-two articles were removed as they were found not to meet the study criteria: 12 articles did not focus on the nurse or midwife's scope of practice and 10 articles were unrelated to nurses or midwives (e.g. DNA-testing, healthcare economics, patient attitudes to a support person in theatre). Full-text articles were then read and assessed with respect to how they answered the overarching research question. Ten articles were excluded as they did not report on nursing or midwifery care. Four articles were unavailable. Seventy-four articles, considered relevant to the study, were included in the synthesis (Figure 1): 27 qualitative, 29 quantitative, 4 mixed-methods studies and 3 systematic reviews. Eleven articles were reports or commentaries.

4.2 | Characteristics of sources of evidence

Each study's aim, setting, method and findings are presented in Appendix S2.

4.3 | Results of individual sources of evidence

Individual sources of evidence are presented in Appendix S2.

4.4 | Synthesis of results (stage five)

While the studies differed in purpose, design, study population and geographical location, all had a focus of nursing or midwifery practise in abortion care. The (74) articles demonstrated variation in work settings, qualifications, training and regulated practice. Three themes emerged from the articles: (a) regulated role, (b) psychosocial care and (c) expanding scope. The first theme related to the legal and clinical context in which abortion care can be delivered by nurses and midwives, as well as the education required to undertake the role. The second theme referred to aspects of abortion care, beyond task-based nursing and midwifery care. The final theme represented articles about nurses and midwives assuming the responsibilities in abortion care, more traditionally controlled by physicians.

4.4.1 | Theme 1: The regulated role

The 74 studies demonstrate that abortion care is delivered across diverse health settings by nurses and midwives who have varying

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TABLE 1 Inclusions/exclusions table

Criteria	Inclusion criteria	Exclusion criteria
Time period	January 2008 onwards (December 2019)	Before January 2008
Type of article	Original research article, reviews, published in a peer-reviewed article. In English; quantitative and qualitative or mixed methods. Discussion papers and reports directly related to the role of nurse/midwife in abortion care	Articles which reported views about the provision of abortion by nurses (i.e. conscientious objectors)
Study focus	Nursing and midwifery care of women who present for abortion	No reference made to the nursing care of women who present for abortion

TABLE 2 MEDLINE search strategy

1. MeSH descriptor: [Abortion, Criminal]
2. MeSH descriptor: [Abortion, Therapeutic]
3. MeSH descriptor: [Abortion, Induced] explode all trees
4. MeSH descriptor: [Abortion, Legal]
5. Termination
6. Terminat* near/3 preg*
7. Medical near/2 terminat*
8. Surgical near/2 terminat*
9. Medical near/2 abortion
10. Surgical near/2 abortion
11. Care near/3 abortion
12. NOT Object*
13. NOT Conscientious
14. OR/1–14
15. MeSH descriptor: [Nursing Care]
16. MeSH descriptor: [Nurse Practitioners]
17. MeSH descriptor: [Nurse Specialists]
18. MeSH descriptor: [Nursing]
19. MeSH descriptor: [Nurse's Role]
20. MeSH descriptor: [Nurses, Community Health]
21. MeSH descriptor: [Nurses]
22. MeSH descriptor: [Midwifery]
23. MeSH descriptor: [Nurse Midwives]
24. MeSH descriptor: [Nurse Clinicians]
25. 15 AND (OR/1–14)

degrees of education and training. Two subthemes were identified: (a) context and law, and (b) qualifications and training.

Subtheme 1—Context and law

Except where nurses and midwives worked in specialist abortion services, abortion care was just one aspect of the nurse or midwives' overall responsibilities. Nurses and midwives worked in obstetric and gynaecological wards, operating theatres, primary practice, community sexual and reproductive health centres, telemedicine clinics, pharmacies and stand-alone abortion clinic contexts across metropolitan rural and remote areas. The broad skill sets of nurses and midwives were seen as helpful in the provision of comprehensive abortion care (CAC; Freedman & Levi, 2014; Hulme-Chambers, Clune, & Tomnay, 2018; Taylor, Safriet, & Weitz, 2009; Yarnall, Swica, & Winikoff, 2009).

Nursing and midwifery work was largely influenced by the work context as well as national law and local policy. Table 3 provides an overview of the laws governing abortion globally and the associated effect on the provision of care by nurses and midwives. However, nurses and midwives did not always have a good understanding of the law (Oppong-Darko, Amponsa-Achiano, & Darj, 2017). Indeed, some countries interpreted laws ambiguously (Cleeve, Nalwadda, Zadik, Sterner, & Klingberg-Allvin, 2019), conservatively or enacted special laws restricting nurse/midwifery involvement (Biggs et al., 2019; Sheldon & Fletcher, 2017; Taylor et al., 2009).

The routine nursing and midwifery tasks described in the articles were pregnancy diagnosis and options counselling (Levi et al., 2009), pharmacological and nonpharmacological pain relief (Lindström, Wulff, Dahlgren, & Lalos, 2011), administration of anti-D, and antibiotic prophylaxis (Cappiello, Beal, & Simmonds, 2011), handling the products of conception (Andersson, Gemzell-Danielsson, & Christensson, 2014; Mauri, Ceriotti, Soldi, & Guerrini Contini, 2015; Michalik et al., 2019; Mizuno, 2011; Nicholson, Slade, & Fletcher, 2010), gestational dating, bimanual examination (Averbach, Puri, Blum, & Rocca, 2018) screening for domestic violence, postabortion contraception care (Purcell, Cameron, Lawton, Glasier, & Harden, 2016), referrals (Grace, 2016), health education (Cappiello et al., 2011; Halldén, Lundgren, & Christensson, 2011), counselling (Hulme-Chambers et al., 2018), prescription of abortion drugs (Simmonds, Beal, & Eagen-Torkko, 2017), administration of abortion drugs, manual vacuum aspiration abortions (MVA) (Berer, 2009; Bridgman-Packer & Kidanemariam, 2018; Paul, Gemzell-Danielsson, Kiggundu, Namugenyi, & Klingberg-Allvin, 2014), postabortion phone counselling (Dawson, Bateson, Estoesta, & Sullivan, 2016), peer education (Puri, Regmi, Tamang, & Shrestha, 2014; Puri, Tamang, Shrestha, & Joshi, 2015), care of or referral for postabortion complications (Hulme-Chambers et al., 2018; Yegon et al., 2019), screening and treatment of sexually transmitted infections and human immunovirus (Yegon et al., 2019) and management of postabortion complications (Cleeve et al., 2019; Paul et al., 2014; Yarnall et al., 2009; Yegon et al., 2019). These tasks were not ubiquitous. A qualitative longitudinal study suggested where policy allowed for specially trained nurses and midwives to provide abortions, access and quality of care improved; however, the changes to clinical operations and staffing created barriers (Battistelli, Magnusson, Biggs, & Freedman, 2018).

Subtheme 2—Qualifications and training

Qualifications and training required to provide abortion nursing and midwifery care were reported in 15 articles. They varied significantly

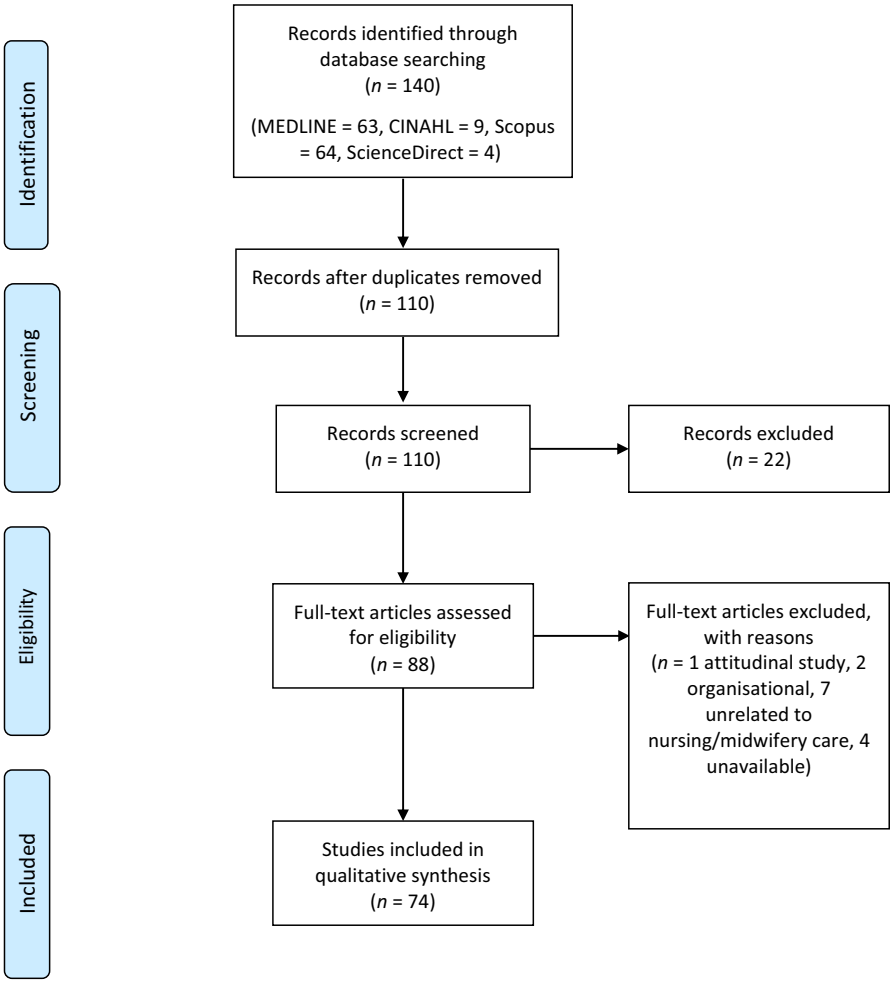

FIGURE 1 PRISMA 2009 flow diagram

across the studies and depended on the regulation of abortion generally and specialist clinical practices specifically, and the country setting. For example, the degree to which qualifications and training were necessary for MVA was not uniform. In Nigeria, MVAs were performed by generalist nurses who did not routinely receive formal education around the practice (Adinma, Adinma, Ikeako, & Ezeama, 2011). Ugandan midwives had similar experiences and performed MVAs for postabortion care with or without specific training and in emergencies would perform dilatation and curettage, and manual removal of placentas (Paul et al., 2014). Tanzanian nurses and midwives reported that they performed postabortion care with inadequate training and supervision (Yegon et al., 2019). Twenty per cent of Ethiopian mid-level healthcare workers reported training in safe abortion care despite the country having the fifth highest rate of maternal deaths in the world (Assefa, 2019). In contrast, Californian certified midwives, nurse practitioners and physician assistants underwent training, based on education programmes used for family practice residence, to perform MVAs. The health practitioners' confidence grew after they became competent and their ability to manage clinical issues increased with experience (Levi, Angel James, & Taylor, 2012; Levi et al., 2018).

In Nepal, nurses and auxiliary nurse midwives in the Rupandehi district received a 3-day training to provide unbiased counselling, MVA, m-top, management of minor complications and early identification and escalation of adverse conditions. Postintervention interviews revealed that nurses and auxiliary nurse midwives were confident about performing m-tops independently (Puri et al., 2014).

Recently, the International Confederation of Midwifery amended its competency standards for basic midwifery education, adding a new competency specific to individualised, culturally sensitive abortion-related care provision (Fullerton, Thompson, Severino, & International Confederation of, 2011). In accordance, the Nigerian Midwifery curriculum has been upgraded to improve postabortion care material. The intervention has increased the quality of instruction as well as the skills of graduates using MVA (Akiode, Fetters, Daroda, Okeke, & Oji, 2010). Ghanaian midwifery schools added CAC to the curriculum in 2007 (Rominski, Lori, Nakua, Dzomeku, & Moyer, 2016). In Poland, the midwifery degree is regulated nationally and requires theoretical and practical preparation of students to provide abortion care, though students feel abortion is inadequately covered in the curriculum (Michalik et al., 2019). A descriptive study carried out across 77 nursing and midwifery schools in Japan found little content devoted to the abortion procedure itself, favouring instead the legal aspects of abortion as well as family planning, emergency contraception, postabortion complications and psychological effects

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TABLE 3 Abortion laws by country

Country	Law	Effect on nurses/midwives and women
Kenya	Abortion illegal except to save the woman's life. Postabortion care is legal	High mortality rate PAC currently only performed by physicians (Makenzius et al., 2017)
Nigeria	Criminal except in certain circumstances	High mortality rate Nurses and midwives can perform postabortion care (Adinma et al., 2011; Akiode et al., 2010; Fawole et al., 2012)
Ethiopia	Abortion is illegal except in the case of rape or incest, a risk to the woman's life or health, foetal malformation, maternal disability or age under 18 years up until foetal viability (28 weeks) (Assefa, 2019). Medical abortion beyond 9 weeks. CAC country model	Services have expanded but still unavailable for many women. Nurses able to provide first-trimester abortions (Bridgman-Packer & Kidanemariam, 2018)
Zambia	Abortion is legal on socio-economic grounds since 1994 (Kishen, Stedman, Kishen, & Stedman, 2010)	Midwives can perform medical and surgical abortions up to 12 weeks of gestation and postabortion care. CAC training was added to the midwifery curricula in 2007
Uganda	Abortion is only legal to save the life of the woman (Paul et al., 2014)	40% of admissions to emergency obstetric units are due to unsafe abortion. Specially trained midwives may perform postabortion care
Ghana	The liberalisation of abortion laws in 1985 to allow abortion in context of rape, defilement, incest, risk to the life or physical/mental health, risk of child suffering (Oppong-Darko et al., 2017). 2003 National Reproductive Health strategy includes access to safe abortion care	Unsafe abortion continues to be a public health challenge. Midwives authorised to provide early abortion (Oppong-Darko et al., 2017)
South Africa	Abortion on demand available up to 12 weeks under the Choice on Termination of Pregnancy Act, 1996	A registered nurse may lawfully perform first-trimester abortions (Kishen, Stedman, Kishen, & Stedman, 2010; Mamabolo & Tjallinks, 2010)
Mozambique	Abortion is legal	Maternal-child nurses provide comprehensive care including ultrasound, administration of misoprostol, MVA, follow-up and postabortion care (Yarnall et al., 2009)
Tanzania	Government committed to postabortion care (Yegon et al., 2019)	Nurses and nurse–midwives treat abortion complications using misoprostol, MVA and curettage. Also expected to provide contraception counselling
Poland	Legal if there is a risk to life, if the pregnancy results from an illegal act, or in the case where a foetal abnormality will impact independent life (Michalik et al., 2019)	Estimated 80–150 thousand illegal abortions annually. Midwives may conscientiously object to providing abortion care
England, Wales and Scotland	Abortion Act 1967 made abortion legal on request up to 24 weeks. The interpretation of the law is disputed, and some believe that surgical abortions could be performed by nurses and midwives as part of the healthcare team (Sheldon & Fletcher, 2017)	Abortion Act 1967—nurses may accept delegated instructions from a registered medical practitioner allowing for nurse-delivered termination services (Cherry & Sokolovs, 2008; Gallagher, Porock, & Edgley, 2010; Kishen et al., 2010; Lipp, 2011). Abortion almost exclusively provided through the National Health Service in hospital gynaecology departments however moving into community-based sexual and reproductive health centres. Misoprostol must be delivered in the healthcare setting
Northern Ireland	Abortion remains illegal (Kishen et al., 2010)	
France	Abortion legal if performed by a qualified medical doctor (Kishen et al., 2010)	Must be performed by a physician; however, nurses are regularly involved in abortion care
Italy	Law no 194 of 22 May 1978 abortion is legal 12 weeks. After 12 weeks, only legal under circumstances that preserve the woman's life or when malformations are detected that could risk the physical or mental maternal health	Registered nurses may conscientiously object to being part of the abortion but not the before/aftercare (Mauri et al., 2015)

(Continues)

TABLE 3 (Continued)

Country	Law	Effect on nurses/midwives and women
Sweden	Abortion is legal under the Swedish Abortion Act of 1974 up to 18 weeks and must be performed by a doctor	Performed by physicians but nurses or midwives are usually involved in caring for the woman (Andersson et al., 2014; Kishen et al., 2010; Kopp Kallner et al., 2015; Lindström et al., 2011)
Norway	Abortion Act of 1978 made abortion legal in the first trimester. Medical abortion was introduced in 1998	In some instances, the nurse can be delegated the whole medical abortion procedure by the physician. Usually, nurses have a more limited role (Kjelsvik et al., 2018)
Nepal	First-trimester abortions became legal in 2002. CAC initiated in 2004	Access to abortion care has increased for many women; however, those in remote areas still have limited access. One in seven maternal deaths is attributable to unsafe abortion (Kishen et al., 2010) Nurses and midwives (as well as auxiliary nurse midwives) can legally provide abortions (Andersen et al., 2016). Medical abortions can be provided up to 63 days of gestation in government-certified health facilities (Averbach et al., 2018)
India	Medical Termination of Pregnancy Act of 1972 up to 20 weeks of gestation	Access to abortion remains limited. Estimates that 3 unsafe abortions are performed to every 2 legal abortions. Carried out in registered facilities by gynaecologists or specially trained allopathic physicians (Jejeebhoy et al., 2011, 2012; Kishen et al., 2010)
Bangladesh	The law permits induced abortion to save the life of the woman. "Menstrual regulation" though vacuum aspiration is available up to 10 weeks of pregnancy	Vacuum aspiration is performed by family-welfare visitors (Kishen et al., 2010)
Kyrgyzstan	Abortion is legal on request without restriction up to 12 weeks' gestation and up to 22 weeks for economic and social reasons	Must be provided by an obstetrician–gynaecologist in public or private institution. Nurses and midwives are involved in the care of women undergoing abortions (Johnson et al., 2018)
Canada	1988 abortion was decriminalised entirely (Kishen et al., 2010)	Must be provided by a medical practitioner (Kishen et al., 2010)
USA	Abortion legal in many US states. Roe v. Wade 1973 enacted due to concern over untrained providers harming women. March 2016, Food and Drug Administration updated the labelling of mifepristone to allow midwives, nurse practitioners and physician's assistant to obtain and prescribe mifepristone without physician supervision (Simmonds et al., 2017). Physician-only laws in some states restrict the provision of abortion (Taylor et al., 2009)	2003 Assembly Bill (154) allows trained nurse practitioners, certified nurse–midwives and physicians assistants to perform aspiration abortions in California (Battistelli et al., 2018; Freedman et al., 2015; Freedman & Levi, 2014). Physician-only abortion law in Arizona (Jackson, 2011). Advance practice clinicians (APCs) provide abortions in Vermont and Montana since 1973; APCs perform medical abortions in 14 states and surgical abortions in six states (Kishen et al., 2010). Certified nurse–midwives can legally provide medical and aspiration abortions in the USA as determined by State law (Levi et al., 2012)
Mexico	Abortion legalised in 2007 (Olavarrieta et al., 2015)	Patient demand still outpaces service delivery. Most abortions are still illegal. Nurses could be trained and authorised to perform medical terminations (Olavarrieta et al., 2015)
Chile	Abortion legalised in 2017 in situations when the woman's life is at risk, for foetal abnormality and for pregnancies resulting from rape (Biggs et al., 2019)	Midwives have a limited role in abortion care as legally, only physicians can perform the procedure
Vietnam	Abortion legal since 1945 and can be performed by a doctor, doctor-assistant or trained midwife (Kishen et al., 2010)	Trained midwives can perform abortions (Kishen et al., 2010)
Japan	Abortion legal up until 21 weeks of gestation for justifiable reasons such as rape, physical health, socio-economic hardship (Mizuno, 2011)	People seeking abortions are cared for within maternity units. Midwives provide care for people undergoing abortions. Medical abortions are still rare (Mizuno, 2014). Nurses and midwives do not have the option to contentiously object (Mizuno, 2014)

(Continues)

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TABLE 3 (Continued)

Country	Law	Effect on nurses/midwives and women
Cambodia	Abortion legal on any grounds in the first trimester and performed by a doctor, medical assistant or midwife at public or private health facilities (Kishen et al., 2010)	Authorised midwives can perform surgical abortions (Yarnall et al., 2009)
Myanmar	Penal code of 1,860 criminalises abortion unless it is performed to save the life of the woman	Unsafe abortion is common and contributes to 10% of maternal deaths countrywide and 50% of maternal deaths in conflict-affected areas (Sheehy, Aung, & Foster, 2015). Commonly performed by untrained traditional birth attendants. Few trained midwives (m-top)
Australia	Legislation differs between states. Restrictions on abortion in most states	Abortions must be performed by a medical doctor. Nurses and midwives assist in the care of the woman during the procedure (Dawson et al., 2016; Hulme-Chambers et al., 2018). Doctors who wish to become medical abortion providers must undergo online training through MS Health. Only pharmacists who are registered providers with the MS-2Step programme can dispense medication abortion drugs

Abbreviations: CAC, comprehensive abortion care; MVA, manual vacuum aspiration.

of abortion (Mizuno, 2014). Comparable results were found in a Canadian study which aimed to understand the curriculum coverage of abortion in nurse practitioner programmes. The national survey of nurse practitioner programme directors revealed 63% of programmes covered ethics of abortion, counselling and post-abortion care, and approximately half of the programmes covered first-trimester abortion procedures (Sheinfeld, Arnott, El-Haddad, & Foster, 2016).

The context of care presented unique educational needs for nurses and midwives. For example, labour and delivery nurses in Quebec, Canada, identified that they needed more knowledge of pre-abortion counselling to assess the woman's understanding of the procedure as well as more training on how to support women who had received abortions through the postpartum period (Parker, Swanson, & Frunchak, 2014). Lack of m-top training opportunities was seen as a barrier to nurse-led medical abortion in the primary health care setting in regional and rural Victoria, Australia (de Moel-Mandel, Graham, & Taket, 2019). A support network for abortion care nurses, established in Wales, provides ongoing professional development to its members to extend their knowledge, expertise and skills (Cherry & Sokolovs, 2008).

4.4.2 | Theme 2: Providing psychosocial care

Nine articles explored broader aspects of nursing and midwifery care referred to here as psychosocial care. English gynaecology nurses from a ward-based abortion service felt that psychological care was one of their major roles. They employed nonjudgemental counselling and interpersonal skills, though this proved challenging for the nurses if women presented for multiple abortions or had an abortion after fertility treatment (Nicholson et al., 2010). Nurses in UK abortion clinics described how they used therapeutic communication to reduce the controversy and shame around the stigmatised procedure (Fullerton et al., 2011) and joint decision-making around contraception uptake (Purcell et al., 2016). Developing the therapeutic relationship and establishing professional boundaries were two important elements of abortion care for labour and delivery nurses in Quebec, Canada (Parker et al., 2014). Nurses and midwives who provided care for women undergoing home abortions in Sweden explained that they adapted their care depending on the woman's need to cope or deal with loss, grief and sorrow associated with the procedure (Lindström et al., 2011).

An exploration of the experiences and perceptions of Swedish nurses and midwives caring for women undergoing late-term abortions found themselves being selective with the information they gave the woman about the procedure to increase comfort and responded to the woman's emotional and existential needs (Andersson et al., 2014). In a similar study conducted in Italy, midwives explained that caring for women undergoing late-term abortions required practical and psychological competence, excellent communication skills and empathy (Mauri et al., 2015).

A qualitative study of Norwegian nurses and doctors who cared for women ambivalent about their abortions explained that they employed a therapeutic use of self as well as intuition to assess the woman's ambivalence. They changed their language so as not to seem confrontational, remained neutral about the woman's choice and pragmatically prepared them for the procedure (Kjelsvik, Tveit Sekse, Moi, Aasen, & Gjengedal, 2018). A phenomenological hermeneutic analysis of midwives who provide abortion care to teenagers in Sweden uncovered that midwives used a variety of psychosocial techniques to engage young women and assist them to make decisions about abortion and contraception. Midwives felt that understanding the teen's social situation was an essential element that allowed them to refer her to a social worker and tailor their preventative care. They also created a space where the young woman could work through her feelings, consider the consequences of terminating or continuing the pregnancy and negotiate low-dosage contraceptives. They employed unconventional contact methods, such as calling the teen's friends when they missed appointments (Halldén

et al., 2011). Providing abortion care to Swedish women from immigrant backgrounds required midwives to adapt their care since some women did not see their bodies as their own, had a lack of understanding about sex and pregnancy, made decisions with their families and came from backgrounds that accepted honour-based violence (Larsson, Fried, Essén, & Klingberg-Allvin, 2016).

4.4.3 | Theme 3: Expanding scope of practice

Expanding the scope of practice to allow nurses and midwives to have a greater role in abortion care was the focus of 27 articles. Three subthemes emerged: (a) as safe as doctors, (b) pragmatism and (c) moving away from the hospital.

Subtheme 1—As safe as doctors

A 2009 summary of evidence article by Yarnall et al. (2009) found that mid-level providers (such as nurses and midwives), especially those who manage normal pregnancies, possess the requisite clinical skills to provide m-tops. Such skills include the administration of medications, assessment of gestational age, diagnosis of ectopic pregnancy, family planning counselling and the management of obstetric complications. A systematic review, by Barnard, Kim, Park and Ngo (Barnard, Kim, Park, & Ngo, 2015), compared the effectiveness or safety of abortion provided by mid-level providers against medical and s-tops performed by doctors. They identified eight studies (three of which were identified by our search protocol), including randomised control trials, prospective cohort studies and observational studies. The quality of evidence varied from high quality to very low quality. The combined data from the s-top rate found no difference between doctors and mid-level providers failure and complication rates. A systematic review by Renner et al. (2013) had similar findings, which is not surprising as the articles selected for the meta-analysis were similar. A 4-year prospective observational cohort study to assess the safety of first-trimester MVA performed by advanced nurses, midwives and physicians assistants across four services in California found that these health providers were no less safe than physicians (Freedman, Battistelli, Gerdts, & McLemore, 2015; Weitz et al., 2013; Weitz, Taylor, Upadhyay, Desai, & Battistelli, 2014). A cohort study conducted in Oregon, USA, compared the outcomes of 669 first-trimester MVA with immediate intra-uterine device insertion between nurse practitioners, certified nurse–midwives and physicians and found no differences in outcomes between provider type (Patil et al., 2016). A 3-month noninferiority trial to examine the effectiveness, safety and acceptability of nurse provision of early m-tops compared to physicians was conducted across three facilities in Mexico City (Olavarrieta et al., 2015). A total of 844 women were randomly assigned to a nurse or physician. Like the previous study, nurses were found to be no less safe than physicians. The study also found that there was no difference between physicians and nurses in determining gestation or the uptake of contraception postabortion. The women rated care provided by the nurse and physician groups as highly acceptable.

A randomised controlled equivalence trial in Sweden assessed nurse/midwife provision of first-trimester m-top where ultrasound was used as part of the protocol. The study found the effectiveness of m-top provided by nurses to be superior to doctors (though there were no differences in patient safety outcomes) (Kopp Kallner et al., 2015). A 12-month randomised controlled equivalence trial conducted across five districts in Nepal. It set out to (a) assess whether first-trimester m-tops provided by mid-level providers were as safe and effective as that provided by doctors and (b) assess the level of satisfaction women who received m-tops felt when the services were provided by trained nurses and auxiliary nurse midwives (independently from doctors) or doctors. The study found that safety and effectiveness were similar between groups (Warriner et al., 2011), and women's satisfaction was also similar between the groups (Tamang et al., 2017). A retrospective review of CAC service register at Tribhuvan University Teaching Hospital in Nepal also found that nurses were as competent as doctors in providing abortions but were underutilised (Sayami, 2019). Studies carried out in India (Jejeebhoy et al., 2011, 2012) concluded that nurses could assess gestation and complete abortions, and perform MVA as well as physicians. Abortion failure rates were equivalent to physicians.

A prospective cohort study carried out by Gebreselassie, Ustá, and Mitchel (Gebreselassie, Ustá, Andersen, & Mitchell, 2012) found that when nurses were consistently able to diagnose complete abortions using clinical history taking and physical examination as proficiently as gynaecologists using ultrasound. The same nurses had a moderate agreement with physicians diagnosing incomplete abortions and ongoing pregnancy. A nonrandomised implementation study of 32 nurses and midwives who provided medical termination to 554 women across four remote services in Kyrgyzstan found that there was a high level of complete abortions with no adverse events or safety issues and a high level of patient satisfaction (Johnson et al., 2018). A multicentre randomised controlled equivalence trial of 1,094 women with incomplete first-trimester abortions in Kenya found that women who were administered misoprostol by midwives to complete their abortions had slightly better outcomes than when administer by physicians (94.8% compared with 94.3%) (Makenzius et al., 2017). An open-label prospective study in Nigeria had similar findings where nurses performed first-line treatment for incomplete abortions using misoprostol (Fawole, Diop, Adeyanju, Aremu, & Winikoff, 2012).

Conversely, an Australian study, which investigated the expansion of general practice to provide m-top, found doctors were resistant to the exclusive provision of m-top by primary care nurses. Study participants felt that nurses lacked skill and experience, and their nursing care was of a lower standard than other countries with nurse-led m-top models of care (Newton et al., 2016). On the other hand, a study investigating the enablers and barriers to decentralising m-top service provision in Victoria found that some general practice providers utilised nurse-led integration models of abortion care. Unsurprisingly, general practitioners and primary care nurses felt that training by providers that had partnered with trusted rural organisations and being able to adapt resources used by rural services

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facilitated the provision of abortion care (Hulme-Chambers et al., 2018). de Moel-Mandel Graham and Taket's (2019) Delphi study exploring a nurse-led model of m-top provision in rural and regional Victoria achieved a consensus that primary health care nurses could provide m-top in collaboration with general practitioners, refer for blood tests and ultrasound scans, interpret pathology, administer mifepristone and prophylactically manage pain. The panel also believed legislation changes were necessary to allow nurses to prescribe m-top medications. They could not reach consensus on nurses managing the m-top process autonomously or the responsibility of the general practitioner managing non-life-threatening complications. The barriers to a nurse-led model of care were training, support from general practitioners and other stakeholders (such as local health professionals), funding models, abortion stigma, and distribution of labour between doctors and nurses.

Subtheme 2—Pragmatism

Under-resourced countries, such as Nepal, Bangladesh, Myanmar and Uganda, pragmatically extend the scope of nurses and midwives, as well as incorporate other auxiliary health professionals (such as auxiliary nurses and female paramedics) to provide abortion or postabortion care (Andersen et al., 2016; Cleeve et al., 2019; K C et al., 2011; Puri et al., 2015). Nonetheless, in some under-resourced settings, such as areas of Uganda, midwives were forced to practice outside of their extended scope, with improvised equipment (Paul et al., 2014), in inadequate facilities and for low pay (Cleeve et al., 2019). The use of auxiliary nurses and midwives in abortion care, without specific training, should be approached cautiously. A mixed-method study describing the knowledge, attitudes and roles of auxiliary nurse midwives and other community health intermediaries in Karnataka, India, demonstrates that the health workers had limited understanding of abortion law, held negative views towards abortion and would not support women in their abortion decision-making (Nandagiri, 2019).

Subtheme 3—Moving away from the hospital

Expanding scope was described in other ways such as in Sweden, where a focus group of nurses and midwives foreshadowed the provision of home abortions. This shift, from the hospital to the home, would give control of the process to the woman. The nurses believed their role would change to be that of advocate, providing phone support and offering advice for pain relief (Lindström et al., 2011). A 12-month observational noninferiority study carried out in semi-urban and remote areas in two Nepali districts compared the safety and effectiveness of m-tops provided by trained auxiliary nurse midwives at six pharmacies and six health facilities (Rocca et al., 2018). M-top provided through pharmacies was as effective as provided through health facilities.

5 | DISCUSSION

This scoping review adds to the literature by consolidating a large body of international research in the field of nursing and midwifery abortion care. The evidence demonstrated that nurses and midwives provide a wide range of abortion-related services and are essential to abortion care delivery. From this review, we have learnt that the nurse and midwife's role in abortion may be over-regulated in many countries. The risk profile of abortion care, especially m-top, appears to be lower than many other roles advanced-practice nurses and midwives already perform. However, we learnt little about the education and training that midwives and especially nurses receive to provide abortion-related care. While some momentum has been made to determine the essential abortion care competencies by Hewitt and Cappiello (2015), further work is needed to establish the extent of abortion content taught across the international undergraduate nursing and midwifery curricula.

Furthermore, although this review illustrates that nurses and midwives are essential providers of abortion care, few articles provided a framework of person-centred abortion care. CAC, identified in four articles, is a framework which incorporates high-quality integrated services, safe induced abortion, treatment of complications, counselling, contraceptive and family planning services and decentralisation of services. It is affordable to both women and health systems and attends to other issues relevant to the woman's health (IPAS, 2011). However, we do not know whether nurses or midwives situate their practice activities within such a framework. Further research is therefore required in this area.

There was evidence that psychosocial care was a central element of abortion care, and this is not surprising given the stigmatised nature of the procedure. Treatment by healthcare staff is a consistent finding in overall satisfaction rates among women seeking abortions (Regmi & Madison, 2010; Taylor et al., 2013). Nevertheless, these findings were overshadowed by the volume of studies that focused on the nurse/midwife's task-based scope of practice.

There was consistent evidence that adequately trained nurses and midwives could work more autonomously, and within nurse-led care models to provide m-top and MVA in the first trimester as well as postabortion care. Legislation, however, acts as a barrier for nurses and midwives and presents a significant access threat to women living in regional or remote areas globally. In an era where safe, self-managed abortions are gaining traction, the current risk profile of the abortion medication, mifepristone, needs review to make it available in the midwifery and nurse practitioner formulary.

5.1 | Limitations

We undertook this review throughout 2019, and information contained in Table 3 may be outdated. Any recent changes to abortion law reform, not captured by the search strategy, are not displayed in this article. We completed our literature search after the first round of database searching. While this could indicate that some articles may have been missed, Nussbaumer-Streit et al. (2018) suggest that when 10 or more studies are combined, there is a reduced risk that conclusions may be false; we found 74 articles. They also found that combining two separate databases (we combined four) increases the

reliability of conclusions. The effectiveness of citation searching for reviews of qualitative data, especially on public health topics, has also been called into question by Cooper, Booth, Varley-Campbell, Britten, and Garside (2018). These topics usually generate large numbers of studies, the data are not needed for meta-analysis and there is difficulty in demonstrating the value of missed studies. Finally, Horsley, Dingwall, and Sampson (2011) recommend citation searching when the identification of all relevant studies through database searching is difficult. We believe that the inclusion of 74 articles indicates that most relevant studies have been identified. Further, the scoping review consolidated findings from varied research topics, study populations, methods and findings and generalisable conclusions should not be drawn from the study. As our search strategy was limited to English, some articles may have been missed.

6 | CONCLUSIONS

In this scoping review, we set out to map research on the nurse/midwife's role and scope of practice in abortion care. The literature was extensive, with many studies focussing on task-based duties and the feasibility of nurses and midwives providing abortions. Several studies explored nursing practices beyond task-based care. Future research should be directed towards abortion care education, nursing practice within the comprehensive care model and nurse-led models of care.

7 | RELEVANCE TO CLINICAL PRACTICE

The findings of this scoping review are relevant for clinical practice. Abortion care is a common procedure performed across many healthcare settings. Currently, nurses and midwives provide technical and emotional care to women who seek abortion care. Governments and regulatory bodies could safely extend the scope of practice to increase women's access to safe abortion care. Introduction of education programmes, as well as embedding practice in person-centred models of care, may improve outcomes for women seeking abortions.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Design and implementation of the search strategy and analysis of the results: LM and CO; and writing of the manuscript: LM, CO, KRS, AT and KB.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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MIFEPREX™ (mifepristone) Tablets, 200 mg
For Oral Administration Only

If Mifeprex* results in incomplete abortion, surgical intervention may be necessary. Prescribers should determine in advance whether they will provide such care themselves or through other providers. Prescribers should also give patients clear instructions on whom to call and what to do in the event of an emergency following administration of Mifeprex.

Prescribers should make sure that patients receive and have an opportunity to discuss the Medication Guide and the PATIENT AGREEMENT.

DESCRIPTION

Mifeprex tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical and biconvex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11ß-[*p*-(Dimethylamino)phenyl]-17ß-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is $C_{29}H_{35}NO_2$. Its structural formula is:

The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 191-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

* Mifeprex is a trademark of Danco Laboratories, LLC.

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CLINICAL PHARMACOLOGY

Pharmacodynamic Activity

The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit and monkey), the compound inhibits the activity of endogenous or exogenous progesterone. The termination of pregnancy results.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women. During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity of prostaglandins.

Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity. The activity of the glucocorticoid dexamethasone in rats was inhibited following doses of 10 to 25 mg/kg of mifepristone. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotropic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

Pharmacokinetics and Metabolism

Absorption

Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 mg/l occurring approximately 90 minutes after ingestion. The absolute bioavailability of a 20 mg oral dose is 69%.

Distribution

Mifepristone is 98% bound to plasma proteins, albumin and α_1-acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance. Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

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Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11ß; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Excretion

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum levels are undetectable by 11 days.

Special Populations

The effects of age, hepatic disease and renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated.

Clinical Studies

Safety and efficacy data from the U.S. clinical trials and from two French trials of mifepristone are reported below. The U.S. trials provide safety data on 859 women and efficacy data on 827 women with gestation durations of 49 days or less (dated from the first day of the last menstrual period). In the two French clinical trials, safety evaluable data are available for 1800 women, while efficacy information is available for 1681 of these women. Success was defined as the complete expulsion of the products of conception without the need for surgical intervention. The overall rates of success and failure, shown by reason for failure, for the U.S. and French studies appear in Table 1.

In the U.S. trials, 92.1% of the 827 subjects had a complete medical abortion, as shown in Table 1. In 52 women (6.3%) expulsion occurred within two days, and resulted from the action of mifepristone (600 mg) alone, unaided by misoprostol, an analog of prostaglandin E_2. All other women without an apparent expulsion took a 400 µg dose of misoprostol two days after taking mifepristone. Many women (44.1%) in the U.S. trials expelled the products of conception within four hours after taking misoprostol and 62.8% experienced expulsion within 24 hours after the misoprostol administration. There were 65 women (7.9%) who received surgical interventions: 13 (1.6%) were medically indicated interventions during the study period, mostly for excessive bleeding; five (0.6%) interventions occurred at the patient's request; 39 women (4.7%) had incomplete abortions at the end of the study protocol; and eight (1.0%) had ongoing pregnancies at the end of the study protocol.

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Women who participated in the U.S. trials reflect the racial and ethnic composition of American women. The majority of women (71.4%) were Caucasian, while 11.3% were African American, 10.9% were East Asian, and 4.7% were Hispanic. A small percentage (1.7%) belonged to other racial or ethnic groups. Women aged 18 to 45 were enrolled in the trials. Nearly two-thirds (66.0%) of the women were under 30 years old with a mean age of 27 years.

In the French trials, complete medical abortion occurred in 95.5% of the 1681 subjects, as shown in Table 1. In 89 women (5.3%), complete abortion occurred within two days of taking mifepristone (600 mg). About half of the women (50.3%) in the French trials expelled the products of conception during the first four hours immediately following administration of misoprostol and 72.3% experienced expulsion within 24 hours after taking misoprostol. In total, 4.5% of women in the French trials ultimately received surgical intervention for excessive bleeding, incomplete abortions, or ongoing pregnancies at the end of the protocol.

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Table 1

Outcome Following
Treatment with Mifepristone and Misoprostol in the U.S. and French Trials

	U.S. Trials		French Trials	
	N	**%**	**N**	**%**
Complete medical abortion	**762**	**92.1**	**1605**	**95.5**
Timing of expulsion				
Before second visit	52	(6.3)	89	(5.3)
During second visit				
– less than 4 hrs after misoprostol	365	(44.1)	846	(50.3)
After second visit				
– greater than 4 hrs but less than 24 hrs after misoprostol	155	(18.7)	370	(22.0)
– greater than 24 hrs after misoprostol	68	(8.2)	145	(8.6)
Time of expulsion unknown	122	(14.8)	155	(9.2)
Surgical intervention	**65**	**7.9**	**76**	**4.5**
Reason for surgery				
Medically necessary interventions during the study period	13	(1.6)	NA	(NA)
Patient request	5	(0.6)	NA	(NA)
Treatment of bleeding during study	NA	(NA)	6	(0.3)
Incomplete expulsion at study end	39	(4.7)	48	(2.9)
Ongoing pregnancy at study end	8	(1.0)	22	(1.3)
Total	**827**	**100**	**1681**	**100**

Note: Mifepristone 600 mg oral was administered on Day 1, misoprostol 400 µg oral was given on Day 3 (second visit).

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INDICATION AND USAGE

Mifeprex is indicated for the medical termination of intrauterine pregnancy through 49 days' pregnancy. For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period in a presumed 28 day cycle with ovulation occurring at mid-cycle. The duration of pregnancy may be determined from menstrual history and by clinical examination. Ultrasonographic scan should be used if the duration of pregnancy is uncertain, or if ectopic pregnancy is suspected.

Any intrauterine device ("IUD") should be removed before treatment with Mifeprex begins.

Patients taking Mifeprex must take 400 µg of misoprostol two days after taking mifepristone unless a complete abortion has already been confirmed before that time (see DOSAGE AND ADMINISTRATION).

Pregnancy termination by surgery is recommended in cases when Mifeprex and misoprostol fail to cause termination of intrauterine pregnancy (see PRECAUTIONS).

CONTRAINDICATIONS

Administration of Mifeprex and misoprostol for the termination of pregnancy (the "treatment procedure") is contraindicated in patients with any one of the following conditions:

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy);
- IUD in place (see INDICATION AND USAGE);
- Chronic adrenal failure;
- Concurrent long-term corticosteroid therapy;
- History of allergy to mifepristone, misoprostol or other prostaglandin;
- Hemorrhagic disorders or concurrent anticoagulant therapy;
- Inherited porphyrias.

Because it is important to have access to appropriate medical care if an emergency develops, the treatment procedure is contraindicated if a patient does not have adequate access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions, and emergency resuscitation during the period from the first visit until discharged by the administering physician.

Mifeprex also should not be used by any patient who may be unable to understand the effects of the treatment procedure or to comply with its regimen. Patients should be instructed to review the Medication Guide and the PATIENT AGREEMENT provided with Mifeprex carefully and should be given a copy of the product label for their review.

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Patients should discuss their understanding of these materials with their health care providers, and retain the Medication Guide for later reference (see PRECAUTIONS).

WARNINGS
(see CONTRAINDICATIONS)

1. Bleeding

Vaginal bleeding occurs in almost all patients during the treatment procedure. According to data from the U.S. and French trials, women should expect to experience bleeding or spotting for an average of nine to 16 days, while up to 8% of all subjects may experience some type of bleeding for 30 days or more. Bleeding was reported to last for 69 days in one patient in the French trials. In general the duration of bleeding and spotting increased as the duration of the pregnancy increased.

In some cases, excessive bleeding may require treatment by vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions. In the U.S. trials, 4.8% of subjects received administration of uterotonic medications and nine women (1.0%) received intravenous fluids. Vasoconstrictor drugs were used in 4.3% of all subjects in the French trials, and in 5.5% of women there was a decrease in hemoglobin of more than 2 g/dL. Blood transfusions were administered in one of 859 subjects in the U.S. trials and in two of 1800 subjects in the French trials. Since heavy bleeding requiring curettage occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

2. Confirmation of Pregnancy Termination

Patients should be scheduled for and return for a follow-up visit at approximately 14 days after administration of mifepristone to confirm that the pregnancy is completely terminated and to assess the degree of bleeding. Vaginal bleeding is not evidence of the termination of pregnancy. Termination can be confirmed by clinical examination or ultrasonographic scan. Lack of bleeding following treatment, however, usually indicates failure. Medical abortion failures should be managed with surgical termination.

PRECAUTIONS

General

Mifeprex is available only in single dose packaging. Administration must be under the supervision of a qualified physician (see DOSAGE AND ADMINISTRATION).

The use of Mifeprex is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

There are no data on the safety and efficacy of mifepristone in women with chronic medical conditions such as cardiovascular, hypertensive, hepatic, respiratory or renal

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disease; insulin-dependent diabetes mellitus; severe anemia or heavy smoking. Women who are more than 35 years of age and who also smoke 10 or more cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone.

Although there is no clinical evidence, the effectiveness of Mifeprex may be lower if misoprostol is administered more than two days after mifepristone administration.

Information for Patients

Patients should be fully advised of the treatment procedure and its effects. Patients should be given a copy of the Medication Guide and the PATIENT AGREEMENT. (Additional copies of the Medication Guide and the PATIENT AGREEMENT are available by contacting Danco Laboratories at 1-877-4 Early Option) (1-877-432-7596). Patients should be advised to review both the Medication Guide and the PATIENT AGREEMENT, and should be given the opportunity to discuss them and obtain answers to any questions they may have. Each patient must understand:

- the necessity of completing the treatment schedule, including a follow-up visit approximately 14 days after taking Mifeprex;
- that vaginal bleeding and uterine cramping probably will occur;
- that prolonged or heavy vaginal bleeding is not proof of a complete expulsion;
- that if the treatment fails, there is a risk of fetal malformation;
- that medical abortion treatment failures are managed by surgical termination; and
- the steps to take in an emergency situation, including precise instructions and a telephone number that she can call if she has any problems or concerns.

Another pregnancy can occur following termination of pregnancy and before resumption of normal menses. Contraception can be initiated as soon as the termination of the pregnancy has been confirmed, or before the woman resumes sexual intercourse.

Patient information is included with each package of Mifeprex (see Medication Guide).

Laboratory Tests

Clinical examination is necessary to confirm the complete termination of pregnancy after the treatment procedure. Changes in quantitative human Chorionic Gonadotropin (hCG) levels will not be decisive until at least 10 days after the administration of Mifeprex. A continuing pregnancy can be confirmed by ultrasonographic scan.

The existence of debris in the uterus following the treatment procedure will not necessarily require surgery for its removal.

Decreases in hemoglobin concentration, hematocrit and red blood cell count occur in some women who bleed heavily. Hemoglobin decreases of more than 2 g/dL occurred in 5.5% of subjects during the French clinical trials of mifepristone and misoprostol.

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Clinically significant changes in serum enzyme (serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, gamma-glutamyltransferase (GT)) activities were rarely reported.

Drug Interactions

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone).

Based on in vitro inhibition information, coadministration of mifepristone may lead to an increase in serum levels of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range, including some agents used during general anesthesia.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed. Results from studies conducted *in vitro* and in animals have revealed no genotoxic potential for mifepristone. Among the tests carried out were: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pompe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; i*n vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice.

The pharmacological activity of mifepristone disrupts the estrus cycle of animals, precluding studies designed to assess effects on fertility during drug administration. Three studies have been performed in rats to determine whether there were residual effects on reproductive function after termination of the drug exposure.

In rats, administration of the lowest oral dose of 0.3 mg/kg/day caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effect on reproductive performance was observed. In a neonatal exposure study in rats, the administration of a subcutaneous dose of mifepristone up to 100 mg/kg on the first day after birth had no adverse effect on future reproductive function in males or females. The onset of puberty was observed to be slightly premature in female rats neonatally exposed to mifepristone. In a separate study in rats, oviduct and ovary malformations in female rats, delayed male puberty,

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deficient male sexual behavior, reduced testicular size, and lowered ejaculation frequency were noted after exposure to mifepristone (1 mg every other day) as neonates.

Pregnancy

Mifepristone is indicated for use in the termination of pregnancy (through 49 days' pregnancy) and has no other approved indication for use during pregnancy.

Teratogenic Effects

Human Data

Over 620,000 women in Europe have taken mifepristone in combination with a prostaglandin to terminate pregnancy. Among these 620,000 women, about 415,000 have received mifepristone together with misoprostol. As of May 2000 a total of 82 cases have been reported in which women with on-going pregnancies after using mifepristone alone or mifepristone followed by misoprostol declined to have a surgical procedure at that time. These cases are summarized in Table 2.

Table 2

Reported Cases (as of May 2000) of On-going Pregnancies Not Terminated by Surgical Abortion at the End of Treatment with Mifepristone Alone or with Mifepristone-Misoprostol

	Mifepristone Alone	Mifepristone-Misoprostol	Total
Subsequently had surgical abortion	**3**	**7**	**10**
No abnormalities detected	*2*	*7*	*9*
Abnormalities detected (sirenomelia, cleft palate)	*1*	*0*	*1*
Subsequently resulted in live birth	**13**	**13**	**26**
No abnormalities detected at birth	*13*	*13*	*26*
Abnormalities detected at birth	*0*	*0*	*0*
Other/Unknown	**26**	**20**	**46**
Total	**42**	**40**	**82**

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Several reports in the literature indicate that prostaglandins, including misoprostol, may have teratogenic effects in human beings. Skull defects, cranial nerve palsies, delayed growth and psychomotor development, facial malformation and limb defects have all been reported after exposure during the first trimester.

Animal Data

Teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure level based on body surface area) were carried out. Because of the antiprogestational activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from decreased progesterone levels.

Nonteratogenic Effects

The indication for use of Mifeprex in conjunction with misoprostol is for the termination of pregnancy through 49 days' duration of pregnancy (as dated from the first day of the last menstrual period). These drugs together disrupt pregnancy by causing decidual necrosis, myometrial contractions and cervical softening, leading to the expulsion of the products of conception.

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Nursing Mothers

It is not known whether mifepristone is excreted in human milk. Many hormones with a similar chemical structure, however, are excreted in breast milk. Since the effects of mifepristone on infants are unknown, breast-feeding women should consult with their health care provider to decide if they should discard their breast milk for a few days following administration of the medications.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The treatment procedure is designed to induce the vaginal bleeding and uterine cramping necessary to produce an abortion. Nearly all of the women who receive Mifeprex and misoprostol will report adverse reactions, and many can be expected to report more than one such reaction. About 90% of patients report adverse reactions following administration of misoprostol on day three of the treatment procedure. Those adverse events that occurred with a frequency greater than 1% in the U.S. and French trials are shown in Table 3.

Bleeding and cramping are expected consequences of the action of Mifeprex as used in the treatment procedure. Following administration of mifepristone and misoprostol in the French clinical studies, 80 to 90% of women reported bleeding more heavily than they do during a heavy menstrual period (see WARNINGS, Bleeding for additional information). Women also typically experience abdominal pain, including uterine cramping. Other commonly reported side effects were nausea, vomiting and diarrhea. Pelvic pain, fainting, headache, dizziness, and asthenia occurred rarely. Some adverse reactions reported during the four hours following administration of misoprostol were judged by women as being more severe than others: the percentage of women who considered any particular adverse event as severe ranged from 2 to 35% in the U.S. and French trials. After the third day of the treatment procedure, the number of reports of adverse reactions declined progressively in the French trials, so that by day 14, reports were rare except for reports of bleeding and spotting.

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Table 3

Type of Reported Adverse Events Following Administration of Mifepristone and Misoprostol in the U.S. and French Trials* (percentages)

	U.S. Trials	French Trials
Abdominal Pain (cramping)	96	NA
Uterine cramping	NA	83
Nausea	61	43
Headache	31	2
Vomiting	26	18
Diarrhea	20	12
Dizziness	12	1
Fatigue	10	NA
Back pain	9	NA
Uterine hemorrhage	5	NA
Fever	4	NA
Viral infections	4	NA
Vaginitis	3	NA
Rigors (chills/shaking)	3	NA
Dyspepsia	3	NA
Insomnia	3	NA
Asthenia	2	1
Leg pain	2	NA
Anxiety	2	NA
Anemia	2	NA
Leukorrhea	2	NA
Sinusitis	2	NA
Syncope	1	NA
Decrease in hemoglobin greater than 2 g/dL	NA	6
Pelvic pain	NA	2
Fainting	NA	2

* Only adverse reactions with incidence >1% are included.

OVERDOSAGE

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No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than threefold that recommended for termination of pregnancy. If a patient ingests a massive overdose, she should be observed closely for signs of adrenal failure.

The oral acute lethal dose of mifepristone in the mouse, rat and dog is greater than 1000 mg/kg (about 100 times the human dose recommended for termination of pregnancy).

DOSAGE AND ADMINISTRATION

Treatment with Mifeprex and misoprostol for the termination of pregnancy requires three office visits by the patient. Mifeprex should be prescribed only by physicians who have read and understood the prescribing information. Mifeprex may be administered only in a clinic, medical office, or hospital, by or under the supervision of a physician, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies. Physicians must also be able to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

Day One: Mifeprex Administration

Patients must read the Medication Guide and read and sign the PATIENT AGREEMENT before Mifeprex is administered.

Three 200 mg tablets (600 mg) of Mifeprex are taken in a single oral dose.

Day Three: Misoprostol Administration

The patient returns to the healthcare provider two days after ingesting Mifeprex. Unless abortion has occurred and has been confirmed by clinical examination or ultrasonographic scan, the patient takes two 200 µg tablets (400 µg) of misoprostol orally.

During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms (see ADVERSE REACTIONS). The patient should be given instructions on what to do if significant discomfort, excessive bleeding or other adverse reactions occur and should be given a phone number to call if she has questions following the administration of the misoprostol. In addition, the name and phone number of the physician who will be handling emergencies should be provided to the patient.

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Day 14: Post-Treatment Examination

Patients will return for a follow-up visit approximately 14 days after the administration of Mifeprex. This visit is very important to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred.

According to data from the U.S. and French studies, women should expect to experience bleeding or spotting for an average of nine to 16 days. Up to 8% of women may experience some type of bleeding for more than 30 days. Persistence of heavy or moderate vaginal bleeding at this visit, however, could indicate an incomplete abortion.

Patients who have an ongoing pregnancy at this visit have a risk of fetal malformation resulting from the treatment. Surgical termination is recommended to manage medical abortion treatment failures (see PRECAUTIONS, Pregnancy).

Adverse events, such as hospitalization, blood transfusion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol must be reported to Danco Laboratories. Please provide a brief clinical and administrative synopsis of any such adverse events in writing to:

Medical Director
Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4-Early Option (1-877-432-7596)

For immediate consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4 Early Option (1-877-432-7596).

HOW SUPPLIED

Mifeprex will be supplied only to licensed physicians who sign and return a Prescriber's Agreement. Distribution of Mifeprex will be subject to specific requirements imposed by the distributor, including procedures for storage, dosage tracking, damaged product returns and other matters. Mifeprex is a prescription drug, although it will not be available to the public through licensed pharmacies.

Mifeprex is supplied as light yellow, cylindrical, bi-convex tablets imprinted on one side with "MF." Each tablet contains 200 mg of mifepristone. Tablets are packaged in single dose blister packets containing three tablets and are supplied in individual cartons (National Drug Code 6487500103).

Store at 25^0C (77^0F); excursions permitted to 15-30^0C (59-86^0F) [see USP Controlled Room Temperature].

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MIFEPREX safely and effectively. See full prescribing information for MIFEPREX.

MIFEPREX® (mifepristone) tablets, for oral use
Initial U.S. Approval: 2000

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

See full prescribing information for complete boxed warning.

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use.

- **Atypical Presentation of Infection. Patients with serious bacterial infections and sepsis can present without fever, bacteremia or significant findings on pelvic examination. A high index of suspicion is needed to rule out serious infection and sepsis. (5.1)**
- **Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. (5.2)**

MIFEPREX is only available through a restricted program called the Mifepristone REMS Program (5 3).
Before prescribing MIFEPREX, inform the patient about these risks. Ensure the patient knows whom to call and what to do if they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort or general malaise for more than 24 hours after taking misoprostol.

----------INDICATIONS AND USAGE----------
MIFEPREX is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. (1)

----------DOSAGE AND ADMINISTRATION----------
- 200 mg MIFEPREX on Day 1, followed 24-48 hours after MIFEPREX dosing by 800 mcg buccal misoprostol. (2.1)
- Instruct the patient what to do if significant adverse reactions occur. (2.2)
- Follow-up is needed to confirm complete termination of pregnancy. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card (3)

----------CONTRAINDICATIONS----------
- Confirmed/suspected ectopic pregnancy or undiagnosed adnexal mass (4)
- Chronic adrenal failure (4)
- Concurrent long-term corticosteroid therapy (4)
- History of allergy to mifepristone, misoprostol, or other prostaglandins (4)
- Hemorrhagic disorders or concurrent anticoagulant therapy (4)
- Inherited porphyria (4)
- Intrauterine device (IUD) in place (4)

----------WARNINGS AND PRECAUTIONS----------
- Ectopic pregnancy: Exclude before treatment. (5.4)
- Rhesus immunization: Prevention needed as for surgical abortion. (5.5)

----------ADVERSE REACTIONS----------
Most common adverse reactions (>15%) are nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Danco Laboratories, LLC at 1-877-432-7596 or medicaldirector@earlyoptionpill.com or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- CYP3A4 inducers can lower mifepristone concentrations. (7.1)
- CYP3A4 inhibitors can increase mifepristone concentrations. Use with caution. (7.2)
- CYP3A4 substrate concentrations can be increased. Caution with coadministration of substrates with narrow therapeutic margin. (7.3)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Risk of fetal malformations in ongoing pregnancy if not terminated is unknown. (8.1)

See 17 for PATIENT COUNSELING INFORMATION, Medication Guide.

Revised: 01/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use. No causal relationship between the use of MIFEPREX and misoprostol and these events has been established.

- **Atypical Presentation of Infection. Patients with serious bacterial infections (e.g., *Clostridium sordellii*) and sepsis can present without fever, bacteremia, or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis *[see Warnings and Precautions (5.1)]*.**
- **Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding *[see Warnings and Precautions (5.2)]*.**

Because of the risks of serious complications described above, MIFEPREX is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Mifepristone REMS Program *[see Warnings and Precautions (5.3)]*.

Before prescribing MIFEPREX, inform the patient about the risk of these serious events. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting, or diarrhea) for more than 24 hours after taking misoprostol.

1 INDICATIONS AND USAGE

MIFEPREX is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Regimen

For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period. The duration of pregnancy may be determined from menstrual history and clinical examination. Assess the pregnancy by ultrasonographic scan if the duration of pregnancy is uncertain or if ectopic pregnancy is suspected.

Remove any intrauterine device (“IUD”) before treatment with MIFEPREX begins [*see Contraindications (4)*].

The dosing regimen for MIFEPREX and misoprostol is:

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- MIFEPREX 200 mg orally + misoprostol 800 mcg buccally
  - *Day One:* MIFEPREX Administration
    One 200 mg tablet of MIFEPREX is taken in a single oral dose.
  - *Day Two or Three:* Misoprostol Administration (minimum 24-hour interval between MIFEPREX and misoprostol)
    Four 200 mcg tablets (total dose 800 mcg) of misoprostol are taken by the buccal route.

    Tell the patient to place two 200 mcg misoprostol tablets in each cheek pouch (the area between the cheek and gums) for 30 minutes and then swallow any remnants with water or another liquid (see Figure 1).

    Figure 1

    

    2 pills between cheek and gum on left side + 2 pills between cheek and gum on right side

Patients taking MIFEPREX must take misoprostol within 24 to 48 hours after taking MIFEPREX. The effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours or more than 48 hours after mifepristone administration.

Because most women will expel the pregnancy within 2 to 24 hours of taking misoprostol *[see Clinical Studies (14)]*, discuss with the patient an appropriate location for them to be when taking the misoprostol, taking into account that expulsion could begin within 2 hours of administration.

2.2 Patient Management Following Misoprostol Administration

During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms *[see Adverse Reactions (6)].*

Give the patient:

- Instructions on what to do if significant discomfort, excessive vaginal bleeding or other adverse reactions occur
- A phone number to call if the patient has questions following the administration of the misoprostol
- The name and phone number of the healthcare provider who will be handling emergencies.

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2.3 Post-treatment Assessment: Day 7 to 14

Patients should follow-up with their healthcare provider approximately 7 to 14 days after the administration of MIFEPREX. This assessment is very important to confirm that complete termination of pregnancy has occurred and to evaluate the degree of bleeding. Termination can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan. Lack of bleeding following treatment usually indicates failure; however, prolonged or heavy bleeding is not proof of a complete abortion.

The existence of debris in the uterus (e.g., if seen on ultrasonography) following the treatment procedure will not necessarily require surgery for its removal.

Patients should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of women may experience some type of bleeding for more than 30 days. Persistence of heavy or moderate vaginal bleeding at the time of follow-up, however, could indicate an incomplete abortion.

If complete expulsion has not occurred, but the pregnancy is not ongoing, patients may be treated with another dose of misoprostol 800 mcg buccally. There have been rare reports of uterine rupture in women who took MIFEPREX and misoprostol, including women with prior uterine rupture or uterine scar and women who received multiple doses of misoprostol within 24 hours. Patients who choose to use a repeat dose of misoprostol should have a follow-up visit with their healthcare provider in approximately 7 days to assess for complete termination.

Surgical evacuation is recommended to manage ongoing pregnancies after medical abortion *[see Use in Specific Populations (8.1)]*. Advise the patient whether you will provide such care or will refer them to another provider as part of counseling prior to prescribing MIFEPREX.

2.4 Contact for Consultation

For consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4 Early Option (1-877-432-7596).

3 DOSAGE FORMS AND STRENGTHS

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card. MIFEPREX tablets are light yellow, cylindrical, and bi-convex tablets, approximately 11 mm in diameter and imprinted on one side with “MF.”

4 CONTRAINDICATIONS

- Administration of MIFEPREX and misoprostol for the termination of pregnancy (the “treatment procedure”) is contraindicated in patients with any of the following conditions:
  - Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy) *[see Warnings and Precautions (5.4)]*
  - Chronic adrenal failure (risk of acute adrenal insufficiency)
  - Concurrent long-term corticosteroid therapy (risk of acute adrenal insufficiency)
  - History of allergy to mifepristone, misoprostol, or other prostaglandins (allergic reactions including anaphylaxis, angioedema, rash, hives, and itching have been reported *[see Adverse Reactions (6.2)]*)
  - Hemorrhagic disorders or concurrent anticoagulant therapy (risk of heavy bleeding)

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- Inherited porphyrias (risk of worsening or of precipitation of attacks)

- Use of MIFEPREX and misoprostol for termination of intrauterine pregnancy is contraindicated in patients with an intrauterine device ("IUD") in place (the IUD might interfere with pregnancy termination). If the IUD is removed, MIFEPREX may be used.

5 WARNINGS AND PRECAUTIONS

5.1 Infection and Sepsis

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of MIFEPREX *[see Boxed Warning]*. Healthcare providers evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. A sustained (> 4 hours) fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (e.g., from *Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting, or diarrhea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. No causal relationship between MIFEPREX and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

5.2 Uterine Bleeding

Uterine bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications, and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock. Counsel patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion *[see Boxed Warning]*.

Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of all subjects may experience some type of bleeding for 30 days or more. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.

Decreases in hemoglobin concentration, hematocrit, and red blood cell count may occur in patients who bleed heavily.

Excessive uterine bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, surgical uterine evacuation, administration of saline infusions, and/or blood transfusions. Based on data from several large clinical trials, vasoconstrictor drugs were used in 4.3% of all subjects, there was a decrease in hemoglobin of more than 2 g/dL in 5.5% of subjects, and blood transfusions were administered to ≤ 0.1% of subjects. Because heavy bleeding requiring surgical uterine evacuation occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

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5.3 Mifepristone REMS Program

MIFEPREX is available only through a restricted program under a REMS called the Mifepristone REMS Program, because of the risks of serious complications *[see Warnings and Precautions (5.1, 5.2)]*.

Notable requirements of the Mifepristone REMS Program include the following:

- Prescribers must be certified with the program by completing the Prescriber Agreement Form.
- Patients must sign a Patient Agreement Form.
- MIFEPREX must only be dispensed to patients by or under the supervision of a certified prescriber, or by certified pharmacies on prescriptions issued by certified prescribers.

Further information is available at 1-877-4 Early Option (1-877-432-7596).

5.4 Ectopic Pregnancy

MIFEPREX is contraindicated in patients with a confirmed or suspected ectopic pregnancy because MIFEPREX is not effective for terminating ectopic pregnancies *[see Contraindications (4)].* Healthcare providers should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy because some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed MIFEPREX.

Patients who became pregnant with an IUD in place should be assessed for ectopic pregnancy.

5.5 Rhesus Immunization

The use of MIFEPREX is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Infection and sepsis *[see Warnings and Precautions (5.1)]*
- Uterine bleeding *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Information presented on common adverse reactions relies solely on data from U.S. studies, because rates reported in non-U.S. studies were markedly lower and are not likely generalizable to the U.S. population. In three U.S. clinical studies totaling 1,248 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally, women reported adverse reactions in diaries and in interviews at the follow-up visit. These studies enrolled generally healthy women of reproductive age without contraindications to mifepristone or misoprostol use according to the MIFEPREX product label. Gestational age was assessed prior to study enrollment using the date of the woman's last menstrual period, clinical evaluation, and/or ultrasound examination.

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About 85% of patients report at least one adverse reaction following administration of MIFEPREX and misoprostol, and many can be expected to report more than one such reaction. The most commonly reported adverse reactions (>15%) were nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness (see Table 1). The frequency of adverse reactions varies between studies and may be dependent on many factors, including the patient population and gestational age.

Abdominal pain/cramping is expected in all medical abortion patients and its incidence is not reported in clinical studies. Treatment with MIFEPREX and misoprostol is designed to induce uterine bleeding and cramping to cause termination of an intrauterine pregnancy. Uterine bleeding and cramping are expected consequences of the action of MIFEPREX and misoprostol as used in the treatment procedure. Most patients can expect bleeding more heavily than they do during a heavy menstrual period *[see Warnings and Precautions (5.2)]*.

Table 1 lists the adverse reactions reported in U.S. clinical studies with incidence >15% of women.

Table 1
Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. Clinical Studies

Adverse Reaction	# U.S. studies	Number of Evaluable Women	Range of frequency (%)	Upper Gestational Age of Studies Reporting Outcome
Nausea	3	1,248	51-75%	70 days
Weakness	2	630	55-58%	63 days
Fever/chills	1	414	48%	63 days
Vomiting	3	1,248	37-48%	70 days
Headache	2	630	41-44%	63 days
Diarrhea	3	1,248	18-43%	70 days
Dizziness	2	630	39-41%	63 days

One study provided gestational-age stratified adverse reaction rates for women who were 57-63 and 64-70 days; there was little difference in frequency of the reported common adverse reactions by gestational age.

Information on serious adverse reactions was reported in six U.S. and four non-U.S. clinical studies, totaling 30,966 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally. Serious adverse reaction rates were similar between U.S. and non-U.S. studies, so rates from both U.S. and non-U.S. studies are presented. In the U.S. studies, one studied women through 56 days gestation, four through 63 days gestation, and one through 70 days gestation, while in the non-U.S. studies, two studied women through 63 days gestation, and two through 70 days gestation. Serious adverse reactions were reported in <0.5% of women. Information from the U.S. and non-U.S. studies is presented in Table 2.

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Table 2
Serious Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. and Non-U.S. Clinical Studies

Adverse Reaction	U.S.			Non-U.S.		
	# of studies	Number of Evaluable Women	Range of frequency (%)	# of studies	Number of Evaluable Women	Range of frequency (%)
Transfusion	4	17,774	0.03-0.5%	3	12,134	0-0.1%
Sepsis	1	629	0.2%	1	11,155	<0.01%*
ER visit	2	1,043	2.9-4.6%	1	95	0
Hospitalization Related to Medical Abortion	3	14,339	0.04-0.6%	3	1,286	0-0.7%
Infection without sepsis	1	216	0	1	11,155	0.2%
Hemorrhage	NR	NR	NR	1	11,155	0.1%

NR= Not reported
* This outcome represents a single patient who experienced death related to sepsis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of MIFEPREX and misoprostol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and infestations: post-abortal infection (including endometritis, endomyometritis, parametritis, pelvic infection, pelvic inflammatory disease, salpingitis)
Blood and the lymphatic system disorders: anemia
Immune system disorders: allergic reaction (including anaphylaxis, angioedema, hives, rash, itching)
Psychiatric disorders: anxiety
Cardiac disorders: tachycardia (including racing pulse, heart palpitations, heart pounding)
Vascular disorders: syncope, fainting, loss of consciousness, hypotension (including orthostatic), light-headedness
Respiratory, thoracic and mediastinal disorders: shortness of breath
Gastrointestinal disorders: dyspepsia
Musculoskeletal, connective tissue and bone disorders: back pain, leg pain
Reproductive system and breast disorders: uterine rupture, ruptured ectopic pregnancy, hematometra, leukorrhea
General disorders and administration site conditions: pain

7 DRUG INTERACTIONS

7.1 Drugs that May Reduce MIFEPREX Exposure (Effect of CYP 3A4 Inducers on MIFEPREX)

CYP450 3A4 is primarily responsible for the metabolism of mifepristone. CYP3A4 inducers such as rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (such as phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum concentrations of mifepristone). Whether this action has an impact on the efficacy of the dose

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regimen is unknown. Refer to the follow-up assessment *[see Dosage and Administration (2.3)]* to verify that treatment has been successful.

7.2 Drugs that May Increase MIFEPREX Exposure (Effect of CYP 3A4 Inhibitors on MIFEPREX)

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum concentrations of mifepristone). MIFEPREX should be used with caution in patients currently or recently treated with CYP 3A4 inhibitors.

7.3 Effects of MIFEPREX on Other Drugs (Effect of MIFEPREX on CYP 3A4 Substrates)

Based on *in vitro* inhibition information, coadministration of mifepristone may lead to an increase in serum concentrations of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

MIFEPREX is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Risks to pregnant patients are discussed throughout the labeling.

Refer to misoprostol labeling for risks to pregnant patients with the use of misoprostol.

The risk of adverse developmental outcomes with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol is unknown; however, the process of a failed pregnancy termination could disrupt normal embryo-fetal development and result in adverse developmental effects. Birth defects have been reported with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol. In animal reproduction studies, increased fetal losses were observed in mice, rats, and rabbits and skull deformities were observed in rabbits with administration of mifepristone at doses lower than the human exposure level based on body surface area.

Data

Animal Data

In teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure based on body surface area), because of the antiprogestational activity of mifepristone,fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from inhibition of progesterone action.

8.2 Lactation

MIFEPREX is present in human milk. Limited data demonstrate undetectable to low levels of the drug in human milk with the relative (weight-adjusted) infant dose 0.5% or less as compared to maternal dosing. There is no information on the effects of MIFEPREX in a regimen with

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misoprostol in a breastfed infant or on milk production. Refer to misoprostol labeling for lactation information with the use of misoprostol. The developmental and health benefits of breast-feeding should be considered along with any potential adverse effects on the breast-fed child from MIFEPREX in a regimen with misoprostol.

8.4 Pediatric Use

Safety and efficacy of MIFEPREX have been established in pregnant females. Data from a clinical study of MIFEPREX that included a subset of 322 females under age 17 demonstrated a safety and efficacy profile similar to that observed in adults.

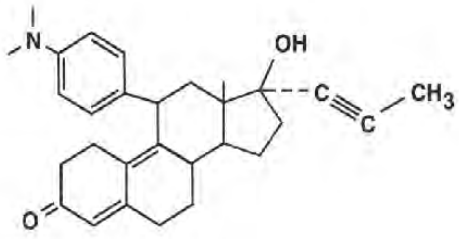
10 OVERDOSAGE

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than 1800 mg (ninefold the recommended dose for medical abortion). If a patient ingests a massive overdose, the patient should be observed closely for signs of adrenal failure.

11 DESCRIPTION

MIFEPREX tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical, and bi-convex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11ß-[*p*-(Dimethylamino)phenyl]-17ß-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is $C_{29}H_{35}NO_2$. Its structural formula is:



The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 192-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit, and monkey), the compound inhibits the activity of endogenous or exogenous progesterone, resulting in effects on the uterus and cervix that, when combined with misoprostol, result in termination of an intrauterine pregnancy.

During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity

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of prostaglandins.

12.2 Pharmacodynamics

Use of MIFEPREX in a regimen with misoprostol disrupts pregnancy by causing decidual necrosis, myometrial contractions, and cervical softening, leading to the expulsion of the products of conception.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women.

Antiglucocorticoid and antiandrogenic activity: Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity. The activity of the glucocorticoid dexamethasone in rats was inhibited following doses of 10 to 25 mg/kg of mifepristone. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotropic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

12.3 Pharmacokinetics

Mifepristone is rapidly absorbed after oral ingestion with non-linear pharmacokinetics for Cmax after single oral doses of 200 mg and 600 mg in healthy subjects.

Absorption

The absolute bioavailability of a 20 mg mifepristone oral dose in females of childbearing age is 69%. Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 ± 1.0 mg/L occurring approximately 90 minutes after ingestion.

Following oral administration of a single dose of 200 mg in healthy men (n=8), mean Cmax was 1.77 ± 0.7 mg/L occurring approximately 45 minutes after ingestion. Mean $AUC_{0-\infty}$ was 25.8 ± 6.2 mg*hr/L.

Distribution

Mifepristone is 98% bound to plasma proteins, albumin, and α_1-acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance.

Elimination

Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11ß; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Excretion

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum concentrations are undetectable by 11 days.

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Specific Populations

The effects of age, hepatic disease and renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed.

Mutagenesis

Results from studies conducted *in vitro* and in animals have revealed no genotoxic potential for mifepristone. Among the tests carried out were: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pompe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; *in vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice.

Impairment of Fertility

In rats, administration of 0.3 mg/kg mifepristone per day caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effects on reproductive performance were observed.

14 CLINICAL STUDIES

Safety and efficacy data from clinical studies of mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally through 70 days gestation are reported below. Success was defined as the complete expulsion of the products of conception without the need for surgical intervention. The overall rates of success and failure, shown by reason for failure based on 22 worldwide clinical studies (including 7 U.S. studies) appear in Table 3.

The demographics of women who participated in the U.S. clinical studies varied depending on study location and represent the racial and ethnic variety of American females. Females of all reproductive ages were represented, including females less than 18 and more than 40 years of age; most were 27 years or younger.

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Table 3
Outcome Following Treatment with Mifepristone (oral) and Misoprostol (buccal) Through 70 Days Gestation

	U.S. Trials	Non-U.S. Trials
N	16,794	18,425
Complete Medical Abortion	97.4%	96.2%
Surgical Intervention*	2.6%	3.8%
Ongoing Pregnancy**	0.7%	0.9%

* Reasons for surgical intervention include ongoing pregnancy, medical necessity, persistent or heavy bleeding after treatment, patient request, or incomplete expulsion.
** Ongoing pregnancy is a subcategory of surgical intervention, indicating the percent of women who have surgical intervention due to an ongoing pregnancy.

The results for clinical studies that reported outcomes, including failure rates for ongoing pregnancy, by gestational age are presented in Table 4.

Table 4
Outcome by Gestational Age Following Treatment with Mifepristone and Misoprostol (buccal) for U.S. and Non-U.S. Clinical Studies

	≤49 days			50-56 days			57-63 days			64-70 days		
	N	**%**	**Number of Evaluable Studies**	**N**	**%**	**Number of Evaluable Studies**	**N**	**%**	**Number of Evaluable Studies**	**N**	**%**	**Number of Evaluable Studies**
Complete medical abortion	12,046	98.1	10	3,941	96.8	7	2,294	94.7	9	479	92.7	4
Surgical intervention for ongoing pregnancy	10,272	0.3	6	3,788	0.8	6	2,211	2	8	453	3.1	3

One clinical study asked subjects through 70 days gestation to estimate when they expelled the pregnancy, with 70% providing data. Of these, 23-38% reported expulsion within 3 hours and over 90% within 24 hours of using misoprostol.

16 HOW SUPPLIED/STORAGE AND HANDLING

is only available through a restricted program called the Mifepristone REMS Program *[see Warnings and Precautions (5.3)].*

MIFEPREX is supplied as light yellow, cylindrical, and bi-convex tablets imprinted on one side with “MF.” Each tablet contains 200 mg of mifepristone. One tablet is individually blistered on one blister card that is packaged in an individual package (National Drug Code 64875-001-01).

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

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17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide), included with each package of MIFEPREX. Additional copies of the Medication Guide are available by contacting Danco Laboratories at 1-877-4 Early Option (1-877-432-7596) or from www.earlyoptionpill.com.

Serious Infections and Bleeding

- Inform the patient that uterine bleeding and uterine cramping will occur [*see Warnings and Precautions (5.2)*].
- Advise the patient that serious and sometimes fatal infections and bleeding can occur very rarely [*see Warnings and Precautions (5.1, 5.2)*].
- MIFEPREX is only available through a restricted program called the Mifepristone REMS Program [*see Warnings and Precautions (5.3)*]. Under the Mifepristone REMS Program:
    - Patients must sign a Patient Agreement Form.
    - MIFEPREX is only dispensed by or under the supervision of certified prescribers or by certified pharmacies on prescriptions issued by certified prescribers.

Provider Contacts and Actions in Case of Complications

- Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, or if the patient experiences complications including prolonged heavy bleeding, severe abdominal pain, or sustained fever *[see Boxed Warning]*.
-

Compliance with Treatment Schedule and Follow-up Assessment

- Advise the patient that it is necessary to complete the treatment schedule, including a follow-up assessment approximately 7 to14 days after taking MIFEPREX *[see Dosage and Administration (2.3)]*.
- Explain that
    - prolonged heavy vaginal bleeding is not proof of a complete abortion,
    - if the treatment fails and the pregnancy continues, the risk of fetal malformation is unknown,
    - it is recommended that ongoing pregnancy be managed by surgical termination *[see Dosage and Administration (2.3)]*. Advise the patient whether you will provide such care or will refer them to another provider.

Subsequent Fertility

- Inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses.
- Inform the patient that contraception can be initiated as soon as pregnancy expulsion has been confirmed, or before resuming sexual intercourse.

MIFEPREX is a registered trademark of Danco Laboratories, LLC.

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Manufactured for:
Danco Laboratories, LLC
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www.earlyoptionpill.com

03/2023

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MEDICATION GUIDE

Mifeprex (MIF-eh-prex) (mifepristone tablets, for oral use

Read this information carefully before taking Mifeprex and misoprostol. It will help you understand how the treatment works. This Medication Guide does not take the place of talking with your healthcare provider.

What is the most important information I should know about Mifeprex?

What symptoms should I be concerned with? Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Seeking medical attention as soon as possible is needed in these circumstances. Serious infection has resulted in death in a very small number of cases. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your healthcare provider. You can write down your healthcare provider's telephone number here _____.

Be sure to contact your healthcare provider promptly if you have any of the following:

- **Heavy Bleeding.** Contact your healthcare provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C).
- **Abdominal Pain or "Feeling Sick."** If you have abdominal pain or discomfort, or you are "feeling sick," including weakness, nausea, vomiting, or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your healthcare provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).
- **Fever.** In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your healthcare provider right away. Fever may be a symptom of a serious infection or another problem.

If you cannot reach your healthcare provider, go to the nearest hospital emergency room.

What to do if you are still pregnant after Mifeprex with misoprostol treatment. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy. In many cases, this surgical procedure can be done in the office/clinic. The chance of birth defects if the pregnancy is not ended is unknown.

Talk with your healthcare provider. Before you take Mifeprex, you should read this Medication Guide and you and your healthcare provider should discuss the benefits and risks of your using Mifeprex.

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What is Mifeprex?

Mifeprex is used in a regimen with another prescription medicine called misoprostol, to end an early pregnancy. Early pregnancy means it is 70 days (10 weeks) or less since your last menstrual period began. Mifeprex is not approved for ending pregnancies that are further along. Mifeprex blocks a hormone needed for your pregnancy to continue. When you use Mifeprex on Day 1, you also need to take another medicine called misoprostol 24 to 48 hours after you take Mifeprex, to cause the pregnancy to be passed from your uterus.

The pregnancy is likely to be passed from your uterus within 2 to 24 hours after taking Mifeprex and misoprostol. When the pregnancy is passed from the uterus, you will have bleeding and cramping that will likely be heavier than your usual period. About 2 to 7 out of 100 women taking Mifeprex will need a surgical procedure because the pregnancy did not completely pass from the uterus or to stop bleeding.

Who should not take Mifeprex?

Some patients should not take Mifeprex. Do not take Mifeprex if you:

- Have a pregnancy that is more than 70 days (10 weeks). Your healthcare provider may do a clinical examination, an ultrasound examination, or other testing to determine how far along you are in pregnancy.
- Are using an IUD (intrauterine device or system). It must be taken out before you take Mifeprex.
- Have been told by your healthcare provider that you have a pregnancy outside the uterus (ectopic pregnancy).
- Have problems with your adrenal glands (chronic adrenal failure).
- Take a medicine to thin your blood.
- Have a bleeding problem.
- Have porphyria.
- Take certain steroid medicines.
- Are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Ask your healthcare provider if you are not sure about all your medical conditions before taking this medicine to find out if you can take Mifeprex.

What should I tell my healthcare provider before taking Mifeprex?

Before you take Mifeprex, tell your healthcare provider if you:

- cannot follow-up within approximately 7 to 14 days of your first visit
- are breastfeeding. Mifeprex can pass into your breast milk. The effect of the Mifeprex and misoprostol regimen on the breastfed infant or on milk production is unknown.
- are taking medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
  Mifeprex and certain other medicines may affect each other if they are used together. This can cause side effects.

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How should I take Mifeprex?

- Mifeprex will be given to you by a healthcare provider or pharmacy.
- You and your healthcare provider will plan the most appropriate location for you to take the misoprostol, because it may cause bleeding, cramps, nausea, diarrhea, and other symptoms that usually begin within 2 to 24 hours after taking it.
- Most women will pass the pregnancy within 2 to 24 hours after taking the misoprostol tablets.

Follow the instruction below on how to take Mifeprex and misoprostol:

Mifeprex (1 tablet) orally + misoprostol (4 tablets) buccally

Day 1:

- Take 1 Mifeprex tablet by mouth.

24 to 48 hours after taking Mifeprex:

- Take 4 misoprostol tablets by placing 2 tablets in each cheek pouch (the area between your teeth and cheek - see Figure A) for 30 minutes and then swallow anything left over with a drink of water or another liquid.
- The medicines may not work as well if you take misoprostol sooner than 24 hours after Mifeprex or later than 48 hours after Mifeprex.
- Misoprostol often causes cramps, nausea, diarrhea, and other symptoms. Your healthcare provider may send you home with medicines for these symptoms.



Figure A (2 tablets between your left cheek and gum and 2 tablets between your right cheek and gum).

Follow-up Assessment at Day 7 to 14:

- This follow-up assessment is very important. You must follow-up with your healthcare provider about 7 to 14 days after you have taken Mifeprex to be sure you are well and that you have had bleeding and the pregnancy has passed from your uterus.
- Your healthcare provider will assess whether your pregnancy has passed from your uterus. If your pregnancy continues, the chance that there may be birth defects is unknown. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy.
- If your pregnancy has ended, but has not yet completely passed from your uterus, your provider will talk with you about other choices you have, including waiting, taking another dose of misoprostol, or having a surgical procedure to empty your uterus.

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When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

What should I avoid while taking Mifeprex and misoprostol?

Do not take any other prescription or over-the-counter medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your healthcare provider about them because they may interfere with the treatment. Ask your healthcare provider about what medicines you can take for pain and other side effects.

What are the possible side effects of Mifeprex and misoprostol?

Mifeprex may cause serious side effects. See "What is the most important information I should know about Mifeprex?"

Cramping and bleeding. Cramping and vaginal bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must follow-up with your healthcare provider approximately 7 to 14 days after taking Mifeprex. See "How should I take Mifeprex?" for more information on your follow-up assessment. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take 24 to 48 hours after Mifeprex. Bleeding or spotting can be expected for an average of 9 to16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of passing the pregnancy.

The most common side effects of Mifeprex treatment include: nausea, weakness, fever/chills, vomiting, headache, diarrhea and dizziness. Your provider will tell you how to manage any pain or other side effects. These are not all the possible side effects of Mifeprex.

Call your healthcare provider for medical advice about any side effects that bother you or do not go away. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Mifeprex.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about Mifeprex. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider for information about Mifeprex that is written for healthcare professionals.

For more information about Mifeprex, go to www.earlyoptionpill.com or call 1-877-4 Early Option (1-877-432-7596).

Manufactured for: *Danco Laboratories, LLC*
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2024 CLINICAL POLICY GUIDELINES FOR ABORTION CARE



NATIONAL ABORTION FEDERATION

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2024
Clinical Policy Guidelines for Abortion Care

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The National Abortion Federation is the professional association of abortion providers. Our mission is to unite, represent, serve, and support abortion providers in delivering patient-centered, evidence-based care.

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Introduction

The National Abortion Federation's (NAF) mission is to unite, represent, serve, and support abortion providers in delivering patient-centered, evidence-based care. An important part of this work is to develop and maintain evidence-based guidelines and standards as well as to educate providers in the latest technologies and techniques.(1) NAF's programs make it possible for people to obtain the highest quality abortion care.

Like its precursors, the 2024 edition of NAF's *Clinical Policy Guidelines for Abortion Care* (CPGs) serve to provide guidance for facilities to use in establishing their clinical policies. The CPGs are developed by consensus, based on rigorous review of the relevant medical literature and patient outcomes.(2-6) These guidelines are intended to provide parameters to ensure access to the highest quality abortion care.

NAF's *Clinical Policy Guidelines* were first published in 1996 and have been revised annually since then. Since inception, they have been based on the methodology described by David Eddy, MD, in *A Manual for Assessing Health Practices and Designing Practice Policies: The Explicit Approach*.(7) Clinical policy guidelines are defined as a systematically developed series of statements, which assist practitioners and patients in making decisions about appropriate health care. They represent an attempt to distill a large body of medical knowledge into a convenient and readily usable format. Since 2018, we have incorporated the Institute of Medicine's recommendations.(8)

When the outcomes of an intervention are known, practitioner choices are limited. But when the outcomes of an intervention are uncertain or variable, and/or when patients' preferences for those outcomes are uncertain or variable, practitioners must be given flexibility to tailor a policy to individual cases. This is addressed by having three types of policies according to their intended flexibility: standards, recommendations, and options:

1) **STANDARDS** are intended to be applied in virtually all cases. Deviations will be rare and difficult to justify.

2) **RECOMMENDATIONS** are steering in nature. They do not have the force of standards, but when not adhered to, there should be documented, rational clinical justification. They allow some latitude in clinical management.

3) **OPTIONS** are neutral with respect to a treatment choice. They merely note that different interventions are available, and that different people make different choices. They may contribute to the educational process, and they require no justification.

NAF's CPGs include a list of references for each section and include discussion material for clarification when appropriate. These guidelines are meant to be living documents, subject to revision as new medical evidence becomes available.

Medline was searched monthly on Pubmed. An automated search using the following terms was created and checked monthly:

((((abortion induced [MeSH Major Topic]) OR mifepristone) OR medical abortion) OR (dilation and evacuation)) OR uterine aspiration.

The search was limited to clinical trials, case reports, comparative studies, reviews, meta-analysis, and systematic reviews in humans from January 1, 2022. The search run on December 31, 2023, yielded 667 results. In addition, abstracts from major conferences, references in articles, and related non-abortion searches (for example, in analgesia and sedation) were run.

Studies were included that addressed CPG topics and either changed, updated, or substantially added support to a current recommendation. Studies were excluded that were not relevant, had poor methodology or inconclusive results, or did not substantially add to a current recommendation.

Thirty-three new papers were included in the 2024 CPGs because they changed one or more statements, supported a new recommendation, or substantially improved the level of evidence supporting a current statement. Changes to each policy statement were drafted by NAF's Interim Medical Advisor, Alice Mark, MD, MSc, and Senior Director of Clinical Services, Reesa Roberts, PA-C, MSPA, based on the included papers. These papers were reviewed by the NAF Clinical Policy Committee and changes to each policy statement were edited and approved by the entire committee. A synthesis of how the new study altered the existing policy statement will be available in an online module.

NAF 2022-2023 Clinical Policy Committee members:

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Tiffany Hailstorks, MD, MPH
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Note: The *Clinical Policy Guidelines for Abortion Care* are not intended to educate members regarding legal and regulatory issues, which may affect abortion practice. It is expected that administrators, staff, and clinicians will be aware of pertinent local, state/provincial/territorial, and national laws as well as the requirements and limitations of their individual duties and scope of professional practice. NAF provider members should ensure that all employees have access to appropriate resources for information and support.

Commitment to diversity, inclusion, equity, and anti-racism: Abortion is affected by structural, institutional, interpersonal, and individual-level racism that affects safety and quality of care, and degrades the abortion experience for many of those who seek it.(9,10) NAF holds itself accountable to anti-racist principles and endorses evidence-based clinical guidelines that are not a source of harm but promote health for people with historically marginalized identities, including but not limited to Black, Indigenous, and People of Color, lesbian, gay, bisexual, transgender, gender expansive, intersex, asexual and two spirit people, immigrants, refugees, people with limited financial resources, people with limited exposure to formal education, people who don't speak the dominant language, young people, people of all body sizes, and people with disabilities, chronic illness, or other conditions.

A note about language: NAF and our members understand and respect that not every person with the capacity for pregnancy identifies as a woman. We embrace and respect each individual's gender identity, expression, and experience, and desire to be inclusive and helpful to all who need information about abortion or support as providers. While we do make an effort to use gender-inclusive language (person/people/they/them/patient) in this document and our other materials, we do also use woman/women in some cases. We do so in order to acknowledge the long history of gender discrimination targeting women, the specialized health care that many of our members provide, and the need to be clear to various audiences.

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Notes on Formatting

As presented here, standards, recommendations, and options are hierarchical in nature. It is therefore expected that clinical practices will favor the highest level of guidance available on a given point. To clarify the relationships of Recommendations and/or Options that are subordinate to higher level Standards and/or Recommendations, NAF's guidelines are numbered and formatted according to the following scheme:

Within each section, **Standards** are numbered consecutively starting with the section number with the standard to the right of a decimal. For example, the first standard in Section 1 will be Standard 1.1.

Recommendations are also numbered consecutively within each main subject heading, with numbers that are placed to the right of a second decimal point. Where a recommendation follows a standard, it is included below the standard and the number of that standard will be found to the left of the decimal point (e.g., Recommendation 1.1.1). Where the recommendation stands alone and is not related to a specific standard, there will be a zero in the position to the left of the decimal point (e.g., Recommendation 1.0.1).

The consecutive numbers denoting *Options* within each main subject heading are placed to the right of the third decimal point. Where an option follows a preceding standard or recommendation, it is indented below that standard or recommendation and the numbers identifying that option will be found to the right of a third decimal point added to the end of the standard or recommendation (e.g., Option 1.1.0.1 or Option 1.1.1.1). Where the option stands alone and is not related to a specific standard or recommendation, zeros will be placed in the position for the standard and recommendation (e.g., Option 1.0.0.1).

1. Who Can Provide Abortions

Policy Statement: Abortion should be decriminalized. Abortion is a safe procedure when provided by qualified individuals.(1) The vast majority of abortions, including uterine aspiration, dilation and evacuation, and medication abortion after the first trimester, can be safely provided in medical offices or freestanding clinics.(2) Telemedicine can be safely used to provide abortion care, including medication abortion provision, informed consent, and follow-up.(3, 4) People may manage all or part of an abortion on their own.(5, 6)

Standard 1.1
Abortion will be provided by trained providers. This category is intended to include physicians from various specialties as well as nurse midwives, nurse practitioners, physician assistants, registered nurses, other health professionals and community-based providers.(7)

Recommendation 1.1.1
Documentation specifying privileges in accordance with each practitioner's scope of practice should be maintained.

Recommendation 1.1.2
Complex Family Planning accreditation or sub-specialty status are not necessary or required for the provision of safe abortion care.

Recommendation 1.1.3
Neither hospital admitting privileges nor transfer agreements are needed to provide safe abortion care.(2)

Recommendation 1.1.4
Community-based providers with appropriate training may safely provide care.(6, 8, 9)

Standard 1.2
People may manage all or part of an abortion on their own. People using self-managed abortion need access to evidence-based information, effective medications, and supportive services before, during, and after the abortion.

Recommendation 1.2.1
Don't engage in any behavior that criminalizes abortion or those who use it.

Standard 1.3
All individuals providing abortions must have received training to competency in abortion care, including the prevention, recognition, and management of complications.

Recommendation 1.3.1
When making changes to clinical practice, consider values clarification for providers and staff to optimize patient-centered care.

Standard 1.4
All individuals providing ancillary services must have appropriate training, for example, in ultrasound, counseling, sedation, laboratory, infection control, and other services.

Standard 1.5
Appropriate referrals must be available for patients who cannot be cared for by an individual or facility.

Discussion: Values clarification is an essential part of hiring, training, and retaining abortion staff. Values clarification should be done routinely but particularly needs to be revisited if a clinic expands its services, increases gestational limits, if staff changes roles at clinic, or when new staff are hired. Resources for values clarification can be found on NAF's members-only website at https://members.prochoice.org in the Learning Lab.

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2. Patient Education, Informed Consent, and Counseling

Policy Statement: A person must give voluntary, informed consent prior to an abortion and express understanding. The goal of abortion education is to give people the knowledge they need to make an informed decision about whether to have an abortion and which type of procedure to choose.

Informed Consent

Standard 2.1
The practitioner must ensure that accurate information is provided about the abortion process and its alternatives, and the potential risks and benefits. The patient must have the opportunity to have any questions answered to their satisfaction prior to intervention.

> *Option 2.1.0.1*
> Information may be provided either on an individual basis, in group sessions, or with appropriate patient information materials, and can be done in person or remotely.(1)

Standard 2.2
Documentation must show that the patient affirms their decision to have an abortion, that their decision is voluntary, and that they are aware of the potential risks and benefits of the abortion procedure. Although other risks may be addressed, at a minimum, the following risks must be included (2-6):

1) Hemorrhage
2) Infection
3) Continuing pregnancy
4) Death.

Recommendation 2.2.1
For abortion procedures (uterine aspiration or dilation and evacuation), the additional risks must be included:

5) Perforation
6) Damage to organs including hysterectomy.

Patient Education and Counseling

Standard 2.3
Each person must have a private opportunity to ask questions about the abortion.(7-9)

Standard 2.4
A person must undergo the abortion as expeditiously as possible in accordance with good medical practice.

Recommendation 2.4.1
Information about aftercare and contraception must be available. The importance of contacting the provider for any concerns should be emphasized.

Recommendation 2.4.2
Evidence-based guidelines for contraceptive counseling should be followed.(10)

Standard 2.5
All reasonable precautions must be taken to ensure confidentiality.

Recommendation 2.5.1
The person should be informed of the communication of information to any third party.

Recommendation 2.5.2
People need to know which individuals or agencies may receive communications regarding services. This information should include confidentiality implications of using insurance or governmental health care coverage.

Discussion: Informed consent and abortion counseling are two different processes. The goal of informed consent is to assure that the person's decision is voluntary and informed, and that they understand the risks and benefits of the abortion procedure. Education and counseling includes a discussion of the feelings and concerns expressed by the patient, which may include help with decision-making and contraceptive choices, values clarification, or referral to other professionals. Although the large majority of people who present for abortion are sure of their decision,(8) a referral to community services should be available if that becomes necessary or the needs of the patient are outside the scope of training of clinic staff.

Where abortion is safe and legal, the risk of death overall is less than 1 per 100,000 abortions.(5, 6, 11) Pregnancy-related deaths are significantly higher.(12)

Risks of pregnancy-related death by country, 2020 WHO data (12)

Country	Maternal mortality ratio*
Canada	11
United States	21
Mexico	59
Colombia	75

*deaths per 100,000 live births

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3. Infection Prevention and Control

Policy Statement: Patients and health care personnel are at risk for exposure to blood borne pathogens, aerosol transmissible disease, and other potentially infectious material. Infectious material may be transmitted to patients when proper engineering* and work-practice controls,† which reduce exposure, are not followed. Proper handling of chemicals and other materials needed for proper disinfection is important to prevent harm to staff. Prevention and treatment of infection will reduce post-abortion morbidity.

Standard 3.1
Proper engineering and work-practice controls must be in place to reduce exposure of patient and staff to infectious agents. Clinics must protect employees and patients from being exposed to biohazardous material.(1)

Standard 3.2
Hands must be washed or disinfected before and after patient contact.(2-4)

Standard 3.3
Personal protective equipment must be provided to all staff.(1, 5-8)

Recommendation 3.3.1
New staff with potential exposure should have an initial training as part of orientation.

Recommendation 3.3.2
Periodic facility-level training should occur at least every three years.

Recommendation 3.3.3
Hepatitis B vaccine should be provided at no cost to the staff.

Standard 3.4
Exposure control plans must be established and followed.(5, 7, 9)

Recommendation 3.4.1
Post-exposure evaluation, prophylaxis, and follow-up should be available to exposed patients or staff for any potentially infectious agent, regardless of source.

Standard 3.5
All instruments coming into contact with patients must be properly cleaned and disinfected between patients.(10)

*Engineering control—available technology and devices that isolate or remove hazards from the workplace, such as puncture-resistant sharps disposal containers, needleless systems for withdrawing medications, and safer sharps devices.

†Work-practice control—an alteration in the way a task is performed that reduces the likelihood that an employee will be exposed to blood or other potentially infectious materials, for example, prohibiting needle recapping.

Standard 3.6
All instruments entering the uterus must be sterile.

Option 3.6.0.1
The cervix and vagina may be cleansed with a bactericidal agent though randomized trials have failed to show a benefit to this practice.(11)

Standard 3.7
Tubing and manual uterine aspirators must be high-level disinfected or sterilized.(10)

Standard 3.8
All tissue removed in the facility must be considered biohazardous and be handled, stored, and disposed of in a manner that minimizes the risk of exposure. A protocol for tissue handling, storage, and disposal must be in place.

Standard 3.9
Sharps containers must be readily available. Sharps containers must be made of rigid, puncture-resistant material, have a tight-fitting lid, and be labeled as hazardous material.

Standard 3.10
Routine antibiotic prophylaxis must be used for uterine aspiration and dilation and evacuation.(12, 13)

Recommendation 3.10.1
All patients having uterine aspiration or dilation and evacuation should receive antibiotics pre-procedure.(11, 14, 15)

Recommendation 3.10.2
Prophylactic antibiotics should not be continued after the day of the procedure.(11, 14, 15)

Option 3.10.2.1
Antibiotics may be initiated at the time of insertion of osmotic dilators.

Option 3.10.2.2
Antibiotics are not required for patients choosing medication abortion.(16) Insufficient evidence exists to support routine antibiotic prophylaxis for medication abortion.

Recommendation 3.10.3
Additional antibiotics are not recommended for endocarditis prophylaxis in patients with heart murmurs or other cardiac conditions.(13, 17, 18)

Recommendation 3.10.4
Patients should be offered or referred for testing for chlamydia and gonorrhea according to local guidelines.(19) Testing should not delay the procedure.

Option 3.10.4.1
Empiric treatment of chlamydia may be considered for patients with history, signs, or symptoms of current infection.

Standard 3.11
Diagnosed infection must be appropriately treated.

Recommendation 3.11.1
For documented infections of the reproductive tract, evidence-based regimens should be followed.(19, 20)

Discussion: Regulatory agency policies (see references) may be helpful in developing exposure plans that protect personnel and patients from potentially infectious material, including aerosol transmissible diseases. A sample exposure control plan can be found in the online learning resources on NAF's members-only site at https://members.prochoice.org. Techniques for collection, labeling, and disposal of biohazardous material and for the processing of instruments are integral to any complete plan.

Expedited partner treatment may be considered for patients with a known diagnosis of a sexually transmitted infection.(21, 22)

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4. Laboratory Practice

Policy Statement: Rh alloimmunization may jeopardize the health of a subsequent pregnancy.(1) There is no evidence that providing anti-D immunoglobulin in early pregnancy prevents alloimmunization and poor outcome in a subsequent pregnancy, however, it is recommended later in pregnancy.(2-7)

Standard 4.1
Rh status testing must be offered to all people with unknown Rh status over 12 weeks from the last menstrual period (LMP) and anti-D immune globulin must be offered to patients over 12 weeks who are Rh negative.

Recommendation 4.1.1
Below 12 weeks from the last menstrual period, patients and providers may forego Rh testing and anti-D immune globulin for patients who are Rh negative.(2-7) This recommendation applies to both medication abortion and aspiration procedures.

Recommendation 4.1.2
If anti-D immune globulin is not administered in the facility, other arrangements for administration must be documented.

Recommendation 4.1.3
A person who is over 12 weeks LMP and declines Rh testing or anti-D immune globulin should sign an informed waiver.

Recommendation 4.1.4
Documentation of Rh status may be obtained by on-site testing, outside source, or self-report.

Recommendation 4.1.5
Additional testing for either sensitization or other antibodies is not required in patients undergoing pregnancy termination, including testing for Du (“weak D”).

Standard 4.2
Anemia and the risk of bleeding must be evaluated.(8)

Recommendation 4.2.1
Hemoglobin or hematocrit testing should be readily available.

Recommendation 4.2.2
Prior to uterine aspiration and medication abortion in the first trimester, hemoglobin/ hematocrit and other laboratory evaluation should be done as indicated by medical history and patient symptoms. Routine hemoglobin or hematocrit has not been shown to improve outcomes.

Recommendation 4.2.3
Hemoglobin or hematocrit should be checked before all abortions after the first trimester.

Discussion: Epidemiologic and clinical evidence indicates that the risk of maternal-fetal hemorrhage caused by early abortion is negligible and Rh testing and provision of Rh immune globulin is not necessary.(2-7) There is no evidence to show that Rh testing and anti-D immune globulin is beneficial in the setting of early abortion, and added testing and treatment is a burden for many patients and providers. Therefore, it is reasonable to forego Rh testing and anti-D immunoglobulin for people having any type of abortion before 12 weeks LMP.

The use of approved slide/tube/spot methods is acceptable for on-site Rh testing.

Moderate or asymptomatic anemia is rarely a reason to delay abortion care.

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5. Limited Sonography in Abortion Care

Policy Statement: The use of ultrasound is not a requirement for the provision of first-trimester abortion care. Proper use of ultrasound may inform clinical decision-making in abortion care.

Standard 5.1
Staff members who perform ultrasound exams and clinicians who interpret those exams must either show documentation of proficiency or complete a program of training. Training must include a period of supervision. Documentation of this training must be maintained.

Standard 5.2
A system of proficiency review must be in place for staff members who perform ultrasound exams and clinicians who interpret those exams.

Standard 5.3
Patients must be informed of the purpose and limitations of the ultrasound exam in the abortion care setting.

Standard 5.4
Patients must be informed of the sonographic diagnosis, including early pregnancy loss.(1, 2)

Standard 5.5
The findings of all ultrasound exams and the interpretation of those findings must be documented in the medical record. This documentation must also include the name(s) of staff who performed and interpreted the exam.(3)

Recommendation 5.5.1
Ultrasound images should be included as part of the documentation, particularly for the purposes of proficiency review.

Recommendation 5.5.2
A standard form for documenting findings and interpretation should be used.

Standard 5.6
A limited ultrasound exam must include the following:

1) a full scan of the uterus in both the transverse and longitudinal planes to confirm an intrauterine pregnancy;
2) evaluation of embryo/fetal number;
3) measurements to document gestational age;(4, 5)
4) evaluation of pregnancy landmarks, such as yolk sac or the presence or absence of fetal/embryonic cardiac activity; and
5) placental location in second trimester.

Recommendation 5.6.1
When clinically indicated, evaluation of other pelvic structures (i.e., adnexal structures and the cul de sac) should be performed and documented or an appropriate referral should be made for further evaluation.

Standard 5.7
When a patient with a prior uterine scar is found to have placenta previa or a low anterior placenta after 14 weeks, or when other placental abnormality is suspected, additional sonographic imaging should be performed on-site or an appropriate referral made.(6-8)

Standard 5.8
Ultrasound equipment must be properly maintained.

Standard 5.9
All ultrasound transducers must be disinfected between patients.

Discussion: Resources for ultrasound training can be found in the Learning Lab on NAF's members-only website at https://members.prochoice.org.

According to the American Institute of Ultrasound in Medicine (AIUM), in collaboration with the American College of Obstetrics and Gynecology and the American College of Radiology, a "limited ultrasound examination" is performed when a specific question requires investigation.(3, 9, 10)

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6. Early Medication Abortion

Policy Statement: Medication abortion is a safe and effective method for early abortion.(1, 2) Adequate counseling and follow-up care will enhance its safety and acceptability. Providing medication abortion by telemedicine is a safe option.(3, 4) For most patients, testing before a medication abortion, including ultrasound, is not required.(5, 6) People can safely manage early medication abortion on their own.

Standard 6.1
Initial evaluation must include pertinent medical history.

Standard 6.2
The patient must be informed about the efficacy, side effects, and risks, including excessive bleeding, infection, and teratogenicity of the medications used.(7)

Recommendation 6.2.1
Breastfeeding is not a contraindication to medication abortion with mifepristone and misoprostol. Patients should be informed that breastfeeding can continue uninterrupted without concern for side effects in infants.(8, 9)

> *Option 6.2.1.1*
> As appropriate, patients may be informed that no evidence-based way to reverse mifepristone exists.(10)
>
> *Option 6.2.1.2*
> Not taking an evidence-based regimen of misoprostol after mifepristone may be associated with unusual bleeding, particularly after 49 days.(11)

Standard 6.3
The patient must be informed that a uterine aspiration may be necessary.

Standard 6.4
Patient instructions must include information about use of medications at home, expected symptoms and side effects, and symptoms of abortion complications.

Recommendation 6.4.1
Providers should discuss what patients may see depending on gestational duration.

Recommendation 6.4.2
For patients who travel for abortion or are using medications prescribed through telehealth, providers should discuss how to safely seek emergency care.

Standard 6.5
The provider must provide an emergency contact service on a 24-hour basis to assist with further care as needed.

Standard 6.6
Confirmation of pregnancy must be documented with a positive pregnancy test and/or ultrasound. Pregnancy dating must be verified to be within the limits of the facility medication abortion protocol.

Recommendation 6.6.1
If an ultrasound has been performed and an intrauterine gestation has not been confirmed, the medication abortion regimen should be offered concurrently with evaluation for pregnancy of unknown location, as outlined in CPG Section 9 Management of Pregnancy of Uncertain Location.

Standard 6.7
IUDs must be removed prior to proceeding with medication abortion.

Recommendation 6.7.1
If an IUD cannot be removed without delaying the medication abortion, the patient should be offered a uterine aspiration.

Standard 6.8
An evidence-based medication abortion regimen must be used.

Recommendation 6.8.1
Where legally available and accessible, mifepristone and misoprostol should be used.(12-14)

Recommendation 6.8.2
A dose of 200mg of mifepristone is recommended for combined mifepristone-misoprostol regimens.(2)

Option 6.8.2.1
Mifepristone may be taken outside the clinic setting.(15)

Recommendation 6.8.3
For medication abortion, oral mifepristone followed by vaginal, buccal, or sublingual misoprostol 800mcg is recommended.(16-21)

Recommendation 6.8.4
An additional dose of misoprostol 800mcg is recommended for patients over 63 days gestational duration.(22,23)

Recommendation 6.8.5
More than two doses of misoprostol may be provided for patients as gestational duration increases or if a patient is remote from care (see Table 1 in the discussion).(24,25)

Recommendation 6.8.6
Where mifepristone is either not legally available or inaccessible, misoprostol-alone regimens or other evidence-based regimens may be offered.(24-27) See discussion for more information.

Standard 6.9
People can safely manage early medication abortion on their own.

Recommendation 6.9.1
People who self-manage abortion may need support from providers at different stages in the abortion process, including determining eligibility, understanding the regimen, accessing effective medications, and managing follow-up or complications.

Recommendation 6.9.2
People who self-manage abortion, along with those who support them through the process, should not be criminalized for their actions.

Standard 6.10
Misoprostol with or without mifepristone can be used for management of pregnancy loss.

Recommendation 6.10.1
Mifepristone and misoprostol are more effective than misoprostol alone for patients with an anembryonic gestation or who have embryonic or fetal demise.(28, 29)

Standard 6.11
Analgesia or other comfort measures must be discussed and offered as needed.

Recommendation 6.11.1
Non-steroidal anti-inflammatories such as ibuprofen are more effective than acetaminophen for pain control.(30)

Recommendation 6.11.2
The risk of routine narcotic analgesics for pain management may outweigh the benefits.(31-33)

Standard 6.12
Patients must be offered a follow-up assessment to confirm absence of ongoing pregnancy. Confirmation can be established by ultrasonography, hCG testing, physical exam, or self-assessment.(34, 35)

Recommendation 6.12.1
For people who do not want further contact with the health care provider, self-assessment of abortion outcomes may be used.

Recommendation 6.12.2
High-sensitivity urine hCG testing should not be checked within four weeks of medication abortion.(36)

Option 6.12.2.1
Multi-level or low-sensitivity urine pregnancy tests may be used.(37-39)

Recommendation 6.12.3
Endometrial thickness should not be used to guide management after medication abortion.(41, 42)

Recommendation 6.12.4
Prolonged courses of misoprostol should not be given routinely to improve success.(43)

Option 6.12.4.1
Additional doses of misoprostol with or without mifepristone may be given for persistent gestational sac or continuing pregnancy.(29, 44)

Standard 6.13
Medications dispensed and prescribed must be documented.

Discussion: Medication abortion regimens and follow-up have evolved rapidly over the past decade and are likely to continue to improve.

The NAF recommended protocol for medication abortion up to 70 days gestation is 200mg mifepristone followed in 24 to 48 hours by 800mcg misoprostol buccally, vaginally, or sublingually. For those who wish to use misoprostol less than 24 hours after mifepristone, the vaginal route is recommended. Repeat dosing of misoprostol should be considered over 63 days and is recommended over 70 days. (See Table 1) In the later first trimester, repeat doses of misoprostol are recommended. For patients with a previous uterine scar, the dose of misoprostol does not need to be adjusted. More information on medication abortion regimens and follow-up may be found in NAF's Learning Lab on the members-only site at https://members.prochoice.org.

Table 1: Efficacy of mifepristone 200mg orally and misoprostol regimens by weeks in selected publications

	Overall efficacy	**Ongoing pregnancy**
57-63 days gestation (18)		
o Misoprostol 800mcg buccal x 1 dose	93.5%	3.1%
64-70 days gestation		
o Misoprostol 800mcg buccal x 1 dose (18)	92.8%	3.0%

o Misoprostol 800mcg buccal q 4 hours x 2 doses (23)	99.6%	0.4%
71-77 days gestation		
o Misoprostol 800mcg buccal x 1 dose (22)	86.7%	8.7%
o Misoprostol 800mcg buccal q 4 hours x 2 doses (23)	97.7%	1.4%
78-84 days gestation (24)		
o Misoprostol 600 sublingually or 800mcg vaginally q 3 hours up to five doses (mean 2.32 doses)	95%	2%
85-90 days gestation (24)		
o Misoprostol 600mcg sublingually or 800mcg vaginally q 3 hours up to five doses (mean 2.73 doses)	92%	5.1%

Mifepristone alone is not as effective as a combined regimen and has a higher risk of ongoing pregnancy. There is no high-quality evidence that progesterone given directly after mifepristone ingestion increases the rate of ongoing pregnancy compared to no intervention.(10) A recent small randomized controlled trial of progesterone vs. placebo after mifepristone was stopped early due to bleeding requiring intervention, especially in patients over 49 days gestation.(11) Laws that require abortion providers to discuss unproven methods to interrupt the abortion process with their patients are a violation of medical ethics in that they require providers to discuss an experimental treatment with no proven benefit.

There is no evidence that mifepristone exposure has a teratogenic effect on an ongoing pregnancy.(46) Misoprostol exposure early in pregnancy doubles the risk of causing major fetal malformations in a continuing pregnancy, from approximately 2% in cases with no exposure to 4% in cases of misoprostol exposure.(47) High-dose methotrexate exposure increases the risk of malformations or pregnancy loss.(48)

If mifepristone is not available, misoprostol-only or other evidence-based regimens may be used. These regimens are all more effective when multiple doses of misoprostol are used. Prolonged follow-up may be required to reach the maximum efficacy without intervention. The efficacy of these regimens for very early pregnancy (that is, pregnancy of unknown location) and pregnancies in the later first trimester are not well studied. People who use these regimens need to understand their efficacy, side effects, and the potential exposure to known teratogens if the pregnancy continues.

Where mifepristone is not available, NAF recommends misoprostol, 800mcg sublingually every three hours for 3-4 doses for people ≤77 days LMP. An extra dose may be provided in case the patient has no bleeding or ongoing symptoms. Patient information, instructions, and a detailed sample protocol may be found on NAF's members-only site at https://members.prochoice.org.

When methotrexate and misoprostol are used, an evidence-based regimen of methotrexate 50mg oral or intramuscular followed in three to five days with misoprostol 800mcg vaginally may be used.(26, 49) Adding repeat doses of misoprostol is likely to improve the efficacy of this regimen.

When letrozole and misoprostol are used, the World Health Organization (WHO) regimen of letrozole 10mg daily by mouth x three days followed by misoprostol 800mcg sublingually on day four is recommended. Adding repeat doses of misoprostol is likely to improve the efficacy of this regimen.(50)

High-sensitivity pregnancy tests, such as those found in the pharmacy, typically detect hCG levels under 25-50mIU/mL. People should not take a high-sensitivity pregnancy test less than four weeks after medication abortion. At four weeks, approximately 20% of people with a successful medication abortion will still have a positive pregnancy test.(36) Providers should be aware that delayed assessment of completion could result in the discovery of an ongoing pregnancy in the second trimester.

If pregnancy loss is diagnosed for a patient presenting for abortion, this must be disclosed to the patient. Patients with pregnancy loss who choose medication management should be offered mifepristone pretreatment prior to misoprostol unless there is evidence the expulsion is actively underway, in which case mifepristone is unlikely to provide additional benefit. Providers can use the same medication regimen for early pregnancy loss as they would with abortion at a similar gestational age. There is limited data that misoprostol may be optimally effective 7-20 hours post mifepristone pre-treatment for early pregnancy loss, and waiting 24 hours may not have added benefit.(51)

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7. Providing Abortion Medications Without a Positive Pregnancy Test

Policy Statement: Providers can prescribe and dispense abortion medications for patients who are at risk for pregnancy for future use (advance provision) or for use in the setting of suspected, but not confirmed, pregnancy (menstrual regulation or "missed period pills"). Once the patient either confirms or suspects they are pregnant and uses medication abortion, the guidelines in CPG 6 for Early Medication Abortion apply.

Standard 7.1
Prior to prescribing and dispensing medication, the patient must be evaluated, either in-person or remotely, and eligibility for medication abortion must be confirmed.

Standard 7.2
The patient needs to be informed about the appropriate time to take medications in relationship to their pregnancy dating, the efficacy, side effects, and risks of medication abortion. They must be instructed on how to use the medications and symptoms of abortion complications.

Recommendation 7.2.1
The patient can contact the provider once they decide to use medications to review dating, eligibility, the medication abortion process, and follow-up.

Recommendation 7.2.2
The provider must offer a follow-up assessment for those who decide to take the medications and want further assessment.

Discussion: Advance provision or "missed period pills" may be acceptable to people who want medication abortion on hand, but there is, as yet, little evidence to show how frequently pills dispensed in this manner are used, and the efficacy and safety of this mode of abortion provision.(1-4)

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8. Procedural Abortion by Aspiration Alone

Policy Statement: Procedural abortion by aspiration is one of the safest procedures in medicine. The following guidelines are intended to outline steps that maximize this safety.

Standard 8.1
Pertinent medical history must be obtained.

Standard 8.2
Pregnancy must be confirmed, and gestational age must be assessed.

Recommendation 8.2.1
When gestational age cannot be reasonably determined by other means, ultrasonography should be used.

Standard 8.3
Appropriate initial evaluation must be performed. Baseline blood pressure and pulse must be obtained for all patients.

Recommendation 8.3.1
Physical exam should be done as indicated by medical history and patient symptoms.

Recommendation 8.3.2
Weight and/or BMI alone are not contraindications to procedural abortion.

Standard 8.4
The cervix should be appropriately dilated for the gestational age.

Recommendation 8.4.1
Cervical dilation may be achieved through the use of rigid cervical dilators. Tapered dilators such as Pratt or Denniston dilators are recommended over non-tapered dilators such as Hegar dilators.(1)

Recommendation 8.4.2
When cervical preparation with misoprostol is used, an evidence-based regimen should be followed.(2-5)

> *Option 8.4.2.1*
> The routine use of misoprostol before procedures may reduce rare complications but must be balanced against increased pain and other side effects for all patients.(5)
>
> *Option 8.4.2.2*
> Osmotic dilators may be considered when cervical dilation is expected to be difficult.(6)

Standard 8.5
First-trimester abortion procedures must be performed by aspiration of the uterus, not by sharp curettage.(7-9)

Recommendation 8.5.1
Uterine aspiration is effective throughout the first trimester including prior to confirmation of a definitive intrauterine pregnancy on ultrasound.(10)

Recommendation 8.5.2
Sharp curettage should not be routinely used after uterine aspiration.

Recommendation 8.5.3
Uterotonics should not be used routinely after first-trimester uterine aspiration.(11)

Discussion: No evidence supports the routine use of sharp curettage or any uterotonic after first-trimester uterine aspiration.

Cervical preparation has limited effectiveness and is not needed before a routine first-trimester abortion. Its use must be balanced against the prolonged time in the facility, side effects, and patient satisfaction. If misoprostol is used for cervical preparation, an evidence-based regimen is misoprostol 400mcg buccally, vaginally, or sublingually, one to three hours prior to the abortion procedure.(4, 5)

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9. Management of Pregnancy of Uncertain Location

Policy Statement: Many patients seek care very early in pregnancy before an intrauterine pregnancy can be visualized on ultrasound.(1, 2) When a patient has a positive pregnancy test and pregnancy of uncertain location, the most common diagnosis is an intrauterine pregnancy, but the possibility of ectopic pregnancy must be considered. For these patients, abortion care should be offered, and the patient must be followed to ensure that the pregnancy has ended. If abortion care is delayed allowing for visualization of pregnancy on ultrasound, the patient must be evaluated by a clinician, ectopic precautions must be given, and a plan for follow-up must be made.

Standard 9.1
The patient must be evaluated by a clinician to assess for the risk of ectopic pregnancy in pregnancy of uncertain location.(3-5)

Recommendation 9.1.1
Evaluation should involve assessment of the history in combination with one or more of the following: physical exam, sonography, serial quantitative hCG, and/or uterine aspiration.(6)

Recommendation 9.1.2
Abortion care should be offered even if pregnancy location is uncertain.(7-9)

Standard 9.2
Each facility must have a written protocol to evaluate pregnancy of uncertain location. All relevant staff at the site must be familiar with the protocol.

Recommendation 9.2.1
This protocol may include referrals as appropriate.

Standard 9.3
All patients with a pregnancy of uncertain location must be informed of the options for evaluation and management. The symptoms and dangers associated with ectopic pregnancy, and a plan for when and how to seek emergency medical attention must be reviewed and documented.

Recommendation 9.3.1
Each facility should have a patient education handout describing ectopic warning signs and the medical record should reflect that the patient has received this handout.

Standard 9.4
When a medication or aspiration abortion is initiated for a patient with a pregnancy of uncertain location, resolution of the pregnancy must be verified and documented. This may be demonstrated by either the examination of aspirated tissue or by following serial serum beta-hCG levels according to evidence-based regimens.

Recommendation 9.4.1
Where it is not possible to follow serial serum beta-hCG levels, urine pregnancy testing may be used.(10)

Standard 9.5
When an intrauterine pregnancy cannot be definitively seen on ultrasound, a clinician must review the patient's history, ultrasound images, and signs and symptoms of ectopic pregnancy. A clinician must discuss the risks and warning factors for ectopic pregnancy with the patient.

Option 9.5.0.1
Serum beta-hCG levels may be used to determine whether a patient is at elevated risk of ectopic pregnancy and needs immediate evaluation if abortion care is deferred.

Standard 9.6
Patient follow-up must continue until one of the following:
1. the diagnosis of ectopic pregnancy has been excluded;
2. clinical resolution of a pregnancy of uncertain location has been ensured; or
3. transfer of care to an appropriate provider has been made and documented.

Standard 9.7
Patients experiencing symptoms suspicious for ectopic pregnancy must be evaluated emergently.

Discussion: Treatment of pregnancy of uncertain location is not the same as "no-test" abortion. Pregnancy of uncertain location describes a situation in which an ultrasound is performed, and an intrauterine pregnancy is not visualized. "No-test abortion" describes a situation in which a patient has a certain or estimated last menstrual period, is otherwise eligible for abortion care, and ultrasound is not used prior to abortion.(11, 12)

Although the majority of patients who present with a low-risk pregnancy of uncertain location (that is, known early LMP, no history of ectopic pregnancy or significant risk factors, no signs and symptoms of ectopic pregnancy) will have an intrauterine pregnancy, ectopic pregnancy is more common in patients with a pregnancy of uncertain location compared to the general population of abortion seekers and needs to be assessed as the abortion proceeds. Providing abortion care to patients with pregnancy of uncertain location will decrease the time to definitive diagnosis of ectopic while at the same time providing most patients with a successful abortion.(1, 2) Abortion care, along with a combination of clinical assessment, pelvic ultrasound, serum quantitative hCG, urine hCG, and/or examination of uterine aspirate can be used to distinguish between an intrauterine and an ectopic pregnancy.(3)

Following medication abortion, hCG can be used to rule out ectopic pregnancy while simultaneously evaluating success of the medication abortion.(1, 2) When medication

abortion is initiated and no pregnancy is visible on ultrasound, patients should understand that the risk of ectopic pregnancy may be higher than the general population of abortion seekers, and the risk of medication abortion failure is higher. As such, follow-up is essential.

For more information and protocols for management of pregnancy of uncertain location, as well as information on diagnosis of early pregnancy on ultrasound, please visit NAF's members-only website at https://members.prochoice.org and access the Learning Lab.

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10. Procedural Abortion by Dilation and Evacuation

Policy Statement: Abortion by dilation and evacuation (D&E) is a safe outpatient procedure when performed by appropriately trained clinicians in medical offices, freestanding clinics, ambulatory surgery centers, and hospitals.(1-6)

Standard 10.1
Pertinent medical history must be obtained, and relevant physical examination must be performed.

Recommendation 10.1.1
Weight and/or BMI alone are not contraindications to D&E.(7-9)

Standard 10.2
Gestational age must be verified by ultrasonography, using a consistent and published table of fetal measurements, prior to the termination of a pregnancy clinically estimated to be more than 14 weeks from LMP.

Standard 10.3
The patient must be appropriately evaluated and prepared for the procedure.

Recommendation 10.3.1
Intravenous access should be established prior to evacuation.

Recommendation 10.3.2
When induced fetal demise is used, it should be provided through an evidence-based protocol.(10-16)

Recommendation 10.3.3
In a patient with a prior uterine scar, after appropriate evaluation to exclude placenta accreta spectrum, the patient may have a procedure in the outpatient setting.(17)

Recommendation 10.3.4
Patients should be given anticipatory guidance on breast symptoms after later abortion or pregnancy loss.

> *Option 10.3.4.1*
> Cabergoline, 1mg orally x one dose may be used immediately after the procedure to reduce breast symptoms and lactation for those who want it.(18)

Standard 10.4
When cervical preparation agents are used overnight or outside the facility, a plan for emergency care must be in place and communicated to the patient.

Standard 10.5
Appropriate dilation of the cervix must be obtained gently and gradually.(19, 20)

Recommendation 10.5.1
Osmotic dilators, misoprostol, mifepristone, transcervical catheter, and/or other cervical preparation agents should be used to facilitate adequate dilation.(21-25)

Recommendation 10.5.2
Local anesthesia should be used for pain management with osmotic dilator placement.(26, 27)

Recommendation 10.5.3
An evidence-based regimen should be used for dosage, timing, and route of misoprostol.(22-24, 28-32)

Option 10.5.0.1
Synthetic osmotic dilators or a foley/Cook catheter and/or misoprostol may be used for same-day cervical dilation.(25, 28, 30, 33)

Standard 10.6
All instruments entering the uterine cavity must be sterile.

Standard 10.7
Evidence-based practices must be used to lower the risk of complications.

Recommendation 10.7.1
Intra-procedure ultrasonography should be used to aid in visualizing instruments, locating fetal parts, verifying an empty uterus, reducing the risk of uterine perforation, and shortening the procedure.(34-36)

Recommendation 10.7.2
Inhaled anesthesia should be avoided if possible due to the increased risk of hemorrhage.(37, 38)

Standard 10.8
Uterotonics must be available to aid in control of uterine bleeding.(17)

Option 10.8.0.1
An intra- or paracervical prophylactic vasoconstrictor can be used to reduce blood loss.(39)

Discussion: Cervical preparation before dilation and evacuation can be achieved with multiple agents either alone or in combination. Misoprostol is commonly used, with a dose of 400mcg supported by most studies.(40)

Induced fetal demise should be provided using an evidence-based regimen. A sample protocol for digoxin injection is available on the NAF members-only site at https://members.prochoice.org. Intraamniotic or intrafetal digoxin may be used.(41, 42) Intracardiac potassium chloride or lidocaine may also be used.(11, 16, 43) Injections may be done either transabdominally or transvaginally.(44, 45) Cord transection may also be used.(46)

Prophylactic use of methergine for prevention of postabortion hemorrhage is not recommended.(47) Prophylactic pitocin for procedures between 18-24 weeks gestation may be considered.(49)

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11. Medication Abortion After the First Trimester

Policy Statement: Medication abortion is a safe and effective method for termination of pregnancies beyond the first trimester when performed by trained clinicians in medical offices, freestanding clinics, ambulatory surgery centers, and hospitals. Induced fetal demise may be particularly important at later gestational ages.

Standard 11.1
Pertinent medical history must be obtained, and relevant physical examination must be performed.

Standard 11.2
Gestational age must be verified by ultrasonography, using a consistent and published table of fetal measurements, prior to the termination of a pregnancy clinically estimated to be more than 14 weeks from LMP.

Standard 11.3
The patient must be appropriately evaluated and prepared.

Recommendation 11.3.1
Intravenous access should be established.

Recommendation 11.3.2
Patients should be given anticipatory guidance on breast symptoms after later abortion or pregnancy loss.

> *Option 11.3.2.1*
> Cabergoline, 1mg orally x one dose may be used immediately after the abortion to reduce breast symptoms and lactation for those who want it.(1)

Standard 11.4
Facilities must have a policy that addresses whether and when to induce fetal demise.

Recommendation 11.4.1
When induced fetal demise is used, it should be provided through a standard protocol.(2-9)

Standard 11.5
Evidence-based regimens of medication abortion must be used.

Recommendation 11.5.1
Mifepristone 200mg followed in 24 to 48 hours by repeat doses of misoprostol should be used, when available and feasible.(10-13)

Option 11.5.1.1
Simultaneous or short interval administration of mifepristone and repeat doses of misoprostol may also be used.(14)

Option 11.5.1.2
Repeat dosing of misoprostol may also be used alone.(15)

Option 11.5.1.3
Oxytocin may be used according to a protocol.

Option 11.5.1.4
Osmotic dilators may be useful at later gestations.(16-18)

Recommendation 11.5.2
Intraamniotic injection or instillation methods should be avoided as they are less effective and result in more complications than mifepristone-misoprostol or misoprostol-alone regimens.(19)

Standard 11.6
Once regular contractions have been confirmed, patients must be observed by health care staff trained to monitor contractions and expulsion, and who can recognize emergent situations.

Standard 11.7
A trained clinician must be available from initiation of induction until post-abortion discharge.

Standard 11.8
Access to surgical management or appropriate referral must be available if surgical intervention is required.

Standard 11.9
The facility and/or clinician should continue care of the patient until completion of the abortion or transfer of care to an appropriate provider is made.

Discussion: Evidence-based regimens for later medication abortion are difficult to compare. Mifepristone increases the efficacy and decreases the total time and doses needed for misoprostol to cause pregnancy expulsion. Misoprostol dosing can be repeated until expulsion with no limit on the number of doses**. For abortion over 12 weeks LMP, the WHO recommends a regimen of mifepristone 200mg orally followed in one to two days by misoprostol, 400mcg buccally, vaginally, or sublingually every four hours until pregnancy expulsion**.(20) The dosage of misoprostol may be adjusted as the pregnancy progresses or with previous cesarean section; however, when those adjustments need to be made is not well established. The risk of uterine rupture during later medication abortion with misoprostol may be

significantly increased for patients with two or more previous cesarean sections, however, the absolute risk remains low.(21) The risks should be balanced with alternative procedures for later abortion.

Caution should be used with osmotic dilators in the second trimester as they may prolong the induction time.(16-18)

Induced fetal demise should be provided using an evidence-based regimen. A sample protocol for digoxin injection is available on NAF's members-only site at https://members.prochoice.org. Intraamniotic or intrafetal digoxin may be used.(22) Intracardiac potassium chloride or lidocaine may also be used.(7-9) Injections may be done either transabdominally or transvaginally.(23)

Uterine curettage or aspiration should not routinely be performed.

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12. Analgesia and Sedation

Policy Statement: Anxiolysis, analgesia, or anesthesia should be provided during abortion procedures for any patient for whom the benefits outweigh the risks, with the aim of providing the appropriate level of analgesia and sedation required for each patient's needs. Patients should be involved in a shared decision-making process about pain control and sedation during the procedure.

Implicit and explicit bias causes providers to undertreat pain for specific populations, including Black, Indigenous, and people of color, and people with substance use disorders.(1-3) All people seeking abortion care are entitled to adequate pain management.

ON THE USE OF SEDATION IN GENERAL - All medications used in procedural sedation have the potential for serious risk. This risk may be reduced to a minimum by adherence to established practice guidelines. Guidelines developed by other organizations concern themselves with anesthesia and sedation delivered primarily in hospital settings and to patients varying widely in age and general health. Regardless of the drug or route of administration, the degree of central nervous system (CNS) depression is the basis for the NAF guidelines.

These guidelines do not address the use of deep sedation or general anesthesia except to identify basic monitoring practices and appropriate providers of such care, who are expected to follow their professional standards in the delivery of anesthesia services. It is expected that those individuals providing deep sedation or general anesthesia will have appropriate emergency medication and equipment in place to ensure the safe care of a patient in the event of an anesthesia complication.

The promulgation of guidelines for the delivery and monitoring of anesthesia care issued by organizations such as the American Society of Anesthesiologists (ASA), the Canadian Anesthesiologists' Society (CSA), the American Dental Society of Anesthesiologists (ADSA), American Society for Gastrointestinal Endoscopy (ASGE), and others have clarified many of the issues related to anesthesia care.

Patient comfort and reduced anxiety are significantly affected by patient counseling and by the presence of family, friends, and supportive staff, and are not solely dependent on pharmacologic measures. Alternative modalities (such as relaxation techniques, acupuncture, hypnosis) may be helpful for some patients. The focus of NAF guidelines for analgesia and sedation, however, is on the safe provision of pharmacologic methods generally used in outpatient abortion facilities.

Definitions(4)

1. Local Anesthesia - Elimination or reduction of sensation, especially pain, in one part of the body by topical application or local injection of a drug. In the context of abortion practice, local anesthesia almost always involves a paracervical block.

2. Minimal Sedation (Anxiolysis) - A drug-induced state during which patients respond normally to verbal commands. Although cognitive function and physical coordination may be impaired, airway reflexes, ventilatory, and cardiovascular functions are unaffected.

3. Moderate Sedation/Analgesia - A drug-induced depression of consciousness during which patients respond purposefully* to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained but may be impaired. This level of sedation was previously referred to as "Conscious Sedation." However, this term is no longer recommended.

4. Deep Sedation/Analgesia - A drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained but may be impaired.

5. General Anesthesia - A drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

Because sedation is a continuum, it is not always possible to predict how an individual patient will respond. Hence, practitioners intending to produce any level of sedation should be able to rescue patients whose level of sedation becomes deeper than initially intended. *Rescue* corrects adverse physiologic consequences of the deeper-than-intended level of sedation (such as hypoventilation, hypoxia, and hypotension) and returns the patient to the originally intended level of sedation.

Standard 12.1
Pain control options must be discussed with the patient.

*Reflex withdrawal from a painful stimulus is NOT considered a purposeful response.

Standard 12.2
When minimal, moderate, deep sedation, or general anesthesia is to be given, patients must be given information about the risks, benefits, and side effects of the medications to be used.

Recommendation 12.2.1
Documentation should include precautions relevant to transient mental impairment.

Option 12.2.0.1
An informed consent form specific for analgesia and sedation may be used.

Standard 12.3
Levels of sedation depend on the patient response, not the route of drug administration. Oral anxiolytics and analgesics given in combination can cause moderate sedation for some patients.

Standard 12.4
The amount of anesthesia given depends on the desired level of sedation and the individual patient response. Patient characteristics such as age, race, parity, body size, weight, or current or past substance use disorder, and use of medication for opioid use disorder should not be used to limit appropriate anesthesia and analgesia.

Standard 12.5
Prior to moderate sedation, a pre-sedation evaluation of the patient must take place.

Recommendation 12.5.1
Evaluation should include a relevant history and review of systems; medication review; targeted exam of the heart, lung, and airway as indicated by the patient's history and review of systems; and baseline vital signs.

Recommendation 12.5.2
For patients receiving moderate sedation who are not at increased risk of aspiration, time from last meal should not limit access to abortion care.(5-7)

Recommendation 12.5.3
A reduced level of sedation, an alternate abortion procedure, or provision of care by an anesthesia professional should be considered for patients with an atypical airway assessment or ASA Physical Status Classification 3 or greater.(8, 9)

Standard 12.6
No additional evaluation is needed prior to paracervical block and/or NSAID administration.

Standard 12.7
The supervising practitioner must be immediately available when sedation is administered.

Standard 12.8
When local anesthesia or sedation is provided, the practitioner responsible for the treatment of the patient and/or the administration of drugs must be appropriately trained, with approval by the medical director or their designee.(9, 10)

Standard 12.9
To administer moderate sedation, a provider must have the following: licensure as appropriate, basic airway skills, the ability to monitor and effectively rescue patients in an emergency, and the ability to screen patients appropriately for sedation.

Standard 12.10
The potential need for intravenous access must be considered prior to administering any level of sedation.

Recommendation 12.10.1
When more than minimal sedation is intended, intravenous access should be maintained at least until discharge criteria are met.

Standard 12.11
Pulse oximetry, with appropriate alarms, must be employed when moderate or deeper levels of sedation are used.

Standard 12.12
When sedation is provided, monitoring must be adequate to detect the respiratory, cardiovascular, and neurological effects of the drugs being administered, and this monitoring must be documented.

Recommendation 12.12.1
The patient should be checked frequently for verbal responsiveness.

Standard 12.13
When moderate sedation or deeper is provided, a person other than the clinician performing the procedure, and who is trained to monitor appropriate physiological parameters, must be present. This person must not be performing duties other than monitoring the patient.(9)

Moderate Sedation

Standard 12.14
When moderate sedation is intended, sedation medication must be started at a reasonable low dose and titrated as needed, based on individual circumstances, such as weight and drug tolerance.(11-13)

Recommendation 12.14.1
The following table should be used for guidance for these commonly used drugs when used for moderate sedation. Similar ranges of other opioids and benzodiazepines may be used.

Option 12.14.1.1
A regimen that includes ketamine may be used as an alternative or in conjunction with opioids for moderate sedation. Please see discussion for more information.(14)

Drug	Usual initial dose	Max initial dose	Usual incremental Dose	Max incremental Dose
Fentanyl	50-100mcg	200mcg	50-100mcg	100mcg
Midazolam	1-3mg	4mg	1-2mg	2mg
Ketamine (when used with fentanyl)	10mg	20mg	10mg	20mg
Ketamine (when used without fentanyl)	20mg	20mg	10mg	20mg

Standard 12.15
When moderate sedation is administered, at least one individual with documented airway skills must be present in the procedure room.

Deep Sedation or General Anesthesia

Standard 12.16
Supplemental oxygen must be used with deep sedation and general anesthesia.

Standard 12.17
The practitioner administering deep sedation or general anesthesia must not be the practitioner performing the abortion.

Recommendation 12.17.1
For deep sedation and general anesthesia, the following should be monitored: continuous pulse oximetry, intermittent blood pressure, and respiration, either by measuring end-tidal CO_2 or clinical observation.

Recommendation 12.17.2
The capability to monitor temperature should be available.

Standard 12.18
Any individual responsible for administering, supervising, or monitoring a patient receiving any level of sedation must have current, health care provider level basic life support (BLS) certification.

Standard 12.19
The practitioner administering deep sedation or general anesthesia must adhere to established professional standards of care.(15)

Nitrous Oxide

Standard 12.20
N_2O must be self-administered by the patient or by a qualified anesthesia provider.

Recommendation 12.20.1
N_2O may be an alternative to local or oral sedation but is less effective for pain management than moderate intravenous sedation.(16, 17)

Standard 12.21
If not self-administered, the provision of N_2O must follow guidelines for patient monitoring for moderate sedation.

Standard 12.22
Equipment for the delivery of N_2O/O_2 must:
1) provide a concentration of N_2O of no more than 70% inspired;
2) provide a minimum of 30% O_2; and
3) be checked and calibrated regularly.

Recommendation 12.22.1
The concentration of nitrous oxide should not routinely exceed 50% in the absence of qualified anesthesia personnel.

Recommendation 12.22.2
Equipment for the delivery of N_2O/O_2 should include an oxygen analyzer.

Recommendation 12.22.3
Due to the potential for occupational exposure, room or personnel monitoring for levels of N_2O should be conducted.

Emergency Equipment

Standard 12.23
Functioning equipment and current medications must be available on-site to handle medical emergencies and must include: an oxygen delivery system, oral airways, epinephrine, and antihistamines.

Standard 12.24
In settings where benzodiazepines and opioids are used, appropriate antagonists, bronchodilators, and bag-valve masks capable of delivering supplemental oxygen must be available.

Recommendation 12.24.1
Facilities should have a specified area for emergency equipment, which includes oxygen, medications, and supplies. A protocol and time schedule for checking equipment and removing expired medications must be in place.

Standard 12.25
In settings where deep sedation and general anesthesia are used, it is expected that providers maintain the appropriate medication and equipment required for an anesthesia emergency.

Recommendation 12.25.1
A defibrillator should be available.

Discussion: The time of last food intake does not increase the risk of moderate sedation.(4-7)

ON THE USE OF N_2O/O_2 - Nitrous oxide has a long history of use for analgesia and sedation, as well as an excellent safety record in the hands of both anesthesiologists and non-anesthesiologists. Occupational exposure to N_2O has been associated with increased risks of neurologic impairment, spontaneous abortion, subfertility, and hepatic and renal disease. Recommendations for safe use of nitrous oxide can be found in the reference section. In addition to employing adequate ventilation and scavenger systems, it is also recommended to deliver 100% oxygen to the patient for five minutes before removing the mask. This will purge the system, and the patient, of any residual nitrous oxide. Occupational exposure can be monitored by asking staff members to wear personal dosimetry badges or by placing an infrared spectrophotometer in the room. Although there is no OSHA standard for N_2O, NIOSH recommends that airborne levels of N_2O be kept below 25 ppm through well-designed scavenger systems and other engineering controls, equipment maintenance, exposure monitoring, and safe work practices.

Ketamine offers an alternative or addition to opioid containing regimens for intravenous moderate sedation. Ketamine is effective in patients with opioid use disorder, allows

clinicians to use a lower dose of opioids in combined regimens, and has a reduced risk of respiratory depression.(14, 18) Ketamine, whether used alone or with an opioid, needs to be combined with a benzodiazepine to prevent adverse side effects, particularly dysphoria and hallucinations. When ketamine is used without an opioid, a higher or repeated dose of benzodiazepine may be required to prevent hallucinations.

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13. Post-Procedure Care

Policy Statement: Appropriate and accessible post-procedure and follow-up care is essential to patients' wellbeing.

Standard 13.1
Patients who want contraception must receive their chosen method immediately following an abortion or appropriate referral should be made.

Recommendation 13.1.1
When desired by the patient, intrauterine contraception or contraceptive implants should be initiated immediately after first-trimester uterine evacuation or second-trimester D&E.(1-3)

Recommendation 13.1.2
When desired by the patient after medication abortion, intrauterine contraception should be initiated as soon as expulsion of the pregnancy is confirmed.(4-6)

Recommendation 13.1.3
When desired by the patient, contraceptive implants should be initiated on the day of mifepristone administration for medication abortion.(7-10)

> *Option 13.1.3.1*
> Depot Medroxyprogesterone acetate (Depo-Provera®) may be given at the time of mifepristone with appropriate counseling.(10-12)

Recommendation 13.1.4
Emergency contraception should be discussed and either dispensed or prescribed to patients who want it.

Standard 13.2
All patients receiving more than minimal sedation or in the second trimester must be continuously observed during the recovery period by a health care worker trained in post-procedure care.

Standard 13.3
Patients who received moderate or deeper sedation must be monitored until determined to be no longer at risk for hemodynamic instability or respiratory depression.

Recommendation 13.3.1
A pulse oximeter with alarms should be used until the patient is alert and ambulatory.

Standard 13.4
A clinician must remain in the facility until all patients are medically stable.

Standard 13.5
The following criteria must be documented prior to discharge: the patient must be ambulatory with a stable blood pressure and pulse, and bleeding and pain must be controlled.

Standard 13.6
The patient must be given oral and written instructions outlining what to expect post-procedure, self-care, and signs and symptoms of complications.

Recommendation 13.6.1
Patients who receive sedation should have access to this information prior to the administration of medication.

Standard 13.7
The facility must provide an emergency contact service on a 24-hour basis, where calls are triaged in accordance with written policies. A recorded message alone is unacceptable.

Standard 13.8
Any non-clinician involved with first-call triage must be trained to take a post-abortion health history and follow clear written guidelines indicating when immediate consultation with a clinician is indicated.

Standard 13.9
Any patient who gives a history suggestive of a post-procedure complication must have access to a clinician. The facility must establish a pathway for physician referral if indicated.

Recommendation 13.9.1
Uterotonic agents should be given as indicated and not on a routine basis. When used, an evidence-based regimen should be followed.

> *Option 13.9.1.1*
> Routine post-procedure follow-up is not required. Clinicians may offer a visit for patients who would like one.(13, 14)

Discussion: A recent study shows that Depot Medroxyprogesterone acetate (DMPA) (Depo-Provera®) given on the day of mifepristone may increase the risk of continuing pregnancy but does not increase the risk of needing aspiration to complete the abortion compared to when it is given at a follow-up visit.(12) Patient satisfaction is higher with immediate DMPA, but six-month use rates and pregnancy rates are the same due to high rates of discontinuation. If a patient understands the potential risk of ongoing pregnancy, DMPA may be offered and given at the time of mifepristone. DMPA given in the 24-48 hours after mifepristone, on the day of misoprostol, does not affect the rate of continuing pregnancy.(15)

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14. Evaluation of Evacuated Uterine Contents

Policy Statement: Identification of appropriate products of conception (POC) following evacuation abortion procedures confirms termination of an intrauterine pregnancy.

Standard 14.1
Termination of pregnancy must be confirmed prior to the patient leaving the facility or further evaluation must be initiated.

Recommendation 14.1.1
Evacuated uterine contents should be examined before the patient leaves the facility.

Recommendation 14.1.2
In first-trimester terminations, flotation of tissue should be used to identify products of conception, including gestational sac.

> *Option 14.1.2.1*
> Backlighting of tissue may be useful.
>
> *Option 14.1.2.2*
> Sending the evacuated uterine contents for additional pathological examination is not required.(1, 2)

Standard 14.2
In the first trimester, when insufficient tissue or incomplete products of conception are obtained, the patient must be reevaluated.

Recommendation 14.2.1
Re-aspiration, serial quantitative hCG, and/or ultrasonographic examination should be considered.(3-5)

Recommendation 14.2.2
Ectopic pregnancy should be considered.

Standard 14.3
After the first trimester, examination of the uterine contents must be performed to identify the placenta and all major fetal parts.

Recommendation 14.3.1
If the above are not identified, ultrasonographic evaluation and uterine exploration under ultrasound guidance should be considered.

Recommendation 14.3.2
The facility and/or clinician should continue care of the patient until completion of the abortion or transfer of care to an appropriate provider is made.

Discussion: One option for additional evaluation if sufficient POC are not identified is the use of serum quantitative hCG tests. A baseline hCG can be drawn and a second hCG can be done in 24-48 hours. If there is a decrease of 50% or more, no further ectopic follow-up is necessary. Otherwise, further evaluation should be initiated including consideration of ectopic pregnancy. In this situation, Section 9 (Management of Pregnancy of Uncertain Location) may be useful.

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15. Emergency Procedures

Policy Statement: Appropriate management of abortion emergencies reduces morbidity and mortality. Hemorrhage can be one of the most serious immediate complications of an abortion procedure. Early recognition of the source of bleeding can reduce morbidity and mortality. Uterine perforation is a complication of abortion that can lead to significant morbidity. Morbidity is related to site of perforation, instrumentation, and gestational age.

Standard 15.1
Protocols for the management of medical emergencies must be in place. These protocols must include indications for emergency transport and written, readily available directions for contacting external emergency assistance (e.g., an ambulance).

Recommendation 15.1.1
Protocols for the following topics should be in place: bleeding, perforation, respiratory arrest/depression, anaphylaxis, and emergency transfer.

Recommendation 15.1.2
Staff should review protocols annually.

> *Option 15.1.2.1*
> Annual drills of the emergency protocols are encouraged.

Recommendation 15.1.3
Clinics should consider developing a transfer agreement with a hospital outlining the means of communication and transport and the protocol for emergent transfer of care.

Standard 15.2
All staff must know their appropriate roles in the management of medical emergencies.

Standard 15.3
Emergency supplies must be in known, appropriate locations and regularly updated.

Standard 15.4
When abortion procedures are being performed, at least one medical staff member with health care provider level basic life support (BLS) training must be present.

Recommendation 15.4.1
All medical staff providing direct patient care should have current health care provider level BLS certification.

Standard 15.5
All facilities must have a protocol for the management of acute hemorrhage.(1) This protocol must address the following items:

1) establishment of intravenous access;
2) administration of uterotonics;
3) evaluation of the cause and/or source of bleeding; and
4) criteria for hospital transfer.

Standard 15.6
The facility must have at least two uterotonics and/or mechanical methods of controlling bleeding.

Standard 15.7
If a perforation occurs or is suspected, even if the patient is asymptomatic, a protocol must address the following items:

1) establishment of intravenous access;
2) additional observation;
3) plan for follow-up including plans for completing the abortion if needed; and
4) criteria for transfer to a hospital such as the following:
    a. intra-abdominal viscera are detected in the uterine cavity, cervix, vagina, suction tubing, or on tissue examination;
    b. fetal parts are detected in the abdominal cavity;
    c. expanding intra-abdominal or retroperitoneal hematoma is detected; or
    d. hemodynamic instability is present.

Recommendation 15.7.1
If the procedure is completed after a suspected perforation, uterine evacuation should be performed under direct ultrasound guidance or laparoscopic visualization.(2, 3)

Discussion: Excessive bleeding during the procedure and in the post-procedure period is almost always due to uterine atony, often caused by incomplete emptying of the uterus. Therefore, the most important initial efforts should be directed at assuring complete evacuation of the uterus and at increasing uterine tone through uterotonics or uterine massage. Problems arise when bleeding is ignored, or its severity underestimated. Clinicians must always remember to do the simple things when confronted with a developing bleeding problem: continue assessment of the blood loss, measure and record vital signs frequently, and assure intravenous access.

The following measures may be used for treatment of post-abortion hemorrhage:

1) uterine massage;
2) methylergonovine (Methergine);
3) oxytocin (Pitocin);
4) vasopressin (Vasostrict);
5) misoprostol (Cytotec);
6) carboprost tromethamine (Hemabate);

7) Tranexamic acid;(4)
8) intrauterine pressure using a Foley or Bakri balloon or vaginal pack; or
9) uterine re-aspiration.

When bleeding continues after assurance of complete uterine emptying and when there are no visible cervical or vaginal lacerations, the clinician must consider other complications such as perforation, coagulopathy, or placenta accreta. The patient may need immediate transfer to manage these conditions.

Perforations are often occult and may be difficult to identify.(5-7) If a perforation is suspected, it is safest to proceed as if there has been a perforation.

In the first trimester, perforations are often asymptomatic and self-healing.(8, 9) Most perforations are midline and/or fundal in location.(10) If they occur before suction, these usually can be managed with observation and close follow-up.(9) A lateral perforation may involve uterine blood vessels and, if so, will be more significant.

In the second trimester, even an asymptomatic perforation may warrant transfer to a hospital for evaluation depending on the instrumentation involved.(11, 12) There may be more significant morbidity due to increased uterine blood flow and the use of larger grasping instruments.

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EXHIBIT B-4

APPENDIX TO PETITIONER GENBIOPRO, INC.'S CITIZEN PETITION DATED JULY 3, 2025[1]

Source	Appendix Starting Page
Appendix Volume I	
108 Cong. Rec. 17366 (Aug. 23, 1962)	GBP-PET00001
Aiken, Abigail R.A. et al., *Safety and Effectiveness of Self-Managed Medication Abortion Provided Using Online Telemedicine in the United States: A Population Based Study*, 10 Lancet Reg'l Health – Ams. 1 (2022), https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(22)00017-5/fulltext	GBP-PET00010
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[1] This Appendix includes all documents cited in the accompanying July 3, 2025 Citizen Petition with the exception of certain documents not required by 21 C.F.R. § 10.20(c). Volumes I, II, III, IV, V, and IX contain copyright restricted materials.

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2

The Safety and Quality of Current Abortion Methods

In the more than 40 years since national legalization of abortion, investigators have conducted randomized controlled trials (RCTs), large retrospective cohort studies, patient and provider surveys, systematic reviews, and other types of research on abortion care and its health effects on women, resulting in an extensive literature. The objective of this chapter is to examine this literature, focusing on the safety and effectiveness of current abortion methods and the extent to which these methods could expose women to the risk of such serious complications as the need for blood transfusion, surgery, or hospitalization. The chapter also examines whether the type of facility or method of sedation or anesthesia affects the risk of adverse outcomes. The chapter is organized as follows:

- The first section describes the clinical assessment, informed consent, patient education, and counseling that precede the abortion procedure.
- The second section addresses the initial clinical assessment.
- The next section describes current abortion methods and, for each method, reviews what is known about the procedure's effectiveness, expected side effects, and risk of complications. Note that, for the purposes of this review, efficacy or effectiveness refers to the successful completion of the abortion without the need for a follow-up aspiration.
- The fourth section turns to postabortion care.
- The fifth section examines the evidence on the use of analgesia, sedation, and anesthesia in abortion care, including its safety and implications for the site of care.
- The following section compares the mortality rates for abortion and other common outpatient procedures.
- The next section presents a brief discussion of state regulation of abortion care.

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- The final, summary section reviews state regulation of abortion safety in light of the clinical evidence presented earlier in the chapter.

The committee's review emphasizes contemporary approaches to abortion care because abortion methods have been refined in response to new evidence. Some research conducted before 2000 is unlikely to reflect the outcomes of how abortions are typically performed in the United States today. As discussed below, for example, the U.S. Food and Drug Administration (FDA)-approved protocol for medication abortion was updated in 2016 based on extensive research showing improved outcomes with a revised regimen (CDER, 2016). Techniques used in aspiration procedures are also safer and more effective than in the past. Sharp metal curettes, once commonly used, are considered obsolete by many professional groups, and their use is no longer recommended for abortion because of the increased (albeit rare) risk of injury (NAF, 2017a; RCOG, 2011, 2015; Roblin, 2014; SFP, 2013; WHO, 2012). New approaches to cervical preparation and the use of ultrasound guidance have also improved abortion safety (Darney and Sweet, 1989; SFP, 2013).

This chapter draws primarily on the scientific literature but also includes the recommendations (i.e., clinical practice guidelines and best practices) of professional groups that provide obstetrical and gynecological care or are concerned with the quality of abortion services. Appendix D summarizes the literature search strategies the committee used to identify the relevant evidence, while Table 2-1 describes the sources of the clinical guidelines cited throughout this report.

PREABORTION CARE

When women seek an abortion, they present with a variety of experiences and needs (Moore et al., 2011; Zurek et al., 2015). Patient-centeredness—a fundamental attribute of quality health care—means "providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions" (IOM, 2001, p. 6). Thus, when women seek an abortion, they should have the opportunity to discuss their questions and concerns and receive support in their decision making. They should also be provided evidence-based information on their procedure options so they can make an informed and independent decision.

TABLE 2-1 Selected Organizations That Issue Clinical Guidelines on Abortion Care

American College of Obstetricians and Gynecologists (ACOG)	A professional membership organization of obstetricians and gynecologists. ACOG produces clinical guidelines and other educational materials for its members and patients.

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National Abortion Federation (NAF)	A standards-based membership organization of abortion facilities (clinics, physicians' offices, and hospitals). To qualify for and maintain NAF membership, providers must meet NAF clinical and safety standards. The standards are revised annually to reflect current evidence and are the basis for members' certification.
Royal College of Obstetricians and Gynaecologists (RCOG)	A global reproductive health professional society based in the United Kingdom. Its more than 14,000 members include individuals involved in obstetrics or gynecology worldwide. RCOG's mission is to improve the standard of care and to advance the science and practice of obstetrics and gynecology.
Society of Family Planning (SFP)	A professional membership organization for qualified individuals who have an interest in family planning demonstrated through training, clinical or laboratory practice, or academic publication. SFP develops clinical guidelines and supports research on contraception and abortion.
World Health Organization (WHO)	The international public health organization of the United Nations, based in Geneva, Switzerland. WHO develops clinical guidelines on reproductive health care with the stated objective of improving health outcomes.

SOURCES: ACOG, 2017a; NAF, 2017b; RCOG, 2017; SFP, 2017; WHO, 2017.

There is little evidence on how preabortion care is typically provided, but there is consensus among professional guidelines that the preabortion encounter includes the following elements (Baker and Beresford, 2009; NAF, 2017a; RCOG, 2015; WHO, 2014):

- individualized, sensitive, and respectful communication;
- cultural sensitivity;
- review of the risks and benefits of the available abortion procedures that is based on evidence and is easy to understand;
- options for pain management, including nonpharmaceutical approaches, analgesia, sedation, and anesthesia;
- support for emotional and other needs as they arise;
- confirmation that the abortion decision is voluntary (not coerced);
- explanation of what will be done before, during, and after the procedure, including the preabortion evaluation;

The Safety and Quality of Abortion Care in the United States, National Academies Press, 2018. ProQuest Ebook Central, http://ebookcentral.proquest.com/lib/nyli/detail.action?docID=5407012.
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- description of what the patient is likely to experience, clear instruction on aftercare, and how to recognize potential complications requiring emergency care;
- whom to call and where to go for services for both routine and follow-up care; and
- information and counseling on future prevention of unintended pregnancy and contraceptive options, including the option to obtain contraception immediately following the procedure.

Patient education, counseling, and informed consent are overlapping components of preabortion care. Patient education refers to the information women should receive regarding the available treatment options and the risks and benefits of these options (Baker and Beresford, 2009). It is also integral to the informed consent process—a legal and ethical obligation to all patients defined by state and federal law, malpractice standards, and professional standards (ACOG, 2015; AMA, 2016; Joint Commission Resources, 2016; Kinnersley et al., 2013). Counseling involves addressing the patient's emotions, expectations, and beliefs about abortion care (Baker and Beresford, 2009).

Health care providers are legally required to obtain patients' informed consent before performing a medical procedure. Specific definitions of informed consent may vary from state to state, but the goal of the informed consent process is well established: to ensure that patients understand the nature and risks of the procedure they are considering and that their decision to undergo it is voluntary (AAAHC, 2016; AMA, 2016; HHS, 2017a; Joint Commission, 2016). The discussion should also include options for analgesia, sedation, or anesthesia, including their associated risks and benefits (AANA, 2016; ASA Committee on Ethics, 2016).

Not every woman wants or needs psychological counseling in addition to patient education before an abortion (Baker and Beresford, 2009; Baron et al., 2015; Brown, 2013; Moore et al., 2011). Some women may wish to discuss the emotional aspects of the abortion with a counselor (Moore et al., 2011), and individualized counseling may be helpful for women having difficulty with their decision (Baker and Beresford, 2009). Women should also be referred to and have access to additional counseling and social services if needed (e.g., for counseling on intimate partner violence, sexual abuse care, rape crisis counseling, mental health services, substance abuse services, and postabortion counseling) (Goodman et al., 2016). As noted in Chapter 1, most women who undergo abortions are poor or low-income. Three-quarters of abortion patients have family incomes below 200 percent of the federal poverty level (Jerman et al., 2016) and thus may benefit from social support services. In addition, although the evidence is drawn largely from non-U.S. data (Australia, Canada, China, New Zealand, and the United Kingdom), epidemiological studies have shown that women who have abortions are disproportionately at risk of interpersonal and other types of violence (Bourassa and Berube, 2007; Evins and Chescheir, 1996; Fanslow et al., 2008; Fisher et al., 2005; Glander et al., 1998; Janssen et al., 2003; Keeling et al., 2004;

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Leung et al., 2002; Russo and Denious, 2001; Saftlas et al., 2010; Steinberg and Russo, 2008; Taft and Watson, 2007; Taft et al., 2004). Little is known about the extent to which abortion patients receive the follow-up social and psychological supports they need. A study of Finnish registry data provides some evidence that monitoring for mental health status in a follow-up visit after abortion may help reduce the consequences of serious mental health disorders (Gissler et al., 2015).

Providing evidence-based information on how to prevent a future unintended pregnancy—including the option to obtain contraception contemporaneously with the procedure—is a standard component of abortion care (Goodman et al., 2016; NAF, 2017a; RCOG, 2015; WHO, 2014). Contraception discussions should be patient-centered, based on principles of informed consent using evidence-based information on the contraceptive alternatives, and guided by the patient's preferences (Goodman et al., 2016; RCOG, 2015). Most contraceptive methods can be administered safely immediately after an abortion (Fox et al., 2011; Goodman et al., 2016; Grimes et al., 2010; Okusanya et al., 2014; Patil et al., 2016; Sääv et al., 2012; WHO, 2014). Recent studies suggest improved contraceptive use with the placement of implants or the initiation of other contraceptive methods at the time of the abortion or when mifepristone is administered for an early medication abortion (Hognert et al., 2016; Raymond et al., 2016a; Whaley and Burke, 2015).

While numerous options for contraception are available, long-acting reversible contraception (LARC) methods are the most effective for pregnancy prevention (ACOG, 2017b; Winner et al., 2012). Further, they are associated with higher rates of continuation, even for adolescents and young women, and fewer repeat abortions compared with other forms of contraception (ACOG, 2017b; Ames and Norman, 2012; Diedrich et al., 2015; Goodman et al., 2008; Goyal et al., 2017; Kilander et al., 2016; Rose and Lawton, 2012; Rosenstock et al., 2012; Winner et al., 2012). A prospective cohort study of women of reproductive age in the St. Louis area—the Contraceptive CHOICE project—assessed the impact of an educational intervention designed to increase awareness of LARC among women who wanted to avoid pregnancy for at least 1 year. The 10,000 women who enrolled in the project had the opportunity to obtain the contraceptive method of their choice at no cost in a variety of clinical settings where they received family planning, obstetrical, gynecological, and primary care (including two facilities providing abortion care) (McNicholas et al., 2014; Secura et al., 2010). The study found that offering LARC at the time of enrollment was well received; 75 percent of the 9,256 participants opted for intrauterine devices (IUDs) or implants. LARC users were more likely than non-LARC users to continue using contraception at 12 and 24 months (86 percent versus 55 percent at 12 months, 77 percent versus 41 percent at 24 months). The generalizability of these findings, however, is uncertain given that the contraceptives were free, and the study population included only women who wanted to avoid pregnancy. The CHOICE

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study also evaluated a structured approach to contraceptive counseling and found that counseling could be provided effectively by trained personnel without a medical background (Madden et al., 2013).

INITIAL CLINICAL ASSESSMENT

Abortion care should always begin with a clinical evaluation, including a pertinent medical history and clinical assessment to assess the presence of comorbidities or contraindications relevant to the procedure. The primary aim of the evaluation is to confirm an intrauterine pregnancy and determine gestation. The physical exam may involve laboratory tests and ultrasonography to confirm an intrauterine pregnancy; assess gestation; screen for sexually transmitted infections (STIs) and cervical infections; document Rh status; or evaluate uterine size, position, and possible anomalies (ACOG and SFP, 2014; Goldstein and Reeves, 2009; Goodman et al., 2016; NAF, 2017a; RCOG, 2015; WHO, 2014). Women whose Rh status is unknown should be offered Rh testing and, if Rh negative, offered Rh immune globulin (ACOG and SFP, 2014, NAF, 2017a; RCOG, 2015). No evidence, however, indicates that Rh immune globulin is needed in pregnancies under 8 weeks' gestation (NAF, 2017a). While it should not delay the abortion procedure, screening for STIs may be appropriate if available (NAF, 2017a ; RCOG, 2015). The contraindications and other circumstances affecting the appropriateness of each abortion method are discussed later in the chapter.

Pregnancy is dated from the first day of the last menstrual period (LMP) and is commonly measured by days' or weeks' gestation (Goldstein and Reeves, 2009). Either clinical evaluation or ultrasound examination can be used to establish gestation (ACOG and SFP, 2014; WHO, 2014). Ultrasound is not required, however, and there is no direct evidence that it improves the safety or effectiveness of the abortion (Kaneshiro et al., 2011; NAF, 2017a; Raymond et al., 2015; RCOG, 2015). In a study of nearly 4,500 medication abortion patients aimed at assessing the feasibility and efficacy of foregoing routine use of ultrasound, Bracken and colleagues (2011) found that LMP date combined with physical examination was highly effective at determining eligibility for medication abortion—patients accurately assessed their eligibility (Bracken et al., 2011).

SAFETY AND EFFECTIVENESS OF CURRENT ABORTION METHODS

Several methods—medication, aspiration, dilation and evacuation (D&E), and induction—are used to perform an abortion depending on weeks' gestation, patient preference, provider skill, need and desire for sedation, costs, clinical setting, and state policies and regulations.

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Medication Abortion

Medication abortion in early pregnancy is accomplished using mifepristone, a progesterone receptor antagonist that competitively interacts with progesterone at the progesterone receptor site, thereby inhibiting the activity of endogenous or exogenous progesterone. This process initiates the breakdown of the endometrium and implanted embryo (Borkowski et al., 2015). Mifepristone, sold under the brand name Mifeprex,[1] is the only medication specifically approved by the FDA for use in medication abortion (Woodcock, 2016). Taken orally, it has been shown to increase sensitivity to prostaglandins and is most commonly used in conjunction with misoprostol, a prostaglandin E1 analogue. Misoprostol causes uterine contractions as well as cervical ripening and can be administered orally, sublingually, buccally, or vaginally.[2] Since mifepristone's initial FDA approval in 2000, an extensive body of research has led to improvements in the drug's protocol, including a lower recommended dosage, an increased period of eligibility from 49 days' to 70 days' (10 weeks') gestation, and a recommendation that the misoprostol be taken buccally rather than sublingually or orally to minimize side effects (Borkowski et al., 2015; Chai et al., 2013). The World Health Organization (WHO) has included mifepristone and misoprostol on its Model List of Essential Medicines since 2005 (WHO, 2015).[3]

Few women have contraindications to medication abortion (ACOG and SFP, 2014). The FDA-approved Mifeprex label states that the drug should not be used for women with confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass; an IUD in place; chronic adrenal failure; concurrent long-term systemic corticosteroid therapy; hemorrhagic disorders or concurrent anticoagulant therapy; allergy to mifepristone, misoprostol, or other prostaglandins; or inherited porphyrias (FDA, 2016a).

BOX 2-1

FDA Risk Evaluation and Mitigation Strategy (REMS) Program for Mifeprex

The FDA REMS program restricts the chain of supply of certain drug products to ensure that the drugs are distributed only by authorized prescribers or pharmacies under specified conditions. The FDA considers the following when determining the necessity of a REMS:

- estimated size of the population likely to use the drug involved;
- seriousness of the disease or condition that is to be treated with the drug;
- expected benefit of the drug with respect to such disease or condition;
- expected or actual duration of treatment with the drug;

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- seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug; and
- whether the drug is a new molecular entity.

As of March 2017, there were 77 approved REMS programs, including that of Mifeprex. A drug requiring a REMS must have at least one of the following:

- a Medication Guide for consumers;
- a communication plan for health care providers; and
- one of six "elements to assure safe use" of the medication (e.g., specifications for prescribers, places and conditions where the drug can be dispensed, and patient monitoring).

The FDA first established a REMS program for Mifeprex in 2011 and revised it in March 2016 along with an update to the drug's label. The revised REMS requirements do not differ substantially from the original. They include the following:

- Mifeprex may be dispensed only to patients in clinics, hospitals, or medical offices under the supervision of a certified prescriber. It cannot be dispensed through retail pharmacies.
- To be certified, health care providers must submit a Prescriber Agreement to the drug's distributor, Danco Laboratories, attesting to their ability to assess duration of pregnancy and to diagnose ectopic pregnancy. They must be able to provide or arrange for surgical intervention as well as access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary. Nonphysicians, such as certified nurse-midwives and other advanced practice clinicians, may prescribe Mifeprex if they have prescription authority under state law.
- Before patients receive the drug, the prescriber must provide the patient the FDA-approved Medication Guide, fully explain the potential risks related to the treatment regimen, and review and complete the Patient Agreement form with the patient.

The revised label

- lowered the recommended Mifeprex dosage to 200 mg;
- extended the gestation period appropriate for its use from 49 days' to 70 days' (10 weeks') gestation;
- eliminated the requirement for an in-person follow-up visit; and
- eliminated mandatory reporting of nonfatal adverse events.

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SOURCES: Borkowski et al., 2015; Dabrowska, 2017; FDA, 2016a,b,c; Gassman et al., 2017; Woodcock, 2016.

Since 2011, the distribution and use of Mifeprex has been restricted under the requirements of the FDA Risk Evaluation and Mitigation Strategy (REMS) program (see Box 2-1). (See Chapter 3 for additional details on REMS requirements for clinicians who prescribe Mifeprex.) Despite the restriction, use of the medication method is increasing, especially in early pregnancy. As noted in Chapter 1, the percentage of all abortions by medication rose by 110 percent between 2004 and 2013 and is expected to increase further (Jatlaoui et al., 2016). In 2014, medication abortions accounted for approximately 45 percent of all U.S. abortions performed <9 weeks' gestation (Jones and Jerman, 2017).

Effectiveness of the Current Medication Regimen

The current FDA-approved regimen for medication abortion is 200 mg of mifepristone taken orally, followed by 800 mcg of misoprostol taken buccally 24 to 48 hours later (FDA, 2016a). A recent systematic review of this regimen—including 33,846 medication abortions—found an overall effectiveness rate of 96.7 percent for gestations up to 63 days (9 weeks) (Chen and Creinin, 2015).[4]

Reversal of Medication Abortion

There has recently been media attention to claims that medication abortions can be "reversed" by taking progesterone after the mifepristone but before taking the misoprostol (Graham, 2017). The claims are based on a case series report of seven patients who did not receive standardized doses or formulations of the medications (i.e., mifepristone or progesterone) (Delgado and Davenport, 2012). Case series are descriptive reports that are considered very low-quality evidence for drawing conclusions about a treatment's effects (Guyatt et al., 2011). In a related subsequent systematic review, Grossman and colleagues (2015) assessed the likelihood of a pregnancy continuing if the abortion medication regimen is not completed (i.e., the mifepristone dosage is not followed by misoprostol). However, the review found that there were insufficient data to conclude that the progesterone treatment is more likely to lead to continued pregnancy compared with expectant management after mifepristone alone.

Expected Side Effects

It is common for medical procedures to result in side effects in addition to the intended outcome. Medication abortions involve cramping, pain, and bleeding, similar to the symptoms of a miscarriage (

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ACOG and SFP, 2014; Borkowski et al., 2015; FDA, 2016a). Vaginal bleeding is expected during and after an abortion and occurs in almost all patients during a medication abortion (FDA, 2016a). Bleeding generally starts as the tissue begins to separate from the endometrium and continues for several days after the abortion is complete. The heaviest bleeding occurs during and immediately following the passage of the gestational sac and lasts 1 to 2 days. Some bleeding and spotting may occur up to 9–16 days.

Like bleeding, uterine pain and cramping are an expected and normal consequence of medication abortion (FDA, 2016a). Cramping can last from a half-day to 3 days (Ngo et al., 2011). Nonsteroidal anti-inflammatory drugs (NSAIDs) are typically recommended to manage the pain. Ibuprofen—after the onset of cramping—has been shown to reduce both pain and later analgesia use (Jackson and Kapp, 2011 ; Livshits et al., 2009). However, some women still report high levels of pain, and pain is commonly reported as the worst feature of the method. Prophylactic regimens for pain management are an area of active research (Dragoman et al., 2016).

Other side effects reported by women who undergo medication abortion include nausea, vomiting, weakness, diarrhea, headache, dizziness, fever, and chills (Chen and Creinin, 2015; FDA, 2016a). About 85 percent of patients report at least one of these side effects, and many patients are expected to report more than one (FDA, 2016a).

Complications

Complications after medication abortion, such as hemorrhage, hospitalization, persistent pain, infection, or prolonged heavy bleeding, are rare—occurring in no more than a fraction of a percent of patients (Chen and Creinin, 2015; FDA, 2016a; Ireland et al., 2015; Kulier et al., 2011; Woodcock, 2016). Obesity (i.e., a body mass index [BMI] of 30 or greater) has not been found to increase the risk for adverse outcomes after medication abortion (Strafford et al., 2009). The Society of Family Planning suggests that medication abortion may be preferable to aspiration abortion when patients, including those with extreme obesity, are at risk of procedural and anesthetic complications (SFP, 2012).

Hemorrhage Prolonged heavy bleeding is rare but may indicate an incomplete abortion[5] or other complications. Hemorrhage requiring assessment or treatment following medication abortion is also rare. The FDA advises that women contact a health care provider immediately if bleeding after a medication abortion soaks through two thick full-size sanitary pads per hour for two consecutive hours (FDA, 2016a). In a study of 11,319 medication abortions performed in California between 2009 and 2010, hemorrhage occurred in 16 cases (0.14 percent) (Upadhyay et al., 2015).

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The need for a blood transfusion—an uncommon occurrence—is an indication of clinically significant hemorrhage. In a study of more than 1,000 women receiving medication abortion in Norway, 1 patient required a transfusion (0.1 percent) and 32 required an aspiration procedure because of continued bleeding (3.0 percent) (Løkeland et al., 2014). In Chen and Creinin's (2015) systematic review of 20 studies and 33,846 women (described above), 0.03 to 0.6 percent of women required a blood transfusion after a medication abortion.

Infection Serious infection occurs rarely after medication abortion; reports of fatal sepsis are exceedingly rare (<1 in 100,000) (FDA, 2011; Woodcock, 2016). Signs and symptoms of serious infection are fever of 100.4°F or higher lasting more than 4 hours, tachycardia, severe abdominal pain, pelvic tenderness, or general malaise with or without fever occurring more than 24 hours after administration of misoprostol (ACOG and SFP, 2014; FDA, 2016a). There is no evidence of a causal relationship between use of mifepristone and misoprostol and an increased risk of infection or death (FDA, 2016a; Woodcock, 2016). The incidence of infection in recent studies ranges from 0.01 to 0.5 percent (Chen and Creinin, 2015; Cleland et al., 2013; Upadhyay et al., 2015). According to the FDA's Adverse Event Reporting System, there were nine reports of severe bacterial infections following medication abortion from November 1, 2012, through April 30, 2015 (Woodcock, 2016). The FDA has concluded that the available evidence does not support the use of prophylactic antibiotics for medication abortion (CDER, 2016).

Need for uterine aspiration Some women require a uterine aspiration after medication abortion because of retained products of conception, persistent pain or bleeding, or ongoing pregnancy (Chen and Creinin, 2015; Cleland et al., 2013; Ireland et al., 2015; Raymond et al., 2013; Upadhyay et al., 2015). Ireland and colleagues (2015) analyzed more than 13,000 electronic medical records documenting the outcomes of medication abortions (up to 9 weeks' gestation) performed in private Los Angeles clinics from November 2010 to August 2013. Of these, 2.1 percent required an unanticipated uterine aspiration either because of an ongoing pregnancy (0.4 percent) or for persistent pain, bleeding, or both (1.8 percent). Other recent estimates of the need for an unanticipated uterine aspiration range from 1.8 to 4.2 percent (Chen and Creinin, 2015). Rates vary in part because of differences in study populations (including weeks' gestation) and in treatment regimens (Cleland et al., 2013; Raymond et al., 2013; Upadhyay et al., 2015).

Impact of Clinical Setting on the Safety and Effectiveness of Medication Abortion

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There is no direct evidence suggesting that specific types of facilities (e.g., ambulatory surgery centers or hospitals) or facility factors (e.g., size of procedure room or corridor width) are needed to ensure the safety of medication abortion. Indeed, most women in the United States return home after taking mifepristone and take the misoprostol 28 to 48 hours later. As a result, medication abortions occur largely in nonclinical settings. Moreover, as described above, a body of research including systematic reviews (Chen and Creinin, 2015; Kulier et al., 2011; Raymond et al., 2013) and large cohort studies (Cleland et al., 2013; Ireland et al., 2015; Upadhyay et al., 2015) demonstrates that complications such as infection, hemorrhage requiring transfusion, or hospitalization occur in fewer than 1.0 percent of patients.

Some research has focused specifically on medication abortion outside the hospital or clinic setting. A variety of studies, for example, have assessed the self-administration of misoprostol after receiving mifepristone in a clinic. This largely observational research shows that home use of misoprostol produces outcomes similar to those of the clinic-supervised method (Clark et al., 2005; Fiala et al., 2004; Guengant et al., 1999; Løkeland et al., 2014; Ngoc et al., 2004; Shannon et al., 2005; Shrestha and Sedhai, 2014).

Other research has assessed the safety and effectiveness of home use of both mifepristone and misoprostol (Chong et al., 2015; Conkling et al., 2015; Platais et al., 2016). In one U.S. prospective nonrandomized study, 400 women with pregnancies up to 63 days' gestation were offered the choice of either clinic-supervised or home use of mifepristone. Of these women, 128 chose home administration, and 272 chose clinic administration; the women did not differ significantly in terms of gravidity, gestation, or other measured characteristics. The women choosing home use were slightly older (27.8 versus 26.0 years) and more likely to be doing paid work (78.9 versus 68.0 percent). Success rates did not differ between the groups (96.3 versus 96.9 percent), and the 2 patients who required hospitalization were in the clinic-supervised group. One patient was diagnosed with an incomplete abortion and underwent a follow-up dilation and curettage procedure, and the other was treated for severe nausea and vomiting (Chong et al., 2015). A related study found that among 301 women offered the choice of home use, the factor most cited by women who chose this option was flexibility in scheduling (Swica et al., 2013).

Telemedicine

Telemedicine is the use of telecommunications and information technology to provide access to health assessment, diagnosis, intervention, consultation, supervision, and information across distance (HHS, 2017b). For medication abortion, the process involves a health care provider's reviewing the relevant medical information and having a discussion with the patient via teleconference. If clinical criteria are

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met, the health care provider remotely dispenses or issues a prescription for the medication abortion regimen (Aiken et al., 2018; Grossman et al., 2011a). Grossman and colleagues (2011a) investigated the effectiveness and acceptability of telemedicine for medication abortion (mean days' gestation was 47 days) compared with face-to-face physician visits in Iowa. Roughly half of the 578 patients were enrolled in the telemedicine option. The success rates for the two options were similar: 98.7 percent for the telemedicine patients and 96.9 percent for the clinic patients. No patient in either group required hospitalization, and there was no significant difference in the occurrence of adverse events. One of the 223 patients in the telemedicine group received a blood transfusion. In a recent 7-year retrospective cohort study in Iowa, researchers compared the rate of clinically significant adverse events (hospital admission, surgery, blood transfusion, emergency department treatment, or death) after medication abortion for 8,765 telemedicine patients and 10,405 in-person patients (Grossman and Grindlay, 2017). The overall rate of adverse events was less than 0.3 percent. The difference between the telemedicine patients (0.18 percent) and in-person patients (0.32 percent) was not statistically significant and was within the authors' margin of noninferiority. This finding indicates that telemedicine provision of medication abortion was not associated with a significantly higher prevalence of adverse events compared with in-person provision.

These reported risks are both low and similar in magnitude to the reported risks of serious adverse effects of commonly used prescription and over-the-counter medications. For example, it has been estimated that the use of NSAIDs is responsible for 3,500 hospitalizations and 400 deaths per year in UK residents aged 60 or older, a risk rate of 0.23 and 0.03 percent, respectively (Hawkey and Langman, 2003). The NSAID-related risk of hospitalization in elderly Medicaid patients in the United States has been estimated to be even higher—1.25 percent in one study (Smalley et al., 1995). The risk of diarrhea with many common antibiotics is as high as 39 percent (McFarland, 1998), and the risk of hospitalization due to the more serious *Clostridium difficile* infection may be as high as 0.02 percent with some antibiotic combinations (Hirschhorn et al., 1994). Taken together, these findings provide additional indirect evidence that no facility-specific factors are needed to ensure the safety of medication abortion, as there is no perceived need for facility-specific factors to ensure the safety of these other common pharmaceuticals. These safety data accord with professional guidelines or best practices according to which routine early medication abortion does not require sophisticated settings and can be safely performed in settings typical for the delivery of women's health care and family planning services (ACOG and SFP, 2014; NAF, 2017a; RCOG, 2015; WHO, 2014).

In their analysis of the Iowa study described above, Grossman and colleagues (2013) conducted a geographic analysis to assess the effect of the telemedicine model on access to medication abortion for

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women in different areas of the state. They found that the proportion of all Iowa abortions that were medication abortions had increased, from 33.4 to 45.3 percent (p <.001), in the 2-year periods before and after telemedicine was introduced. The increase was especially notable among women living in more remote areas. Women who lived more than 50 miles from an abortion clinic that provided only surgical abortions were 16 percent more likely to have a medication abortion (adjusted odds ratio [aOR] = 1.16; 95% confidence interval [CI] = 1.05, 1.28). The proportion of medication abortions at the study sites had also increased from 46 to 54 percent after telemedicine was introduced (p <.001). Overall, women in Iowa had a 46 percent greater likelihood of having an earlier abortion (<14 weeks' gestation) (aOR = 1.46; 95% CI = 1.22, 1.75).

Aspiration Abortion

Aspiration is a minimally invasive and commonly used gynecological procedure (Meckstroth and Paul, 2009; Roblin, 2014).[6] The procedure time is typically less than 10 minutes (Edelman et al., 2001; Goldberg et al., 2004). As noted in the previous chapter, aspiration is currently the most common abortion method used in the United States regardless of gestation, accounting for almost 68 percent of abortions in 2013.[7] The method may be used up to 14 to 16 weeks' gestation. Aspiration is also used in cases of early pregnancy loss (miscarriage) and management of incomplete abortion for medication abortion.

The first steps in the procedure are cervical dilation and priming (when appropriate) so that the contents of the uterus can be evacuated. Cervical dilation is usually done using tapered mechanical dilators and is recommended over routine priming except for adolescents and others for whom cervical dilation may be challenging (Allen and Goldberg, 2016). Cervical priming is accomplished with either osmotic dilators[8] or pharmacological agents (e.g., misoprostol), or both. When placed in the cervix, the osmotic dilator absorbs moisture from the tissues surrounding the cervix and gradually swells to slowly open the cervical orifice (os). The pharmaceutical agents are prostaglandin analogues or progesterone antagonists, such as the drug misoprostol, which is also used in medication abortion.

After cervical dilation and, when indicated, priming, a suction cannula (plastic or metal tube) is inserted through the cervix into the uterus. The cannula is attached to a vacuum source—an electric vacuum pump for electric vacuum aspiration or a handheld, hand-activated aspirator (syringe) for manual vacuum aspiration—to empty the uterine contents. Ultrasound guidance is sometimes used (RCOG, 2011).

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See later in this chapter for a discussion of the use of sedation and anesthesia during abortion procedures, including the implications for personnel needs and facility requirements.

Effectiveness of Aspiration Abortion

Recent comparisons of aspiration and medication abortion methods indicate that aspiration may be only slightly more effective than medication abortion in early pregnancy. In Ireland and colleagues' (2015) study of private Los Angeles clinics described in the prior section, the efficacy rate for almost 17,000 aspiration abortions performed up to 9 weeks' gestation was 99.8 percent, compared with 99.6 percent for medication abortions[9] for the same gestational period (Ireland et al., 2015).

Expected Side Effects

As in medication abortion, bleeding, uterine pain, and cramping are expected and normal consequences of aspiration abortion.

Complications

Aspiration abortions rarely result in complications. In a recent retrospective analysis of California fee-for-service Medicaid claims data, 57 of almost 35,000 women (0.16 percent) were found to have experienced a serious complication (hospital admission, surgery, or blood transfusion) after an aspiration abortion (Upadhyay et al., 2015). A systematic review on aspiration-related complications documents a somewhat higher complication rate (ranging from 0 to 5 percent), but a large proportion of the studies in that review included now outdated procedures, including dilation and sharp curettage (White et al., 2015).

In a historical cohort study, Guiahi and colleagues (2015) analyzed the outpatient medical records of women who had undergone an aspiration abortion between January 2009 and March 2014 in a Colorado clinic. The researchers compared the outcomes of women with (n = 587) and without (n = 1,373) medical comorbidities, including diabetes, hypertension, obesity (weight ≥200 lb or BMI ≥30), HIV, epilepsy, asthma, thyroid disease, and/or bleeding and clotting disorders having aspiration abortions. The researchers found no difference in the rate of complications between the women with at least one comorbidity and those with no comorbidity (odds ratio [OR] = 0.9; 95% CI = 0.5, 1.6).

Need for repeat aspiration Repeat aspiration is most often required for retained products of conception after an abortion. Rates of <0.1 to 8.0 percent have been reported for this complication, related to gestation, experience of the provider, and use of ultrasound guidance (White et al., 2015). Studies

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showing the highest rates of repeat aspiration included women at ≤6 weeks' gestation and were conducted more than 20 years ago (Bassi et al., 1994). Tissue inspection is recommended after aspiration abortion, regardless of gestation, but products of conception may be difficult to identify prior to 7 weeks' gestation (NAF, 2017a; SFP, 2013). Additional protocols, including magnification of aspirate, follow-up by serum beta-hCG estimation, and flotation of tissue with backlighting may be used to confirm abortion completion (NAF, 2017a; RCOG, 2011; SFP, 2013).

Hemorrhage Hemorrhage requiring transfusion or other treatment (medication administration or repeat aspiration) complicates 0.0 to 4.7 percent of aspiration abortions, with more recent studies reporting a rate of 1.3 percent (Upadhyay et al., 2015; White et al., 2015). In the California Medicaid study, 0.13 percent of aspiration procedures were complicated by hemorrhage (Upadhyay et al., 2015).

Infection Current clinical guidelines recommend routine antibiotic prophylaxis before all aspiration abortions (NAF, 2017a; RCOG, 2015; SFP, 2011b; WHO, 2014). Like any invasive procedure, aspiration abortion carries some risk of infection. If untreated, an upper genital tract infection subsequent to abortion can lead to chronic pelvic pain, dyspareunia, ectopic pregnancy, and infertility (Low et al., 2012). Serious infection after aspiration, however, is rare. In a 2012 systematic review, the Cochrane Collaboration evaluated the effectiveness of perioperative antibiotics in preventing upper genital tract infection (including infection of the uterus and fallopian tubes) (Low et al., 2012). The researchers concluded that universal antibiotic prophylaxis is effective in preventing infection after an aspiration procedure: the incidence of upper genital tract infection among women who received prophylactic antibiotics was 59 percent of that among women who received a placebo. The rate of infection was 5.8 percent among women who received antibiotics (n = 3,525) and 9.4 percent among women in the placebo group (n = 3,500).

In a more recent systematic review of complications following aspiration abortion (up to 14 weeks' gestation), White and colleagues (2015) report that 0.0 to 0.4 percent of 188,395 women undergoing aspiration abortions required intravenous (IV) antibiotics after the procedure in 11 of 12 office-based settings. In Upadhyay and colleagues' (2015) analysis of almost 35,000 aspiration abortions in California, 94 women (0.27 percent) developed an infection after the procedure. Most infections after outpatient aspiration procedures are treated with oral antibiotics, with up to 0.4 percent of patients with infection requiring IV antibiotic administration (White et al., 2015).

Uterine perforation Uterine perforation involves injury to the uterine wall, as well as potential injury to other abdominal organs. While the risk of uterine perforation in older studies has been reported as ≤0.1

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to 2.3 percent, the majority of more recent studies of aspiration abortion report no cases of uterine perforation or note that perforations that occurred were successfully managed conservatively without the need for additional surgery or hospitalization (White et al., 2015). In the study of almost 35,000 California Medicaid-covered aspiration abortions referenced above, 0.01 percent resulted in a perforation (Upadhyay et al., 2015).

Cervical laceration Cervical laceration (injury to the cervix from instrumentation) is also very rare, with most studies reporting none or 1 case (<0.1 to 0.6 percent) (Ohannessian et al., 2016; White et al., 2015). In a study evaluating the risks of aspiration abortion in teens versus adults, an increased risk of cervical laceration was noted for adolescent patients (0.5 versus 0.2 percent), but this study was conducted prior to current approaches to cervical preparation (Cates et al., 1983; White et al., 2015). Use of osmotic dilators was common in older studies, but the more common approach today is medical, using misoprostol 2 to 3 hours prior to the procedure (Allen and Goldberg, 2016; O'Connell et al., 2009). While current recommendations do not include routine use of medical or mechanical cervical preparation because of the delay that would result, misoprostol is commonly used in nulliparous women and young adolescents between 12 and 14 weeks' gestation (Allen and Goldberg, 2016).

Dilation and Evacuation

Fewer than 9 percent of abortions in the United States occur after 13 weeks' gestation (Jatlaoui et al., 2016). The D&E method, sometimes referred to as a second-trimester surgical abortion, appears to account for the majority of procedures performed between 14 and 20 weeks' gestation. Precise estimates of the rate of abortions by type during these weeks are not available. Reports often cite CDC surveillance statistics as suggesting that D&Es account for up to 96 percent of abortions between 14 and 20 weeks' gestation (ACOG, 2013; Hammond and Chasen, 2009). However, the oft-cited CDC data are actually aggregate estimates that include not only D&E but also other methods (Jatlaoui et al., 2016; Pazol et al., 2009).

D&E techniques have evolved in the decades since the method was first developed (ACOG, 2013; Hammond and Chasen, 2009; Lohr et al., 2008). The procedure is typically performed in two stages, although the specific approaches to cervical preparation, instrumentation, and other aspects may vary (Grossman et al., 2008; Ibis Reproductive Health, 2015; Lohr et al., 2008). The procedure itself generally takes less than 30 minutes (Ben-Ami et al., 2009; Grossman et al., 2008, 2011b). The first step is cervical preparation, dilating the cervix with laminaria (or other type of osmotic dilator) and/or a prostaglandin (e.g., misoprostol). Slow dilation is recommended (e.g., over a few hours, overnight, or

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sometime repeated over 24 to 48 hours) to minimize the need for supplemental manual or mechanical dilation (Grossman et al., 2008; Lohr et al., 2008). With a greater degree of dilation, the uterus is more easily emptied, instruments are easier to use, and procedure time is shortened (Hern, 2016). Once dilation is adequate and analgesia, sedation, and/or anesthesia have been administered, the amniotic fluid is aspirated (Lohr et al., 2008; WHO, 2014). Before 16 weeks' gestation, suction aspiration may suffice to empty the uterus. At 16 weeks, forceps extraction may also be required. Beyond 16 weeks, suction is not effective, and forceps should be used to remove fetal parts and the placenta. A curette and/or additional suction are also used to remove any remaining tissue or blood clots. Following the procedure, the provider examines the tissue to confirm that the evacuation was complete. Patients should be observed following the procedure to monitor for any postoperative complications (Hammond and Chasen, 2009; Lohr et al., 2008).

Ultrasonography is recommended so the physician can visualize the surgical instruments, locate fetal parts, and confirm an empty uterus (NAF, 2017a). Routine intraoperative ultrasonography has been demonstrated to significantly reduce the risk of uterine perforation and shorten the time required to complete the procedure (Darney and Sweet, 1989).

Performing D&E procedures requires advanced training and/or experience (Cates et al., 1982; Hern, 2016; Lohr et al., 2008; RCOG, 2015; WHO, 2012). Chapter 3 reviews the required clinical skills for performing abortions.

Complications

Although the risk of complications increases with weeks' gestation (Bartlett et al., 2004; Grossman et al., 2008; Zane et al., 2015), a range of retrospective cohort studies, case series, chart reviews, and a prospective case series have shown D&E to be effective with minimal rates of complications, ranging from 0.05 to 4 percent (ACOG, 2013; Autry et al., 2002; Bryant et al., 2011; Cates et al., 1982; Frick et al., 2010; Grimes et al., 1977; Grossman et al., 2008; Jacot et al., 1993; Mauelshagen et al., 2009; Peterson et al., 1983).

One study, however, suggests that a history of multiple prior cesarean deliveries may significantly increase the risk of a major complication. In a multivariable logistic analysis of 2,973 D&Es performed between 2004 and 2007 at an urban public hospital, Frick and colleagues (2010) found an overall rate of major complications (i.e., transfusion required; disseminated intravascular coagulation; or a reoperation involving uterine artery embolization, laparoscopy, or laparotomy) of about 1.0 percent. However, women with two or more prior cesarean sections had a sevenfold increased risk of a major complication (OR = 7.37; 95% CI = 3.35, 15.80) (Frick et al., 2010). A history of one prior cesarean section was not

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associated with an increased risk of complications, although the authors note that a larger sample might lead to different results.

Obesity has also been studied as a possible risk factor for women undergoing D&E abortions (Benson et al., 2016; Lederle et al., 2015; Murphy et al., 2012). In a retrospective cohort study of 4,968 women undergoing aspiration and D&E abortions at a large outpatient clinic in 2012–2014, obesity was not associated with increased risk of complications[10] (Benson et al., 2016). The same conclusion resulted from a retrospective cohort study of 4,520 D&Es performed in a hospital-based abortion practice in 2009–2013 and a retrospective review of 1,044 women undergoing D&E or dilation and suction (D&S)[11] between 13 and 24 weeks' gestation in 2007–2010 (Lederle et al., 2015; Murphy et al., 2012). Lederle and colleagues (2015) found no association between BMI and D&E complications[12] after adjustment for age, ethnicity, prior vaginal delivery, prior cesarean delivery, and gestational duration. Murphy and colleagues (2012) compared complication rates, operative times, and anesthesia times between obese and nonobese (BMI <30) women and found no significant difference in complication rates. Finally, a retrospective analysis of D&E procedures performed between 2009 and 2014 found an association between obesity and increased risk for complications[13] in abortions performed after 14 weeks' gestation (Mark et al., 2017). Complications increased by BMI category,[14] and the increase in complications in women with Class III obesity was significant (OR = 5.04; 95% CI = 1.65–15.39).

Hemorrhage In studies of abortions performed in the year 2000 or later, D&E-related hemorrhage requiring transfusion or other treatment occurred in 0.0 to 1.0 percent of cases (Frick et al., 2010; Grossman et al., 2011a; Mauelshagen et al., 2009).

Infection Routine antibiotic prophylaxis is recommended for all surgical abortions (ACOG, 2013; NAF, 2017a; RCOG, 2015; WHO, 2014). Infection after a D&E is uncommon, with rates ranging from 0.0 to 2.0 percent (Autry et al., 2002; Grossman et al., 2011a; Mauelshagen et al., 2009). In the California Medicaid study described above, Upadhyay and colleagues (2015) found that 0.3 percent or 18 of 8,837 abortions performed after 13 weeks' gestation resulted in an infection, although these procedures included both D&Es and inductions.

Cervical lacerations Injuries to the cervix and uterus have decreased significantly with routine cervical preparation prior to D&E (ACOG, 2013). Recent studies have reported rates of 0.02 to 3.3 percent (Autry et al., 2002; Frick et al., 2010). The risk of cervical laceration is associated with mechanical dilation, nulliparity, advanced gestation, and provider inexperience (ACOG, 2013). Thus, as noted above, performing D&E procedures requires advanced training and/or experience.

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Uterine perforation While uterine perforation is more common in D&E than in aspiration procedures, the incidence remains quite low and is likely related to the availability of cervical preparation and ultrasound guidance (Grossman et al., 2008). Limited clinician experience and underestimation of the duration of pregnancy are also factors that have been associated with uterine perforation (Grossman et al., 2008). A 1989 study compared the incidence of perforation during 810 D&E procedures with and without sonography (Darney and Sweet, 1989). Using ultrasound to guide the use of intrauterine forceps clearly improved the safety of the procedure: the rate of perforation declined significantly from 1.4 to 0.2 percent. Studies dating from 2010 to 2015 report perforation rates ranging from 0.2 to 0.8 percent (Frick et al., 2010; Upadhyay et al., 2015).

The facility requirements that are appropriate for D&Es depend on the level of sedation and anesthesia that is used. (See later in this chapter for a review of the use of analgesia, sedation, and anesthesia during abortions.)

Induction Abortions

As noted in Chapter 1, abortion terminology can be confusing. All abortion methods are sometimes referred to as “induced,” and the term “medical” is often used to describe any nonsurgical method regardless of how early or late in pregnancy it occurs. In this section, the term “induction abortion” refers specifically to nonsurgical abortions that use medications to induce labor and delivery of the fetus. Relevant research and clinical guidelines use varying lower and upper gestation limits. In practice, the gestational parameters for induction vary depending on the facility, patient and provider preference, and state laws and regulations (SFP, 2011a).

Induction abortions are rarely performed in the United States; in 2013, they accounted for approximately 2 percent of all abortions at 14 weeks’ gestation or later (Jatlaoui et al., 2016). For many women in the United States, D&E is often the preferred alternative because induction is more painful, its timing is less predictable and slower (sometimes taking more than 24 hours), and it is more expensive (see below) (ACOG, 2013; Ashok et al., 2004; Grimes et al., 2004; Grossman et al., 2008; Kelly et al., 2010; Lohr et al., 2008). In some clinical settings, however, D&E is not an option because the available clinicians lack the necessary experience and/or training in D&E procedures (SFP, 2011a).[15] In addition, D&E abortions are illegal in Mississippi and West Virginia.[16]

Optimal Medication Regimen for Induction Abortions

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The medication regimens for performing an induction abortion have evolved and improved in response to a growing body of research—most notably with respect to the combined use of mifepristone and misoprostol (Gemzell-Danielsson and Lalitkumar, 2008; Wildschut et al., 2011). The safety and efficacy of different medications and medication regimens for inducing abortion has been assessed in RCTs, retrospective analyses, prospective observational studies, and systematic reviews (Ashok et al., 2002, 2004; Constant et al., 2016; Goh and Thong, 2006; Gouk et al., 1999; Hamoda et al., 2003; Kapp et al., 2007; Mauelshagen et al., 2009; Ngoc et al., 2011; Sonalkar et al., 2017; Wildschut et al., 2011).

In a systematic review of the effectiveness and side effects of different induction abortion medication regimens, the Cochrane Collaboration identified 36 RCTs that used various agents and methods of administration. The researchers concluded that a combination of mifepristone and misoprostol is the most effective approach and requires the shortest amount of time (Wildschut et al., 2011).

Guidelines developed by the American College of Obstetricians and Gynecologists (ACOG) and endorsed by the Society of Family Planning (SFP) and the Society of Maternal-Fetal Medicine recommend an alternative misoprostol regimen when mifepristone is not available (ACOG, 2013). Although effective, misoprostol-only regimens take longer (Wildschut et al., 2011) and as a result, are likely to be more costly to the patient with respect to time, discomfort, and out-of-pocket expense.

The National Abortion Federation (NAF) guidelines note that, when performed by trained clinicians, induction abortions can be provided in medical offices, clinics, or higher-level health care facilities (NAF, 2017a).

Complications

The expected side effects of induction abortions are similar to those described above for medication abortions at or before 10 weeks' gestation: cramping, pain, and bleeding, as well as nausea, vomiting, diarrhea, chills, and headache (Borgatta, 2011; Ngoc et al., 2011; Wildschut et al., 2011). The side effects are a result of the medications that are used for induction, the abortion process itself, or the medications used to manage pain (Borgatta, 2011).

The literature on complications resulting from induction abortions is limited by a variety of factors. The available research is a mix of study designs analyzing a variety of treatment protocols and patient populations that differ in important ways, including weeks' gestation, parity, fetal anomaly, and the pharmaceutical regimens and agents used to induce labor (Goyal, 2009; SFP, 2011a). All of these factors may affect patient outcomes. Moreover, while the research on the outcomes of medication and aspiration abortions draws on the outcomes of thousands of patients, the study samples for research on inductions are relatively small and thus have limited statistical power. Nevertheless, the available evidence

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consistently finds that induction abortion rarely leads to serious complications, although they occur more often than in D&E procedures (Bryant et al., 2011; Grossman, et al., 2008; Mauelshagen et al., 2009; SFP, 2011b).

In addition, among women with a prior cesarean delivery, the use of prostaglandins (particularly misoprostol) to induce labor during a normal vaginal delivery has been associated with an increased risk of uterine rupture—a potentially life-threatening condition (Lydon-Rochelle et al., 2001). Because methods to induce abortion are similar to those used to induce vaginal deliveries, research has assessed whether women with a prior cesarean are at similar risk of uterine rupture when undergoing an induction abortion. The evidence suggests that misoprostol-induced abortions are safe after a cesarean. Uterine rupture has been documented in fewer than 0.4 percent of induction abortions among women with a prior cesarean (Berghella et al., 2009; Goyal, 2009).

POSTABORTION CARE

Clinical guidelines suggest that, regardless of abortion method, routine in-person follow-up care is not necessary. However, clinicians may choose to offer an in-person follow-up visit to women 7–14 days after the procedure to confirm the absence of ongoing pregnancy and to assess recovery (NAF, 2017a; WHO, 2014). In the case of medication abortion, which usually occurs in a nonclinical setting, confirmation of termination of the pregnancy is the primary concern after the abortion. The FDA advises that follow-up is needed to confirm complete termination of pregnancy, but that termination can be confirmed by medical history, clinical examination, hCG testing, or ultrasound (FDA, 2016a). Similarly, NAF advises that confirmation can be established by any of these methods in an office, by telephone, or through electronic communication (NAF, 2017a).

Before a woman leaves a facility after an abortion procedure (or after she has taken the appropriate medication in the case of medication abortion), she should receive instructions on what to expect after the procedure, self-care, resuming intercourse, recognizing signs and symptoms of complications, and how and where to seek assistance if needed (NAF, 2017a; RCOG, 2015; WHO, 2014). Fertility goals and future pregnancy should be discussed, and if a woman opts for contraceptive counseling or a method of contraception, it should be provided before she leaves the facility (NAF, 2017a; RCOG, 2016; WHO, 2014). Other treatment (pain medication, medication for RhD-negative patients, emotional support) and referrals for other services (STI/HIV counseling and testing, abuse support services, psychological or social services, and services of other physician specialists) should also be provided before discharge, as needed (RCOG, 2016; WHO, 2014).

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As with any other procedure, women who receive minimal, moderate, or deeper sedation should be monitored continuously during a recovery period until they have been evaluated and determined to be no longer at risk for hemodynamic instability or respiratory depression (NAF, 2017a). Prior to discharge, women must be ambulatory with stable blood pressure and pulse, bleeding and pain must be controlled, and these criteria must be documented (NAF, 2017a).

USE OF ANALGESIA, SEDATION, AND ANESTHESIA IN ABORTION CARE

Patient comfort not only is of critical interest to the patient but also affects the ability of the clinician to perform a procedure safely and effectively (Allen et al., 2013). People differ in their experience of and tolerance for pain. In their review of pain relief for obstetrical and gynecological procedures in outpatient settings, Allen and colleagues (2013) observed that anxiety, depression, and a woman's expectation of pain are strong predictors of her actual experience of pain during a procedure.

NAF recommends that providers involve women in the analgesia/sedation/anesthesia decision and that the choice be based on the individual patient's needs and an assessment of the risks and benefits (NAF, 2017a). The pain management approach that is best for women undergoing medication, aspiration, D&E, or induction abortions depends not only on which method is used but also on weeks' gestation, the patient's preferences for pain control, her comorbidities (if any), the availability of equipment and specialized personnel, provider preferences, cost, and facility licensure (Allen et al., 2012, 2013; NAF, 2017a; Nichols et al., 2009; RCOG, 2015). Results of a 2002 survey of NAF administrators and providers offer some insight into providers' preferred methods for pain control during aspiration abortions. Almost half (46 percent) of the 110 survey respondents preferred using local and/or oral medication, 33 percent preferred local plus IV sedation, and 21 percent preferred deep sedation or general anesthesia (O'Connell et al., 2009). The survey also elicited information regarding pain control for D&E and induction abortions. Most clinics that offered combined local and IV conscious sedation or general anesthesia used these methods for more than 80 percent of their patients (O'Connell et al., 2008).

The literature on the effectiveness of nonpharmacological approaches to reducing pain during abortion is inconclusive (Tschann et al., 2016). While a variety of methods have been assessed, including relaxation techniques (e.g., focused breathing, visualization, vocal coaching, and positive suggestion), hypnosis, aromatherapy, and abortion doulas, more definitive research is needed.

Pain Management During Aspiration, D&E, and Induction Abortions

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The pharmaceutical options for pain management during an abortion range from oral analgesics (e.g., NSAIDs), to local anesthesia (typically a paracervical block), to minimal sedation/anxiolysis, to moderate sedation/analgesia, to deep sedation/analgesia, to general anesthesia (NAF, 2017a). Along this continuum, the physiological effects of sedation have increasing clinical implications and, depending on the depth of sedation, may require special equipment and personnel to ensure the patient's safety (see Tables 2-2 and 2-3). The greatest risk of using sedative agents is respiratory depression.

The American Society of Anesthesiologists (ASA) issues clinical standards for the safe use of pain medications and anesthesia in the types of outpatient clinical settings where abortions are provided (ASA, 2013, 2014b, 2015). The standards use a physical health classification system—ASA I through ASA VI—to guide clinicians' decisions about anesthesia options. ASA I patients are healthy, and ASA II patients have mild systemic disease;[17] both are medically eligible for all options up to deep sedation in office-based settings. The vast majority of abortion patients—young women—are in these categories. Women with severe systemic disease (ASA III and IV) require further medical assessment and may be eligible for deep sedation (monitored anesthesia care [MAC]) or general anesthesia in an accredited ambulatory surgery center (ASC) or hospital. Table 2-2 shows the ASA levels of sedation and their effects on cognitive, respiratory, and cardiovascular function.

TABLE 2-2 Levels and Effects of Analgesia, Sedation, and Anesthesia

Effect on	Minimal Sedation/ Anxiolysis[a]	Moderate Sedation/ Analgesia[b]	Deep Sedation/ Analgesia	General Anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response with repeated or painful stimulation	Unarousable by painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

[a] Minimal sedation includes local anesthesia, e.g., in the form of a paracervical block.

[b] Moderate sedation is sometimes described as "conscious sedation."

SOURCES: ASA, 2015; ASA Task Force, 2002.

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Safeguards for Managing Complications and Emergencies During an Abortion

The key safeguards—for abortions and all outpatient procedures—are whether the facility has the appropriate equipment, personnel, and emergency transfer plan to address any complications that might occur. While data on the use of specific pain management methods during an abortion are very limited, studies that report outcomes for patients after an abortion find that current pain management methods are safe when appropriate precautions are followed (Dean et al., 2011; Gokhale et al., 2016; Renner et al., 2012).

TABLE 2-3 Minimum Facility Requirements Related to Level of Sedation for Medication, Aspiration, and Dilation and Evacuation (D&E) Abortions

	Minimum Facility Requirements[a]			
Abortion Method	Equipment to Monitor Oxygen Saturation, Heart Rate, and Blood Pressure	Equipment to Monitor Ventilation (e.g., end-tidal carbon dioxide)[b]	Emergency Resuscitation Equipment	Emergency Transfer Plan
Medication	—	—	—	—
Aspiration with moderate sedation[a]	√	—	√	√
D&E				
Deep sedation, or monitored anesthesia care (MAC)	√	√	√	√
General anesthesia	√	√	√	√

NOTES: Checkmarks denote American Society of Anesthesiologists (ASA) minimal facility requirements as they relate to the level of sedation used in medication, aspiration, and D&E abortions.

[a] These requirements are for healthy patients or patients with mild systemic disease, i.e., ASA physical health status classifications ASA I and ASA II. Women with severe systemic disease (i.e., ASA III and IV) should be evaluated, and consideration should be given to using deep sedation (MAC) or general anesthesia in an accredited facility such as an ambulatory surgery center or hospital.

[b] End-tidal carbon dioxide monitoring refers to the noninvasive measurement of exhaled carbon dioxide.

SOURCES: Allen et al., 2013; ASA, 2013, 2014a,b, 2015; ASA Task Force, 2002.

Facility Requirements

Table 2-3 shows the ASA minimal facility requirements as they relate to the level of sedation used in medication, aspiration, and D&E abortions. No special equipment or emergency arrangements are

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required for medication abortions. If moderate sedation is used during an aspiration abortion, the facility should have emergency resuscitation equipment and an emergency transfer plan, as well as equipment to monitor oxygen saturation, heart rate, and blood pressure. D&Es that involve deep sedation or general anesthesia should be provided in similarly equipped facilities that also have equipment to monitor ventilation (e.g., end-tidal carbon dioxide) (ASA Task Force, 2002).

New insights into the safe provision of sedation and anesthesia for abortions in outpatient settings are forthcoming. A unique research project, currently ongoing, is comparing the relative safety, cost, and complications of providing abortions in office-based settings and ASCs (ANSIRH, 2017; Roberts, 2017). The investigators are using a national private insurance claims database containing approximately 50 million patient records to compare adverse events, including anesthesia-related outcomes, in the two settings. The study's results were not available when the committee prepared this report. However, analyses of large-scale databases suggest that the risk of hospital admission after outpatient surgery (involving deep sedation) is rare for healthy patients undergoing procedures that last less than 120 minutes (Fleisher et al., 2007). As noted earlier, aspiration abortions typically take 10 minutes, and D&E procedures less than 30 minutes.

Personnel Requirements

The use of sedation and anesthesia also has important implications for personnel. If moderate sedation is used, it is essential to have a nurse or other qualified clinical staff—in addition to the person performing the abortion—available to monitor the patient (ASA Task Force, 2002; NAF, 2017a). Both deep sedation and general anesthesia require the expertise of an anesthesiologist or certified registered nurse anesthetist (CRNA) to ensure patient safety.

Evidence on Complications of Analgesia, Sedation, and Anesthesia During Abortions

This section reviews the available evidence on complications related to pain management during aspiration, D&E, and induction abortions. As noted above, NSAIDs reduce the discomfort of pain and cramping safely and effectively during a medication abortion.

Aspiration Pain Management

Paracervical blocks are used routinely to reduce the pain of cervical dilation during aspiration procedures (Allen et al., 2013; Nichols et al., 2009). Moderate and deep sedation are also options for aspiration abortion. The blocks are effective in decreasing pain related to cervical dilation and uterine

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aspiration, although administration of the block itself is painful (Allen et al., 2013; Renner et al., 2012), and some providers use other medications to reduce the pain of the injection (Allen et al., 2013). Because some women report experiencing moderate to significant procedural pain even with the block, researchers are trying to identify an optimal approach to pain management without sedation during aspiration (Allen et al., 2013; O'Connell et al., 2009; Renner et al., 2012, 2016).

Adverse events related to the use of local anesthesia, regardless of the clinical circumstances, are rare (Nichols et al., 2009). In a recent retrospective cohort study, Horwitz and colleagues (2018) used electronic medical record data to assess whether obesity increased the risk of anesthesia-related complications[18] after an aspiration abortion with moderate IV sedation. The study, based in several Massachusetts outpatient clinics, included 20,381 women. Complications were rare and not associated with BMI[19] (Horwitz et al., 2018).

The White and colleagues (2015) systematic review described above identified 11 studies that report patient outcomes related to the use of local anesthesia, moderate sedation, or general anesthesia for aspiration abortions. Anesthesia-related complications were rare regardless of the clinical setting or level of sedation: ≤0.2 percent of office-based procedures and ≤0.5 percent of procedures in surgical centers and hospital-based clinics.

D&E Pain Management

A typical D&E regimen includes a paracervical block supplemented with either moderate sedation (using benzodiazepines and/or opiates) or deep sedation with propofol (without intubation) (NAF, 2017a ; RCOG, 2015; WHO, 2012, 2014). In office settings, deep sedation should be used only for healthy patients (ASA I) or patients with mild systemic disease (ASA II), and strict fasting guidelines should be followed before the procedure (ASA Task Force, 2002).

Two large-scale, retrospective analyses have demonstrated the safety of using deep sedation for aspiration and D&E abortions in clinic settings (Dean et al., 2011; Gokhale et al., 2016). Dean and colleagues (2011) assessed the experience of 62,125 women who had an aspiration or D&E abortion (up to 24 weeks' gestation) using deep sedation with propofol (without intubation) in a high-volume licensed clinic in New York State between 2001 and 2008.[20] Deep sedation was provided only to medically eligible patients who followed strict fasting guidelines. The procedures were monitored by an anesthesiologist or CRNA. The researchers reviewed the medical records of all women who were transferred to a hospital (n = 26) because of complications and found that no hospital transfers occurred because of an anesthesia complication.

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In a more recent study, Gokhale and colleagues (2016) assessed the outcomes for 5,579 aspiration and D&E abortions using IV sedation (without intubation) at a freestanding abortion clinic in Cleveland from 2012 to 2013. Patients were screened for medical eligibility and followed fasting guidelines. Sedation was administered by registered nurses or by CRNAs if propofol was administered. There were no hospital transfers for anesthesia-related indications. Naloxone was required for opioid reversal in 0.2 percent of patients. The study also compared outcomes for obese and nonobese women; no differences were found.

Induction Pain Management

There is little research on how best to manage pain during an induction (Jackson and Kapp, 2011). Comparisons of different analgesic regimens are not available, and the optimal approach to effective treatment of pain is not well established (Wiebe and Renner, 2014). The options will depend on the provider's resources and the particular clinical circumstances. Nulliparous women may require more analgesia compared with multiparous women (Ashok et al., 2004). The levels of pain in later-gestation induction abortions are said to be similar to those in normal delivery, but the committee found no studies documenting this (Smith et al., 2016; Viviand et al., 2003).

MORTALITY

Death associated with a legal abortion in the United States is an exceedingly rare event. As Table 2-4 shows, the risk of death subsequent to a legal abortion[21] (0.7 per 100,000) is a small fraction of that for childbirth (8.8 per 100,000) (Bartlett et al., 2004; Zane et al., 2015).[22] Abortion-related mortality is also lower than that for colonoscopies (2.9 per 100,000), plastic surgery (0.8 to 1.7 per 100,000), dental procedures (0.0 to 1.7 per 100,000), and adult tonsillectomies (2.9 to 6.3 per 100,000). Comparable data for other common medical procedures are difficult to find.

TABLE 2-4 Comparison of Mortality Rates for Abortion, Childbirth, Colonoscopy, Dental Procedures, Plastic Surgery, and Tonsillectomy, United States

Procedure (Study Period)	Mortality Rate (number of deaths per 100,000 procedures)
Abortion (legal) (1988–2010)	0.7
Childbirth (1988–2005)	8.8

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Colonoscopy (2001–2015)	2.9
Dental procedures (1999–2005)	0.0 to 1.7
Plastic surgery (2000–2012)	0.8 to 1.7
Tonsillectomy (1968–1972)	2.9 to 6.3

NOTE: Reported tonsillectomy rates were recalculated to reflect the rate per 100,000 procedures.

SOURCES: Baugh et al., 2011; Raymond and Grimes, 2012; Raymond et al., 2014; Reumkens et al., 2016; Zane et al., 2015.

The CDC monitors abortion-related deaths through its Pregnancy Mortality Surveillance System (Jatlaoui et al., 2017). The surveillance data underscore the increased risk of having an abortion later in pregnancy. Zane and colleagues (2015) assessed differences in abortion-related mortality by race, maternal age, and weeks' gestation using data from the CDC surveillance system. Among the 16.1 million legal abortions performed from 1998 to 2010, there were 108 deaths (0.7 per 100,000). Twenty deaths occurred among high-risk women whose pregnancy was life threatening. Infection and anesthesia complications were the most frequent cause of death for procedures performed up to 13 weeks' gestation. After 13 weeks, the deaths reported were due primarily to infection or hemorrhage.

The researchers found that weeks' gestation was the strongest predictor of abortion-related mortality. At 8 weeks' gestation or less, the death rate was 0.3 per 100,000; after 17 weeks, the rate was 6.7 per 100,000. Death rates were approximately three times as high for black women as for white women—similar to the disparities found in pregnancy outcomes overall (Creanga et al., 2012, 2015, 2017; MacDorman et al., 2017). From 2011 to 2013, for example, the overall maternal mortality ratio for non-Hispanic black women was 3.4 times higher than that for non-Hispanic white women (Creanga et al., 2017). A study of maternal mortality in 2013 to 2014 found a 22 percent lower ($p = .02$) mortality rate for Hispanic women compared with non-Hispanic white women; in 2008–2009, the mortality rate for Hispanic women was similar to that for non-Hispanic white women, but the difference was attributed to the 28 percent increase ($p < .001$) in mortality for non-Hispanic white women (MacDorman et al., 2017). MacDorman and colleagues (2017) note that almost all of the increase in maternal mortality was among woman aged 40 and older and for nonspecific causes of death.

STATE REGULATION OF ABORTION CARE

States play an essential role in ensuring the safety of health care services, especially through their licensure of clinicians and health care facilities. In every state, clinicians and inpatient facilities (e.g.,

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hospitals, rehabilitation centers) must be licensed by a state board or agency to provide health care services legally (Chaudhry et al., 2013). State licensure may require the facility to be accredited by an independent accrediting organization. Regardless, Medicare and Medicaid, as well as private insurers, require accreditation for inpatient facilities and ASCs to be eligible for reimbursement (CMS, 2012). ASCs provide surgical services to patients not requiring hospitalization when the expected duration of services does not exceed 24 hours (CMS, 2016). In most states, ASCs must also be licensed to provide outpatient surgery, and in many states, ASCs must be accredited (ACFAS, 2017).[23]

Unlike other health care procedures provided in office-based settings, abortions are subject to a wide array of regulations that vary by state. Except for abortion, states typically regulate individual, office-based health services only when the service involves using sedation or general anesthesia (and depending on the level of sedation) (Jones, 2017). Twenty-five states regulate office-based procedures (other than abortion). In 23 of these states,[24] the regulation is triggered by the level of sedation, and in most cases, it requires that the facility be either accredited or licensed by the state in order to offer patients moderate or deep sedation (Jones, 2017; Jones et al., 2018).[25]

State abortion regulations often have a direct impact on the delivery of abortion care. They may stipulate the type of clinician that is allowed to perform an abortion independently of the relevant scope of practice laws (e.g., qualified advanced practice clinicians [APCs] or physicians without hospital privileges may be barred from performing abortions); how the informed consent process is conducted (e.g., providers may be required to misrepresent the risks of the procedure); the abortion method that is used (e.g., D&Es may be banned); the timing and scheduling of procedures (e.g., women may have to wait 18 to 72 hours after a counseling appointment); the physical attributes of the clinical setting (e.g., procedure room size, corridor width); and other basic elements of care. In most states, the regulations apply to all abortion methods regardless of weeks' gestation, use of sedation, or the invasiveness of the procedure.

See Table 1-1 in Chapter 1 for a listing of abortion-specific regulations by states as of September 1, 2017.

SUMMARY

The clinical evidence presented in this chapter on the provision of safe and high-quality abortion care stands in contrast to the extensive regulatory requirements that state laws impose on the provision of abortion services. These requirements may influence the efficiency of abortion care by requiring medically unnecessary services and multiple visits to the abortion facility, in addition to requiring that

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care take place in costlier and more sophisticated settings than are clinically necessary. These requirements go beyond the accepted standards of care in the absence of evidence that they improve safety. Some requirements, such as multiple visits and waiting periods, delay abortion services, and by doing so may increase the clinical risks and cost of care. They may also limit women's options for care and impact providers' ability to provide patient-centered care. Furthermore, many of these laws have been documented to reduce the availability of care by imposing unneeded regulations on abortion providers and the settings in which abortion services are delivered. The implications of abortion-specific regulations for the safety and quality of abortion care are described below.

Delaying the Procedure

The clinical evidence makes clear that legal abortions in the United States—whether by medication, aspiration, D&E, or induction—are safe and effective. Serious complications are rare; in the vast majority of studies, they occur in fewer than 1 percent of abortions, and they do not exceed 5 percent in any of the studies the committee identified. However, the risk of a serious complication increases with weeks' gestation. As the number of weeks increases, the invasiveness of the required procedure and the need for deeper levels of sedation also increase. Thus, delaying the abortion increases the risk of harm to the woman.

State regulations that require women to make multiple in-person visits and wait multiple days delay the abortion. If the waiting period is required *after* an in-person counseling appointment, the delay is exacerbated (Roberts et al., 2016; Sanders et al., 2016; White et al., 2017). Restrictions on the types of providers and on the settings in which abortion services can be provided also delay care by reducing the availability of care (Baum et al., 2016; Fuentes et al., 2016; Gerdts et al., 2016; Grossman et al., 2014, 2017).

Financial burdens and difficulty obtaining insurance are frequently cited by women as reasons for delay in obtaining an abortion (Bessett et al., 2011; Drey et al., 2006; Finer et al. 2006; Foster and Kimport, 2013; Foster et al., 2008; French et al., 2016; Janiak et al., 2014; Kiley et al., 2010; Roberts et al., 2014; Upadhyay et al., 2014). As noted in Chapter 1, 33 states prohibit public payers from paying for abortions, and other states have laws that either prohibit health insurance exchange plans (25 states) or private insurance plans (11 states) sold in the state from covering or paying for abortions, with few exceptions.[26]

Counseling and Informed Consent

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Long-established ethical and legal standards for informed consent in health care appear to have been compromised in the delivery of abortion care in many areas of the country. Thirty-five states have abortion-specific regulations requiring women to receive counseling before an abortion is performed, and abortion patients in many of these states are offered or given inaccurate or misleading information (verbally or in writing) on reversing medication abortions, risks to future fertility, possible breast cancer risk, and/or long-term mental health consequences of abortion (Guttmacher Institute, 2017a) (see Table 1-1 in Chapter 1). As noted earlier in this chapter, the principal objective of the informed consent process is that patients understand the nature and risks of the procedure they are considering (AAAHC, 2016; AMA, 2016; HHS, 2017a; Joint Commission, 2016). However, legally requiring providers to inform women about risks that are not supported and are even invalidated by scientific research violates the accepted standards of informed consent. For example, some states require that providers inform women that abortion puts them at greater risk for breast cancer; mental health disorders; and difficulties in having a healthy, successful pregnancy (Guttmacher Institute, 2017a) (see Table 1-1 in Chapter 1 for a detailed list of states' informed consent requirements). Three states require providers to inform women that a medication abortion can be reversed after the woman takes mifepristone (Guttmacher Institute, 2017a). This information is not supported by research that meets scientific standards. See Chapter 4 for an in-depth review of the long-term health effects of abortion.

Medication Abortion

There is no evidence that the dispensing or taking of mifepristone tablets requires the physical presence of a clinician[27] or a facility with the attributes of an ASC or hospital to ensure safety or quality. The effects of mifepristone occur after women leave the clinic, and extensive research shows that serious complications are rare. The risks of medication abortion are similar in magnitude to the risks of taking commonly prescribed and over-the-counter medications such as antibiotics and NSAIDs. In 35 states, however, only physicians are permitted to give women the mifepristone tablet(s) required to begin the process of medication abortion (RHN, 2017). In 19 states, the clinician (a physician or other provider if allowed) must be physically present to provide the medication, thus prohibiting the use of telemedicine to prescribe the medication remotely for abortion (Guttmacher Institute, 2017b). In 17 states, medication abortions must be performed in a facility that meets the structural standards of ASCs even though the abortion will occur outside the clinical setting, and there is no evidence to suggest that these regulations improve safety or quality.

Aspiration Abortions

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Aspirations are minimally invasive and commonly used for a variety of purposes in gynecology practices, including for early pregnancy loss (miscarriage). Aspiration abortions are performed safely in office-based settings and can be provided by appropriately trained APCs, as well as family practice physicians and OB/GYNs. If moderate sedation is used, the procedure should be performed in a facility that meets the relevant ASA facility standards. There is no evidence that performing aspiration abortions in ASCs increases the safety or efficacy of the procedure. The state regulations described above also affect aspiration abortion procedures: 44 states do not allow APCs to perform aspirations, and 16 states mandate that the procedure be performed in an ASC-like facility.

D&E and Induction Abortions

D&E is usually the medically preferred method for abortions at 14 weeks' gestation or later. The alternative—induction—is more painful, slower, and more expensive. D&Es are banned in Mississippi[28] and West Virginia[29] except if the woman's physical health or life is severely threatened.

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[1] Mifeprex is manufactured and distributed by Danco Laboratories. Danco is the only distributer of Mifeprex in the United States.

[2] A sublingual medication is dissolved under the tongue. Buccal medications are placed between the gums and the cheek.

[3] Where permitted under national law and where culturally acceptable (WHO, 2015).

[4] The review also included 332 abortions that were performed between 64 and 70 days' gestation; the efficacy rate for these procedures was 93.1 percent.

[5] An "incomplete abortion" occurs when parts of the products of conception are retained in the uterus.

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[6] There is no standard terminology for this type of abortion. As noted in Chapter 1, this report uses the term "aspiration abortion," although others commonly refer to the same procedure as "surgical abortion," "vacuum aspiration," "suction curettage," or "suction evacuation."

[7] Centers for Disease Control and Prevention (CDC) surveillance reports use the catchall category of "curettage" to refer to nonmedical abortion methods. The committee assumed that CDC curettage estimates before 13 weeks' gestation refer to aspiration procedures and that curettage estimates after 13 weeks' gestation are D&E procedures.

[8] Laminaria, small tubes made of dried seaweed, and manmade sterile sponges are common types of osmotic dilators.

[9] $p < .001$.

[10] Complications assessed included need for uterine reaspiration (including same-day reaspiration), uterine perforation, cervical laceration, infection, emergency department visit or hospitalization, and excessive blood loss (defined as estimated blood loss greater than or equal to 100 mL).

[11] Dilation and curettage/suction denoted procedures performed when no other instruments besides suction were used; 5.3 percent of procedures in the study were D&S.

[12] Complications assessed included cervical laceration, hemorrhage, uterine atony, anesthesia complications, uterine perforation, disseminated intravascular coagulation, retained products of conception, and major complications (defined as those requiring hospitalization, transfusion, or further surgical intervention).

[13] Complications assessed included hemorrhage, need for repeat evacuation, uterine perforation, cervical laceration, medication reaction, unexpected surgery, or unplanned admission to the hospital.

[14] The cohort was classified into categories based on the WHO classification of underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9), obese Class I (BMI 30–34.9), obese Class II (BMI 35–39.9), and obese Class III (BMI 40 or greater).

[15] See Chapter 3 for a review of factors contributing to the dearth of trained providers.

[16] Both states allow exceptions in cases of life endangerment or severe physical health risk to the woman.

[17] ASA II patients (mild systemic disease) have no functional limitations and well-controlled disease, such as controlled hypertension or diabetes (without systemic effects), mild lung disease, or mild obesity (BMI between 30 and 40) (ASA, 2014a).

[18] The primary outcome assessed was supplemental oxygen administration. Secondary outcomes included reversal agent administration, anesthesia-related adverse events, and intraoperative lowest level of consciousness.

[19] Obesity groups (BMI = 30–34.9; BMI = 35–39.9; BMI ≥40) were compared with women with BMI <25.

[20] One patient received an endotracheal intubation.

[21] The CDC defines an abortion-related death as "a death resulting from a direct complication of an induced abortion, an indirect complication caused by a chain of events initiated by an abortion procedure, or the aggravation of a pre-existing condition by the physiologic or psychological effects of the abortion" (Jatlaoui et al., 2016, p. 4).

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[22] The CDC calculates the rate of abortion mortality using deaths reported to the CDC Abortion Surveillance System and dividing them by the estimated number of abortion procedures in the United States (CDC, 2017; Jones and Jerman, 2014).

[23] According to the American College of Foot and Ankle Surgeons, 46 states require ASCs to be licensed, and 28 states (including the District of Columbia) require accreditation (ACFAS, 2017).

[24] The 23 states are Alabama, Arizona, Arkansas, California, Connecticut, Delaware, Florida, Indiana, Kansas, Louisiana, Mississippi, Nevada, New Jersey, New York, Ohio, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Virginia, and Washington.

[25] Personal communication, B. S. Jones, Advancing New Standards in Reproductive Health (ANSIRH), July 3, 2017.

[26] Exceptions are limited and vary by state. They are often made for pregnancies resulting from rape or incest, pregnancies that endanger the woman's life or severely threaten the health of the woman, and cases of fetal impairment.

[27] Chapter 3 reviews the clinical competencies needed to provide safe and high-quality abortions, as well as state regulations regarding the role of APCs.

[28] Mississippi Unborn Child Protection from Dismemberment Abortion Act, Mississippi HB 519, Reg. Sess. 2015–2016 (2016).

[29] Unborn Child Protection from Dismemberment Abortion Act, West Virginia SB 10, Reg. Sess. 2015–2016 (2016).

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What the new FDA commissioner says about possible restrictions on abortion medication

Apr 24, 2025 6:30 PM EDT

Many conservatives want the FDA to impose tighter restrictions on mifepristone and misoprostol, which can be delivered by mail. The medication accounted for 63 percent of U.S. abortions in 2023. Amna Nawaz spoke with the new FDA commissioner, Dr. Marty Makary, about what the agency may do.

Read the Full Transcript

Notice: Transcripts are machine and human generated and lightly edited for accuracy. They may contain errors.

Amna Nawaz:

Now to the new Food and Drug Administration commissioner, Dr. Marty Makary, and a wide-ranging conversation I had with them earlier today as part of Semafor's World Economy Summit.

Among the many topics we discussed, mifepristone and what plans the FDA may have in store for medication abortion, which accounted for 63 percent of U.S. abortions in 2023. Many conservatives want the FDA to impose tighter restrictions on mifepristone and misoprostol, which can be delivered by mail.

Here is some of what Dr. Makary said.

On mifepristone, do you expect to take action further restricting the pill?

Dr. Marty Makary, FDA Commissioner:

I have no plans to take action on mifepristone.

Amna Nawaz:

Could that be changed over the course of your tenure, given the pressure that I know has come from a lot of the political forces at play on this?

Dr. Marty Makary:

GBP-PET00631

So, look, I believe as a scientist, you got to evolve as the data comes in.

And, as you may know, there is an ongoing set of data that is coming into FDA on mifepristone. So if the data suggests something or tells us that there's a real signal, then I — we can't promise we're not going to act on that data that we have not yet seen.

Amna Nawaz:

But if that new data contradicts the decades of data that said that it's overwhelmingly safe and effective, you would go with the new data, rather than the precedent of decades of data?

Dr. Marty Makary:

Well, it's very hypothetical, right, because you're talking about the strength of the data, the safety of the data, the reliability of the data. So it's very hypothetical what you're asking, but in general I'm a data guy.

Amna Nawaz:

Commissioner Makary also seemed to agree today that the federal government should reverse itself and no longer recommend the COVID booster for children. HHS Secretary Robert F. Kennedy Jr. is reportedly considering that.

Previous scientific panels have found it safe and beneficial to prevent kids from getting seriously ill, but Makary told me today he believes that evidence is insufficient.

By — **Amna Nawaz**

Amna Nawaz serves as co-anchor and co-managing editor of PBS News Hour.

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GBP-PET00632

Original Research

Acceptability and Feasibility of Phone Follow-up After Early Medical Abortion in Vietnam

A Randomized Controlled Trial

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OBJECTIVE: To investigate phone follow-up with a semiquantitative urine pregnancy test and symptom checklist as a replacement for universal clinic follow-up after medical abortion.

METHODS: One thousand four hundred thirty-three women seeking early medical abortion at four hospitals in Vietnam were randomized to clinic or phone follow-up. Women allocated to clinic follow-up returned to the hospital for confirmation of abortion outcome 2 weeks after mifepristone administration. Women assigned to phone follow-up completed a semiquantitative pregnancy test at initial visit to determine baseline human chorionic gonadotropin range and again at home 2 weeks later. Clinic staff called women to review the pregnancy test results and symptom checklist. Women who screened positive were referred to the clinic. Effectiveness, feasibility, and acceptability of the follow-up methods were assessed.

RESULTS: The rate of ongoing pregnancy was not significantly different between the two groups (clinic: 2.7% phone, 2.5%, relative risk 0.9, 95% confidence interval 0.99–1.02). Eighty-five percent of women in the phone group did not need an additional clinic visit. Phone follow-up was highly effective in screening for ongoing pregnancy with a sensitivity and specificity of 92.8% and 90.6%, respectively. Specificity of the pregnancy test alone (eg, without the symptom checklist) was higher (95.7%).

CONCLUSION: Phone follow-up offers a feasible and effective approach to identify women with ongoing pregnancy after early medical abortion. When used with the semiquantitative pregnancy test, the symptom checklist offered no additional benefit and decreased the specificity of the screening. Given its effectiveness and ease of use, the semiquantitative pregnancy test alone could replace routine clinic follow-up after early medical abortion.

CLINICAL TRIALS REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT01150422.

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LEVEL OF EVIDENCE: I

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Despite the high efficacy and safety of early medical abortion using a combined regimen of mifepristone plus misoprostol, clinic follow-up remains an integral part of standard medical abortion service delivery globally.[1,2] In-person clinic visits can be costly and time-consuming for both the woman and the health care system. In many clinics, a transvaginal ultrasound examination is performed routinely. Some women find that the additional follow-up visit decreases the acceptability of medical abortion[1] and it is not uncommon for women to fail to return for the 2-week follow-up appointment.

Preprocedure and postprocedure system of serum human chorionic gonadotropin (hCG) measures are accurate in identifying ongoing pregnancies after medical abortion.[3–5] Quantitative serum hCG testing to confirm successful medical abortion is commonly used in the United States and Europe and recommended as a means of follow-up by the Royal College of Obstetricians and Gynecologists and the World Health Organization.[6,7]

Urine pregnancy tests offer another way to measure hCG levels after medical abortion.[8–10] Semiquantitative pregnancy tests have been used successfully in two subsequently published medical abortion studies in the United States and Vietnam. In both studies, the test correctly identified all of the ongoing pregnancies among study participants.[11,12]

The goal of this study was to test the efficacy and feasibility of a service delivery protocol that replaces the routine clinic visit with ultrasonographic examination with sequential semiquantitative pregnancy tests and a standardized self-administered follow-up questionnaire administered over the phone.

MATERIALS AND METHODS

This multicenter study enrolled women seeking early medical abortion at four hospitals (Hung Vuong Hospital, National Ob-Gyn Hospital, Hanoi Ob-Gyn Hospital, and HocMon General District Hospital) in Vietnam. The most common treatment regimen used for early medical abortion services at the hospitals consists of oral 200 mg mifepristone followed in 24–48 hours by 800 micrograms buccal misoprostol administered at home. Women presenting for early medical abortion at one of these four facilities were screened for participation and those meeting the eligibility criteria were enrolled. Eligibility criteria included intrauterine pregnancy less than or equal to 63 days of gestation; no known contraindications to abortion with mifepristone, misoprostol, or both; general good health; ability to provide informed consent and willingness to return for follow-up; literate and able to complete an at-home symptom checklist; and possessing a working, personal phone number. Women not eligible or choosing not to participate in the study received standard clinic follow-up.

Participants were randomly assigned to one of two study groups: 1) clinic follow-up (eg, standard care); or 2) phone follow-up. Standard care entailed a clinic visit 2 weeks after mifepristone administration. At the visit, each participant was interviewed about her clinical condition and underwent bimanual examination and transvaginal ultrasonography to confirm her abortion status. In the event of an ongoing pregnancy, immediate surgical evacuation was offered. Women with incomplete abortion at follow-up were given the option of immediate surgical completion or an additional dose of misoprostol followed by a clinic visit 1 week later. All additional clinic visits, additional treatment received, or both were recorded on study forms. Once complete abortion was ascertained, participants were asked about their future preferences and satisfaction and acceptability with the follow-up procedure and released from the study.

Women randomized to phone follow-up were scheduled for a telephone call 2 weeks after mifepristone administration. Women assigned to phone follow-up were asked to use a urine-based semiquantitative pregnancy test before swallowing mifepristone to locate the range of their hCG before the abortion (baseline). In contrast to typical urine-based pregnancy tests, the semiquantitative pregnancy test provides estimates of hCG levels by individual strips reading sequential ranges of hCG: at least 25 milli-international units/mL, at least 100 milli-international units/mL, at least 500 milli-international units/mL, at least 2,000 milli-international units/mL, and at least 10,000 milli-international units/mL. A study nurse explained how to perform the semiquantitative pregnancy test and provided each participant with an additional test, a urine sample cup, an information sheet explaining how to perform and interpret the test, and a questionnaire to use at home. Tests were conducted by dipping the test panel into the urine sample cup and stirring it for a minimum of 10 seconds to achieve strip saturation. Either first morning or random urine could be used. The tests were then placed face up on a flat surface and read approximately 15 minutes later. Each woman's baseline hCG as determined by the semiquantitative test was noted on her at-home symptom checklist. Participants were instructed to complete the pregnancy test and the symptom checklist before their scheduled telephone follow-up weeks later. On the assigned date, participants were contacted by phone by the clinic staff. During the call, a study nurse reviewed the pregnancy test result and checklist responses with the woman. The pregnancy test result at follow-up was compared with the baseline result and a drop of at least one bracket was considered a success. In the event that she had not performed the pregnancy test at the time of the call, she was asked to perform the test immediately and the nurse would call back in approximately 30 minutes.

The symptom checklist used was derived from an earlier study[12] and included the following questions: 1) Did you experience less than 2 days of heavy bleeding during treatment? 2) Are you experiencing any of

the following symptoms now: breast tenderness, nausea or morning sickness, frequent urination, or exhaustion or tiredness or both? 3) Do you still feel pregnant? If the woman answered "yes" to any of the questions on the checklist or her pregnancy test was invalid or indicated an increase or no change in the hCG level, she was asked to return to the clinic for follow-up. If a woman screened negative for referral, she was released from the study after the call. Participants who screened positive for clinic referral were asked by the health care provider to return for any reason or requested a clinic visit were scheduled for additional clinic follow-up. During the follow-up phone call, participants were also asked about the satisfaction and acceptability of the phone follow-up procedure.

Participants were randomized to a study group by opening the next sequentially numbered sealed opaque envelope. The envelopes were prepared by staff at Gynuity Health Projects in New York. Randomization was stratified by study site using random blocks of eight to ensure equal distribution in the two study groups. Regardless of study group, any participant failing to return for the follow-up visit or make the scheduled telephone follow-up call was contacted by telephone up to three times by a study provider.

The sample size was based on the least common outcome of interest: ongoing pregnancy after medical abortion. Based on previous studies conducted in Vietnam, we estimated that ongoing pregnancy would occur in approximately 2.0% of medical abortion cases.[12,13] Assuming that routine clinic-based follow-up will diagnose 100% of ongoing pregnancies, we designed the study to have 80% power to demonstrate that phone follow-up (using a semiquantitative pregnancy test in combination with a self-administered checklist) would be as effective as standard clinic-based follow-up in detecting ongoing pregnancies with an α of 0.05. To achieve this, we estimated that 28 ongoing pregnancies (14 in each study arm) would be needed, with a total sample size of 1,400 participants (700 in each study arm).

Data entry and analysis were performed using SPSS 15.0. Study data were entered and cleaned in Vietnam for analysis jointly by the investigators in Vietnam and New York. The two study groups were compared using *t* tests or the Mann-Whitney *U* test for continuous variables and χ^2 or Fisher's exact tests for categorical variables. The main study outcomes were compared using relative risks (RRs), 95% confidence intervals (CIs), and *P* values. A *P* value $<.05$ was considered statistically significant. Sensitivity and specificity of the pregnancy test and checklist in detecting ongoing pregnancy was also calculated. Ethical approvals were obtained at Hung Vuong Hospital, Hoc Mon General District Hospital in Ho Chi Minh City, and National Hospital in OBGYN and Hanoi OBGYN Hospital in Hanoi, Vietnam, and the trial is registered at clinical trials.gov as NCT01150422.

RESULTS

One thousand four hundred thirty-three women were enrolled at the study sites between May 26, 2010, and April 14, 2011. Seven hundred thirteen women were randomized to the phone follow-up group and 720 women assigned to clinic follow-up (Fig. 1). There was no statistically significant difference between the two groups (Table 1). The medical abortion outcomes for the two groups are presented in Table 2. There were no statistically significant differences in rates of complete abortion without surgical evacuation (clinic: 94.6% [626/662], phone: 94.8% [672/709], RR 1.002, 95% CI 0.977–1.028) or ongoing pregnancy between the two groups (clinic: 2.7% [18/720], phone: 2.5% [18/713], RR 0.934, 95% CI 0.985–1.019).

In the phone follow-up group, 2.2% of women (16/713) did not complete the scheduled follow-up call because they came to the clinic early (Table 2; Fig. 1). Seven women had a complete abortion without surgical evacuation. Four women underwent a uterine evacuation for a continuing pregnancy. Five participants had aspirations for other reasons including profuse bleeding (n=1) and woman's request (n=4). One woman made an interim visit to the clinic 10 days after mifepristone administration and was hospitalized for treatment of a suspected infection. She received intravenous antibiotics and her fever resolved after 4 days.

In the clinic follow-up group, 1.4% of women (10/720) made an interim visit to the study clinic before their scheduled appointment (Table 2; Fig. 1). Half of women who returned early (5/10) underwent a uterine evacuation for an ongoing pregnancy confirmed by ultrasonography. Two women underwent an evacuation for retained products of conception. The remaining women (n=3) had a successful abortion confirmed by ultrasonography.

Most women in both study arms completed follow-up. In the phone follow-up group, almost all women who did not make an interim visit to the clinic had their telephone follow-up as scheduled (99.4% [693/697]). Four women (0.6% [4/697]) could not be contacted and were classified as lost to follow-up. In the clinic follow-up group, 8.1% (58/710) did not return for their scheduled 2-week clinic visit. The difference between the two study groups in the proportion of women lost to follow-up (0.6%

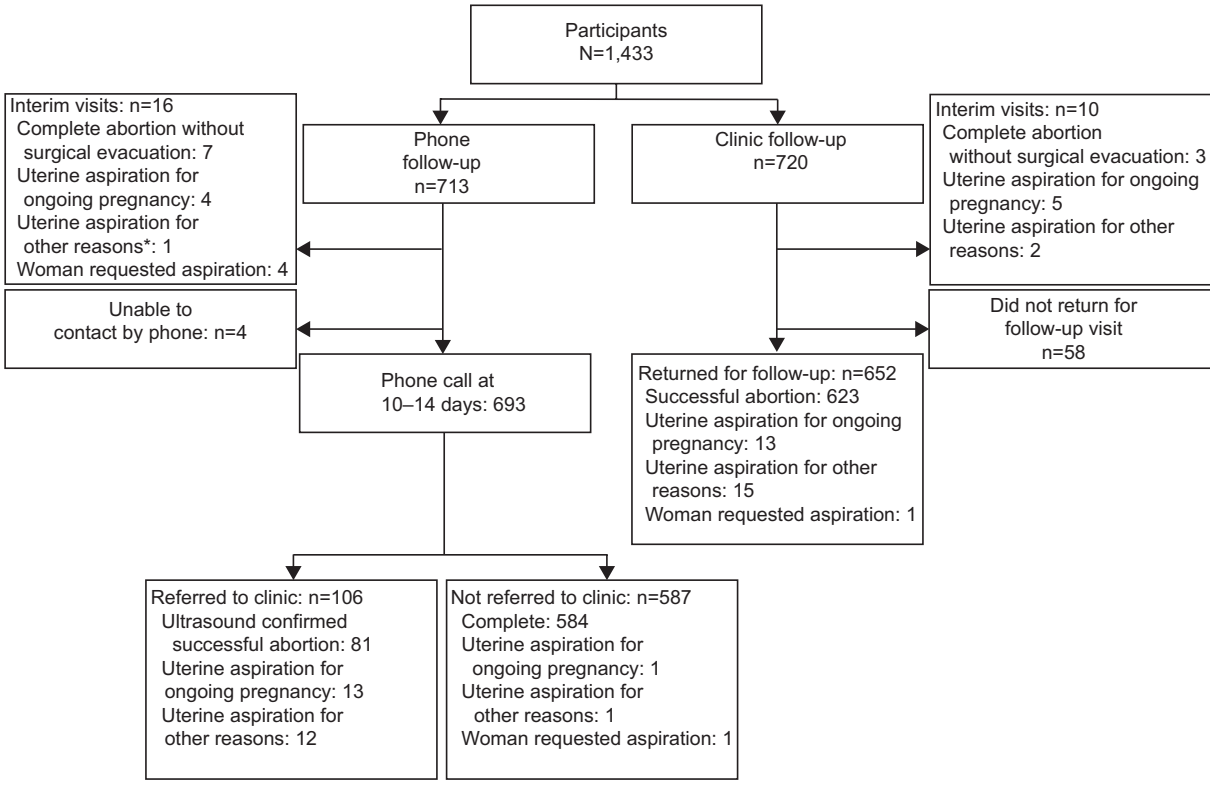

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flow chart. *Uterine aspiration for other reasons includes evacuation for retained products of conception, incomplete or missed abortion, or heavy bleeding.

Ngoc. Phone Follow-up After Early Medical Abortion. Obstet Gyncol 2014.

compared with 8.2%) was statistically significant (RR 0.070, 95% CI 0.025–0.191).

In the clinic follow-up group, most women who returned for a scheduled appointment had a successful medical abortion confirmed by ultrasonography (95.5% [623/652]) (Fig. 1). At this visit, 13 women received a uterine aspiration for an ongoing pregnancy (1.9% [13/652]). Fifteen women underwent an aspiration for other medical reasons and one woman requested a surgical evacuation.

Most women in the phone follow-up group who were contacted were not referred to the clinic for additional medical abortion related care (84.7% [587/693]) (Fig. 1). In the phone follow-up group, only 15% of women (106/693) were referred to the clinic for additional follow-up care after their phone assessment (Fig. 1). More than one third of these women referred reported either no change or an increase in hCG from the time of mifepristone administration (39.6% [42/106]). More than half of these women reported a positive response to one of the checklist questions (56.6% [60/106]). Almost one fourth of women referred to the clinic for follow-up (25.4% [27/106]) screened negative on both tests, ie, reported a decrease in hCG from the time of mifepristone administration and answered "no" to all of the symptom checklist questions. Among the women referred without

Table 1. Participant Characteristics

Characteristic	Phone Follow-Up (n=713)	Clinic Follow-Up (n=720)	*P*
Age (y)	27±5.9 (15–45)	27±5.5 (18–46)	.248
Level of education*			.505
No formal education	0.1 (1)	0.0 (0)	
Primary school (1–5 y)	2.4 (17)	1.8 (13)	
Secondary school (6–12 y)	55.0 (392)	57.6 (414)	
University level or higher	42.4 (302)	40.6 (289)	
At least 1 previous surgical abortion	29.9 (213)	33.2 (239)	.191
At least 1 previous medical abortion	18.1 (129)	17.1 (123)	.628

Data are mean±standard deviation (range) or % (n) unless otherwise specified.

* One woman in alternative care group missing data on education (n=712).

Table 2. Medical Abortion Outcome

Outcome	Phone Follow-Up (n=713)	Clinic Follow-Up (n=720)	Relative Risk (95% CI)
Unknown, lost to follow-up	0.6 (4)	8.1 (58)	0.070 (0.025–0.191)
Returned to the clinic early	2.2 (16/713)	1.4 (10/720)	1.616 (0.738–3.536)
Complete abortion without surgical evacuation	94.8 (672)	94.6 (626)	1.002 (0.977–1.028)
Reason for surgical evacuation			
Ongoing pregnancy	2.5 (18)	2.7 (18)	0.934 (0.985–1.019)
Other reasons*	2.0 (14)	2.6 (17)	0.769 (0.382–1.547)
Woman's request	0.7 (5)	0.2 (1)	4.669 (0.547–39.856)

CI, confidence interval.
Data are % (n) or % (n/N) unless otherwise specified.
* Other reasons include evacuation for retained products of conception, missed abortion, or heavy bleeding.

a positive screen test (n=27), the reported reasons for referral included ongoing bleeding (25.9% [7/27]), suspected ongoing pregnancy based on other symptoms (25.9% [7/27]), inconclusive pregnancy test (18.5% [5/27]), woman felt anxious (11.1% [3/27]), or other reasons (18.5% [5/27]) (data not shown).

The outcomes of the 106 women in the phone follow-up group who were referred to the clinic for further follow-up are presented in Figure 1. All women who were referred returned to the clinic. Most women who were referred (76.4% [81/106]) had successful medical abortions confirmed by ultrasonography. Thirteen women underwent a uterine evacuation for an ongoing pregnancy confirmed by ultrasonography. Twelve women underwent a surgical evacuation for other medical reasons. All nine cases of missed abortion were identified by no decrease or change in hCG from initial baseline at the time of the scheduled phone follow-up call.

Three women who screened negative and were not asked to return to the clinic for follow-up subsequently received additional medical abortion-related care. In one case, the woman reported in her phone interview that she had experienced more than 2 days of bleeding, had no pregnancy symptoms, and that her pregnancy test result showed a decrease in hCG level. Still, she returned to the clinic 5 days later and was diagnosed with an ongoing pregnancy. Another woman underwent an aspiration for retained products of conception when she returned to the clinic 9 days after her phone interview (study day 23). A third woman returned to the clinic 10 days after her phone call (study day 24) and requested a surgical evacuation for management of ongoing bleeding.

Most women (98.8% [685/693]) who did not make an interim visit to the clinic and were successfully contacted by phone had a functional pregnancy test result recorded at the phone follow-up. In eight cases, the test line did not appear and the result was not readable. Among women with a functional pregnancy test (n=685), the sensitivity and specificity of the pregnancy test alone for the identification of ongoing pregnancy was 92.8% and 95.7%, respectively (Table 3). The specificity was slightly lower with the use of the pregnancy test and symptom checklist (90.6%) and the screen-positive rate slightly higher (11.1% for the combined symptom checklist and pregnancy test compared with 6.1% for the pregnancy test alone).

Fourteen women in the phone follow-up group who did not make an interim visit to the clinic were diagnosed with an ongoing pregnancy at or after the follow-up visit. The results of the two follow-up screening methods are shown in Table 4. The semiquantitative pregnancy test identified 92.8% (13/14) of ongoing pregnancies. The symptom checklist alone identified 71.4% (10/14) of ongoing pregnancies. One woman with an ongoing pregnancy was not identified by either the checklist or the pregnancy test.

We also examined the estimated hCG levels reported by women on the day of their follow-up call. More than one third of women (37.8% [259/685]) reported a result of less than 25 milli-international units/mL. Most women (94.7% [649/685]) reported an hCG level of less than 2,000 milli-international units/mL when they administered the second urine pregnancy test. Most women who were diagnosed with an ongoing pregnancy on or after the follow-up appointment (n=14) reported an hCG level of 10,000 milli-international units/mL or above (85.7% [12/14]). However, two women reported lower levels of at least 500 milli-international units/mL and at least 25 milli-international units/mL, respectively.

Women in the phone follow-up group were asked about the feasibility and acceptability of the pregnancy test and symptom checklist during their follow-up phone call (Table 5). Most participants completed the checklist (98.3% [681/693]) and the semiquantitative pregnancy test (99.1% [687/693]). Almost all women

Table 3. Sensitivity and Specificity and Positive and Negative Predictive Values of Phone Follow-up With Checklist and Semiquantitative Pregnancy Test for Detection of Ongoing Pregnancy After Medical Abortion

Screen	Sensitivity	Specificity	Screen-Positive	Positive Predictive Value	Negative Predictive Value
Phone follow-up with semiquantitative pregnancy test and symptom checklist* (n=684)	92.8 (66.1–98.8)	90.6 (88.1–92.7)	11.1 (8.9–13.7)	17.1 (8.9–13.7)	99.8 (99.1–99.9)
Increase or no change in hCG level based on results of semiquantitative pregnancy test† (n=685)	92.8 (66.1–98.8)	95.7 (93.8–97.1)	6.1 (4.5–8.2)	30.9 (17.6–47.1)	99.8 (99.1–99.9)
Answer "yes" to any checklist questions‡ (n=691)	71.4 (41.9–91.4)	92.6 (90.4–94.5)	8.6 (6.8–11.0)	16.7 (8.3–28.5)	99.4 (98.4–99.8)

hCG, human chorionic gonadotropin.
Data are % (95% confidence interval).
* Excludes women who made an interim visit to the clinic (n=16) or who the clinic was unable to contact (n=4) or who had an invalid pregnancy test (n=8) or incomplete checklist (n=1).
† Excludes women who made an interim visit to the clinic (n=16) or who had an invalid test (n=8).
‡ Excludes women who made an interim visit to the clinic (n=16) or an incomplete checklist (n=1).

reported that completion of the checklist and pregnancy test was easy or very easy (checklist: 97.3% [673/691]; semiquantitative pregnancy test: 97.5% [674/691]).

Women in both groups were asked about their preference for follow-up should they require another medical abortion in the future (Table 5). In the phone follow-up group, most women (88.3% [606/686]) indicated that they preferred to complete their follow-up at home with a phone call from the health care provider. In the clinic follow-up group, fewer women (39.9% [256/242]) reported that they would opt for phone follow-up at home in the future.

DISCUSSION

Phone follow-up after medical abortion is a safe and effective alternative to clinic-based follow-up after medical abortion. The data from this study show that phone follow-up with a semiquantitative urine pregnancy test and symptom checklist could enable 85% of women to avoid a routine follow-up visit without any decrease in safety. The semiquantitative urine pregnancy test and symptom checklist accurately screened for ongoing pregnancy and resulted in fewer women being lost to follow-up.

Women reported the hCG levels measured with the semiquantitative pregnancy test at 2 weeks after mifepristone administration. A follow-up system using only a high sensitivity pregnancy test at follow-up could successfully identify all ongoing pregnancies but would still require nearly two thirds of women to return to the clinic for follow-up. In contrast, only 5.3% of women reported a value greater than 2,000 milli-international units/mL at the follow-up call, but two women diagnosed with an ongoing pregnancy reported levels of at least 500 milli-international units/mL and at least 25 milli-international units/mL. A follow-up scheme using a single low-sensitivity pregnancy test would permit fewer women to return to the clinic but could still fail to identify cases of ongoing pregnancy after medical abortion.

The semiquantitative urine pregnancy test was more successful at screening for ongoing pregnancy earlier than high- and low-sensitivity urine pregnancy tests used in previous research.[9] In the present study, women were able to confirm their abortion outcome 2 weeks after mifepristone administration with repeat semiquantitative pregnancy tests with a higher sensitivity and specificity (92.8% and 95.7%, respectively).

Table 4. Identification of Ongoing Pregnancy (n=14) by Pregnancy Test and Symptom Checklist Among Women in the Phone Follow-up Group

		Ongoing Pregnancy Identified by Semiquantitative Pregnancy Test	
Ongoing pregnancy identified by symptom checklist		Yes	No
	Yes	10	0
	No	3	1

Women in the phone follow-up group with an ongoing pregnancy diagnosed at an interim visit to the clinic (n=4) were excluded from the analysis.

Table 5. Feasibility and Acceptability of Follow-up

	Phone Follow-Up	Clinic Follow-Up
Woman completed checklist* (n=693)	98.3 (681)	—
Ease of completion of checklist (n=691)		
Very easy	12.4 (86)	—
Easy	84.7 (587)	—
Neither easy nor difficult	2.2 (115)	—
Difficult	0.4 (3)	—
Woman completed pregnancy test	99.1 (687)	—
Ease of completion of pregnancy test (n=691)		
Very easy	14.4 (100)	—
Easy	82.8 (574)	—
Neither easy nor difficult	2.5 (17)	—
Preference for future medical abortion follow-up†		
At the clinic	10.5 (72)	60.0 (385)
At home with phone follow-up	88.3 (606)	39.9 (256)
No preference	1.2 (8)	0.2 (1)

* Excludes women who made an interim visit to clinic (n=16) or were lost to follow-up (n=4).
† Phone follow-up: n=686; clinic follow-up: n=642; five women in phone follow-up group did not respond to question.

Two previous studies have also documented that the semiquantitative pregnancy test effectively detects continuing pregnancy when performed 1–2 weeks mifepristone administration.[11,12]

Although the phone follow-up failed to identify one woman who was later identified with an ongoing pregnancy, she still returned to the clinic for follow-up but was not clear about why she had come. Counseling, together with the semiquantitative pregnancy test, may help to ensure that women can safely and effectively assess their postabortion status at home and identify when they need to return.

This study used both the semiquantitative pregnancy test and a symptom checklist to help women assess their postabortion status. The semiquantitative pregnancy test was highly effective at identifying ongoing pregnancies. When used with the semiquantitative pregnancy test, the symptom checklist appears to offer no additional value for identifying cases of ongoing pregnancy. Indeed, the one case of ongoing pregnancy missed in the phone follow-up group was not detected by either the participant's self-reported pregnancy test or symptom checklist (Table 4). The results from this study confirm previous reports that symptomatic assessment of ongoing pregnancy is not highly specific.[14]

The study has several limitations. The results obtained in a single country, Vietnam, may not be generalizable to other settings. The large majority of participants reported having completed at least secondary school education; results may differ among women with lower levels of educational attainment. It is possible, although highly unlikely, that some of the participants in the phone follow-up group may have sought additional abortion care elsewhere. Given that all outcomes, including the number of ongoing pregnancies, were similar in the two randomized study groups, we feel that ascertainment of ongoing pregnancy was equally good in both groups.

Additional research should seek to further simplify service delivery, perhaps with pictorial phone-based assessment of the pregnancy test results for various settings. It might also be possible to document the downward trend in hCG earlier than 2 weeks postmifepristone. If so, this would allow for more expeditious integration of other aspects of service delivery such as provision of postabortion contraception, which also deserves greater attention. More documentation about novel service delivery modalities such as the one described in this article should contribute to international efforts to encourage task shifting in medical care. In the case of medical abortion follow-up, this could mean giving women more of the responsibility to manage their follow-up at home.

The introduction of semiquantitative tests in lieu of universal clinic-based follow-up would simplify care and potentially reduce costs for women and the health care system by providing an alternative follow-up tool to confirm the absence of an ongoing pregnancy. Such efforts may be especially beneficial in resource-poor countries, where clinics may be overcrowded and understaffed with limited access to serum hCG testing and transvaginal ultrasonography.

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Research Article
Sexual health

10-year evaluation of the use of medical abortion through telemedicine: a retrospective cohort study

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Objective To provide a descriptive overview and evaluate changes in the use and outcome of abortions provided worldwide by telemedicine in the past 10 years.

Design Retrospective cohort study.

Setting Multi-country.

Population/Sample 30 344 women who completed the follow-up survey of the telemedical abortion service Women on Web from January 2009 till January 2020.

Methods Analyses of follow-up surveys, binary logistic regressions to test the association between year and outcomes.

Main outcome measures Rate of complete abortions, surgical interventions, ongoing pregnancies, blood transfusions per year, socio-economic situation, knowledge on medical abortion, acceptability of receiving service, appropriateness of method and the likelihood of recommending the service to a friend.

Results Medical abortions were provided to 81 683 women, of whom 30 344 (37.2%) completed the follow-up survey. In total, 26 076 women reported doing the medical abortion, of whom 1.5% reported an ongoing pregnancy, 10.2% a surgical intervention and 0.6% a blood transfusion. Acceptability of the service was 99%, and 59.2% of the users reported previous knowledge of medical abortion. We found a significant increase in complete abortions in 2019 (odds ratio 1.92; 95% CI 1.59–2.31) and decrease in surgical interventions (odds ratio 0.49; 95% CI 0.40–0.60) compared with 2009.

Conclusion Low follow-up rates present a limitation in analysing trends in telemedical abortion usage. However, our findings suggest that it is a highly acceptable method around the world and that there has been an increase in complete abortions by telemedical abortions and a decrease in surgical interventions in the last 10 years.

Keywords medical abortion, mifepristone, self-managed abortion, telemedicine.

Tweetable abstract In the last 10 years, there has been an increase in complete abortions and decrease in surgical interventions of telemedical abortion.

Linked article This article is commented on by Patricia A. Lohr, p. 160–161 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.16905.

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Introduction

Around 44% of pregnancies worldwide are unintended and approximately half of these result in induced abortion.[1] Restrictive laws on access to abortion services do not decrease abortion rates but increase the likeliness of abortions to be unsafe.[2] Approximately 700 million women of reproductive age live in countries with restrictive abortion laws.[3] Additional barriers to access services, irrespective of legal setting, include long-waiting lists, long-distance, lack of transport, high costs and stigma.[4] Among the 56 million abortions that were estimated to take place yearly between 2010 and 2014, 25 million (45%) were estimated to be unsafe.[5] In 2014, at least 22 800 women worldwide died as a direct result of unsafe abortion.[1]

The increased access and use of medical abortion have been described as revolutionary, because they are believed to have helped to decrease abortion-related morbidity and mortality globally.[6–8] Medical abortion with a combination of mifepristone and a prostaglandin analogue was first

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developed in the 1980s.[9] Subsequently, the method has been demedicalised while maintaining high efficacy, safety and acceptability. This development included home use of misoprostol, simplified follow up and task shifting to mid-level providers and to women themselves.[10–13]

Telemedicine in terms of abortion care refers to the use of telecommunications technology by healthcare professionals, to provide information, counselling, and provision and clinical guidance of medical abortion.[14] Telemedicine has become increasingly available and is a promising solution to make abortion services more accessible, particularly for those living in rural areas and legally restricted settings.[15,16] Studies of the use of medical abortion in the first trimester through telemedicine have found it to be non-inferior to the in-clinic provision of services.[17–19] Similarly, emerging evidence is showing that medical abortion in the first trimester through telemedicine is safe, effective and an acceptable method for women.[14]

However, gaps remain in evidence on medical abortion through telemedicine, and a comprehensive overview of trends in the usage is lacking.[20] Two recent reviews on self-managed abortion identified critical areas of future research, including further evidence on physical, social and emotional experiences, and that study settings include diversity in legal restrictions, geographic and social context.[15,20] Therefore, this study aims to provide a descriptive overview and evaluate changes in the use and outcome of abortion provided by the telemedical abortion service Women on Web (WoW) in the past 10 years.

Methods

Study design

This study was a retrospective cohort study, using a quantitative approach to evaluate the changes observed over time in the use and outcome of medical abortion by analysing the data of WoW.

Study setting

WoW is a non-profit organisation, providing telemedicine services since 2006. Services include the provision of information, medical guidance and medical abortion for women living in countries with restricted access to safe abortion.[21] WoW mainly provide their services through their website.[21] Women opting for a medical abortion complete an online consultation with a medical doctor. If they are <9 or 10 weeks pregnant (depending on the country of residence) and have no contraindications, abortion pills can be sent with detailed instructions for use. Gestation is established based on women's self-reported last menstrual period. Women are advised but not required to have an ultrasound to establish gestation and confirm completion. WoW requests a donation of between 70 and 90 euros, but the service is provided on a sliding scale or for free in case of financial hardship.

Study population

A total of 81 683 women were sent medical abortion medication between 2009 and 2019. To be included in the main data analysis, women had to report that they used the medical abortion medication in the follow-up survey. Women who did not go through with the abortion and did not return follow-up surveys were excluded for data analysis.

Patient involvement

There was no patient or public involvement in the design or conduct of the study. However, the service that WoW provides is designed to address the priorities and experiences of people who access the service. Hence, the research questions were informed by the needs of people who rely on WoW to access abortion. The Medical Abortion Reporting Efficacy (MARE) guidelines were followed for reporting the main outcomes.[22] Core outcome sets were not applicable. No funding was received for this study.

Data collection

Data including the consultation and follow-up survey were self-reported through the WoW website. Data were transported to an Excel file and anonymised. Follow-up surveys were sent via e-mail 5 weeks after the shipment of medication. If needed, a reminder was sent after another 2 weeks. Similar to follow-up instruments in clinical settings, the survey consisted of 30 questions that included information on completed treatment, how the pregnancy was confirmed, perceived adverse effects, any visits or contacts for medical care, any treatment received, how information was accessed and emotions after the procedure. Although WoW has been active since 2006, we included data from the year 2009 onwards because this was the year that WoW changed its data collection system.

Measurements

Main outcomes included: rate of reported ongoing pregnancy, surgical intervention, blood transfusions per year, socio-economic situation, knowledge on medical abortion, acceptability of receiving telemedical abortion service method, appropriateness of medical abortion method and the likelihood of recommending telemedical abortion service to a friend.[14,15] Ongoing pregnancy is defined as the failure of medical abortion.[22] MARE guidelines recommend defining a medical abortion to be successful when there is a 'successful expulsion of the intrauterine pregnancy without the need for surgical intervention', i.e. a complete abortion.[22] Lastly, a blood transfusion is an adverse event that is often measured as an indication of safety.[20]

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Countries were initially divided into United Nations geographic regions and sub-regions.[23] As the frequencies of evaluations and representation of countries were shown to be extremely varied, this was considered to be a misleading classification. As a result, only the ten countries where most of the medical abortion services were provided were included for an overview, as they accounted for 84.3% of the total sample, and 84.9% after applying the inclusion criteria.

Statistical analysis

Data were cleaned using Microsoft Excel and further analysed in IBM SPSS 26 (IBM, Armonk, NY, USA). Invalid or missing answers were corrected or deleted by evaluating women's comments or subsequent responses throughout the follow-up survey. If contradictory information was provided in the survey, e-mail correspondence was checked in the WoW database for the original answer. Descriptive statistical analysis was performed on demographic information and main outcomes. For questions with multiple answers, new categories were created, and variables were re-coded into binary variables in accordance with previous studies.[14,19,22,24,25] Seven age categories were created; <20, 20–24, 25–29, 30–34, 35–39, 40–44, ≥45 years based on previous literature and for the purposes of summarising the data, but age was included as a continuous variable in logistic regression analysis.[24] Follow-up surveys from Ireland and Northern Ireland were grouped, in accordance with previous research using WoW data.[24] A binary logistic regression analysis was performed to test associations further. Four regressions were run for the total sample and year, adjusted for age. The year 2009 was set as the reference category.

Results

An overview of the study population is presented in Table 1. Abortion pills were provided to 81 683 women between 2009 and 2019. A total of 30 344 (37.2%) women from 183 different countries completed the follow-up evaluation between January 2009 and December 2019, of which 26 076 (85.6%) reported that they used the abortion pills and were included in the main data analysis. In all, 4268 (14.1%) were excluded because they did not report using the abortion pills, because they decided to continue the pregnancy (n = 737, 2.4%), had a spontaneous miscarriage meanwhile (n = 1839, 6.1%), decided to use another method (n = 1040, 3.4%), realised they were not pregnant after all (n = 39, 0.1%), did not receive the medicines (n = 121 0.4%), had an ectopic pregnancy (n = 4, 0.0%) or left the question blank (n = 488, 1.6%). The ten countries with the most follow-up surveys for each United Nations geographic region were included for an overview. Of these, the ten countries with the highest frequency of follow-up surveys were: Poland (n = 11 902), Ireland and Northern Ireland (n = 3059), Thailand (n = 1422), Chile (n = 1346), South Korea (n = 1155), Brazil (n = 1121), United Arab Emirates (n = 601), Philippines (n = 565), Japan (n = 486) and Malaysia (n = 470). The incidence of missing data in the completed follow-up surveys was relatively low, ranging from 0.5 to 0.7% and was deleted from the subsequent regression analysis.

A summary of the main outcome measures is presented in Table 2. Ongoing pregnancy was reported by 1.5% (n = 404) of women while 87.9% (n = 22 926) reported a complete abortion. The overall rate of blood transfusion was 0.6% (n = 155). As a proxy of economic situation, we found that 9175 (35%) who made a donation for the service reported that it was difficult to find the money. In 8.5% of cases (n = 2223), the service was fully donated. Just over half of the women reported previous knowledge of medical abortion. A large majority of women (96.6%; n = 25 178) found medical abortion to be the appropriate method for them, and 99% (n = 25 186) found it to be acceptable to have the telemedical abortion at home with WoW support. Overall, 96.1% (n = 25 071) would recommend WoW services to other women in a similar situation.

Results from logistic regression analyses are summarised in Table 3. Year of treatment was significantly associated with all outcomes, except for knowledge about medical abortion. Models were adjusted for age, which had an odds ratio and 95% CI close or equal to 1, indicating no association for each outcome. Overall, the chance of having a complete abortion increased with time, (odds ratio 1.92; 95% CI 1.59–2.31) in 2019 versus 2009. The risk of having surgical intervention significantly decreased from 2012 onwards, with an odds ratio of 0.49 (95% CI 0.40–0.60) in 2019 versus 2009.

Discussion

Main findings

This large study including 30 344 women from 183 countries using medical abortion provided by telemedicine identified several changes in the use and outcome of medical abortion provided by WoW over 10 years. A significant association was found between the year of treatment and outcome measures. There was a significant increase in reported complete abortions, a decrease in surgical intervention, and an overall low rate of ongoing pregnancy and blood transfusions. The service was highly acceptable and medical abortion was considered an appropriate method in almost all cases. There were significant fluctuations in financial hardship but these did not show a specific trend. There was no significant change in knowledge about medical abortion over the years.

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Table 1. Overview of data

	n (%)
Total number of women who completed the consultation and were sent the abortion pills	81 683
Did not complete follow-up evaluation survey	51 339 (63.0)
Returned follow-up evaluation surveys	30 344 (37.0)
Did not do the abortion	4268 (14.1)
Did not answer if they did the abortion	488 (1.6)
Used other method	1040 (3.4)
Spontaneaous miscarriage	1839 (6.1)
Decided to continue pregnancy	737 (2.4)
Did not receive pills by post	121 (0.4)
Not pregnant	39 (0.1)
Ectopic pregnancy	4 (0.0)
Completed follow-up evaluation survey and used the abortion pills	26 076 (85.9)

Country*					**Total (*n* = 26 076)**
Africa	428 (1.7)	Asia	5296 (20.5)	Europe	15 636 (60.0)
Morocco	77 (0.3)	Thailand	1422 (5.5)	Poland	11 902 (45.6)
Egypt	59 (0.2)	South Korea	1155 (4.4)	NI & Ireland	3059 (11.7)
Senegal	57 (0.2)	United Arab Emirates	601 (2.3)	Great Britain	227 (0.9)
Nigeria	55 (0.2)	Philippines	565 (2.2)	Hungary	130 (0.5)
Kenya	54 (0.2)	Japan	486 (1.9)	Malta	122 (0.5)
Algeria	44 (0.2)	Malaysia	470 (1.8)	Germany	72 (0.3)
Trinidad and Tobago	31 (0.1)	Indonesia	279 (1.1)	Spain	52 (0.2)
Namibia	25 (0.1)	Saudi Arabia	124 (0.5)	Isle of Man	37 (0.1)
Zimbabwe	25 (0.1)	Singapore	100 (0.4)	Lithuania	19 (0.1)
South Africa	21 (0.1)	Oman	94 (0.4)	Italy	16 (0.1)
Americas	3351 (13.0)	Oceania	188 (<1)		
Chile	1346 (5.2)	Australia	101 (0.4)		
Brazil	1121 (4.3)	New Zealand	51 (0.2)		
Argentina	276 (1.1)	Fiji	10 (0.0)		
Mexico	188 (0.7)	Samoa	7 (0.0)		
Costa Rica	129 (0.5)	Cook Islands	6 (0.0)		
Colombia	83 (0.3)	Micronesia	4 (0.0)		
Guatemala	68 (0.3)	Northern Marina Island	3 (0.0)		
Dominican Republic	54 (0.2)	Papa New Guinea	2 (0.0)		
Paraguay	43 (0.2)	Solomun Islands	2 (0.0)		
Venezuela	43 (0.2)	Vanatu	2 (0.0)		

*To facilitate overview, the ten countries with the highest number of evaluations for each UN geographic regions were included.

Strengths and limitations

A key limitation is the low response rate, which appeared to decrease over time. If the likelihood of responding was related to the patient's experience and outcome, then this would be a source of bias in our results. A high loss to follow up was to be expected and is a persistent challenge within abortion research given the high level of stigma associated, and in this case also included countries with legal restrictions to access abortion services.[11,26] In other studies, the follow-up rate was improved by analysing email correspondence and phone calls; however, it was not feasible to include these because of the high number of participants and language groups.[21] There is limited information about reasons for follow-up participation; however, a previous study suggests that those who have a complication or failure are more likely to report back than in the case of a successful abortion.[11] A limitation of self-managed medical abortions is that only self-reported data are available, and in a study like ours, we cannot be sure that women follow the instructions on intervals and dosage. Hence, there is a possibility that the continuing pregnancies are due to non-adherence to the regimen. Following the advice of the WHO, women are advised to administer one mifepristone orally and after 24 hours

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Table 2. Frequency table of the use and outcome of medical abortion

	Total (n = 26 076)	Brazil (n = 1121)	Chile (n = 1346)	Ireland & NI (n = 3059)	Japan (n = 486)	Malaysia (n = 470)	Philippines (n = 565)	Poland (n = 11 902)	S. Korea (n = 1155)	Thailand (n = 1422)	UAE (n = 601)
Use and outcome, *n* (%)											
Age (years)											
Average (Minimum–Maximum)*	27.8 (12–55)	26.4 (12–49)	27.1 (14–55)	29.7 (13–54)	28.5 (15–47)	26.9 (14–44)	26.3 (15–44)	27.8 (13–54)	25.7 (13–48)	25.8 (14–45)	30.2 (15–52)
<20	2305 (8.8)	131 (11.7)	109 (8.1)	156 (5.1)	35 (7.2)	47 (10.0)	58 (10.3)	1116 (9.4)	127 (11.0)	209 (17.7)	10 (1.7)
20–24	7004 (26.9)	396 (32.9)	385 (28.6)	565 (18.8)	114 (23.5)	138 (29.4)	194 (34.3)	3283 (27.6)	425 (36.8)	475 (33.5)	71 (11.8)
25–29	6840 (26.2)	291 (26.0)	423 (31.4)	806 (26.3)	126 (25.9)	144 (30.6)	165 (29.2)	2887 (24.3)	352 (30.5)	353 (24.9)	199 (33.1)
30–34	5390 (20.7)	209 (18.6)	264 (19.6)	782 (25.6)	114 (30.6)	81 (17.2)	85 (15.0)	2407 (20.2)	149 (12.9)	231 (16.3)	198 (32.9)
35–39	3299 (12.7)	82 (7.3)	121 (9.0)	530 (17.3)	68 (14.0)	43 (9.1)	49 (8.7)	1629 (13.7)	70 (6.1)	120 (8.5)	89 (14.8)
40–44	1109 (4.3)	32 (2.9)	39 (2.9)	199 (6.5)	28 (5.8)	17 (3.6)	14 (2.5)	520 (4.4)	29 (2.5)	31 (2.2)	30 (5.0)
≥45	125 (0.5)	7 (0.6)	5 (0.4)	21 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	58 (0.5)	3 (0.3)	1 (0.1)	4 (0.7)
Missing	4							2		2	
Ongoing pregnancy											
Yes	404 (1.5)	22 (2.0)	13 (1.0)	53 (1.7)	12 (2.5)	6 (1.3)	9 (1.6)	147 (1.2)	22 (1.9)	33 (2.3)	9 (1.5)
Missing	119 (0.5)	7 (0.6)	2 (0.1)	25 (0.8)	3 (0.6)	1 (0.2)	5 (0.9)	52 (0.4)	4 (0.3)	2 (0.1)	1
Surgical intervention											
Yes	2660 (10.2)	193 (17.2)	119 (8.8)	140 (4.6)	23 (4.7)	24 (5.1)	49 (8.7)	1567 (13.2)	80 (6.9)	93 (6.5)	34 (5.7)
Missing	192 (0.7)	26 (2.3)	0 (0.0)	8 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	145 (1.2)	2 (0.2)	0 (0.0)	1 (0.2)
Complete abortion											
Yes	22 926 (87.9)	902 (80.5)	1214 (90.2)	2845 (93.0)	448 (92.2)	440 (93.6)	502 (88.8)	10 146 (85.2)	1050 (90.9)	1296 (91.1)	559 (93.0)
Missing	116 (0.4)	7 (0.6)	2 (0.1)	24 (0.8)	3 (0.6)	1 (0.2)	5 (0.9)	50 (0.4)	4 (0.3)	2 (0.1)	1 (0.2)
Blood transfusion	155 (0.6)	10 (0.9)	11 (0.8)	29 (0.9)	4 (0.8)	1 (0.2)	1 (0.2)	59 (0.5)	6 (0.5)	3 (0.2)	2 (0.3)
Was it difficult to find money for the donation?											
Yes	9175 (35.2)	393 (35.1)	625 (46.4)	953 (31.2)	238 (49.0)	170 (36.2)	276 (48.8)	4286 (36.0)	269 (23.3)	586 (41.2)	123 (20.5)
No	14 600 (56.0)	615 (54.9)	583 (43.3)	2019 (66.0)	233 (47.9)	252 (53.6)	200 (35.4)	6736 (56.6)	806 (69.8)	614 (43.2)	438 (72.9)
Got the service donated	2223 (8.5)	106 (9.5)	134 (10.0)	81 (2.6)	15 (3.1)	48 (10.2)	86 (15.2)	836 (7.0)	79 (6.8)	220 (15.5)	37 (6.2)
Missing	78 (0.3)	7 (0.6)	4 (0.3)	6 (0.2)	0 (0.0)	0 (0.0)	3 (0.5)	44 (0.4)	1 (0.1)	2 (0.1)	3 (0.5)
Did you know about medical abortion before?											
Yes	15 435 (59.2)	679 (60.6)	959 (71.2)	1886 (61.7)	238 (49.0)	249 (53.0)	354 (62.7)	7306 (61.4)	524 (45.5)	504 (35.4)	367 (61.1)
No	10 500 (40.3)	433 (38.6)	378 (28.1)	1149 (37.6)	245 (50.4)	219 (46.6)	206 (36.5)	4542 (38.2)	626 (54.2)	915 (64.3)	230 (38.3)
Missing	141 (0.5)	9 (0.8)	9 (0.7)	24 (0.8)	3 (0.6)	2 (0.4)	5 (0.9)	54 (0.5)	5 (0.4)	3 (0.2)	4 (0.7)
Was medical abortion an appropriate method for you?											
Yes (Satisfied)	25 178 (96.6)	1083 (96.7)	1314 (97.6)	2960 (96.8)	469 (96.5)	461 (98.1)	549 (97.2)	11 475 (96.4)	1104 (95.6)	1387 (97.5)	582 (96.8)

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Table 2. (Continued)

	Total (*n* = 26 076)	Brazil (*n* = 1121)	Chile (*n* = 1346)	Ireland & NI (*n* = 3059)	Japan (*n* = 486)	Malaysia (*n* = 470)	Philippines (*n* = 565)	Poland (*n* = 11 902)	S. Korea (*n* = 1155)	Thailand (*n* = 1422)	UAE (*n* = 601)
No (Not satisfied)	749 (2.8)	27 (2.4)	26 (2.0)	93 (3.0)	16 (3.3)	9 (1.9)	12 (2.1)	348 (2.9)	34 (2.9)	32 (2.3)	17 (2.8)
Missing	149 (0.6)	11 (1.0)	6 (0.4)	6 (0.2)	1 (0.2)	0 (0.0)	4 (0.7)	79 (0.7)	17 (1.5)	3 (0.2)	2
How did you feel about the possibility of having a medical abortion at home with Women on Web support?											
I thought it was acceptable	25 186 (99.0)	1107 (98.8)	1327 (98.6)	3038 (99.3)	482 (99.8)	468 (99.5)	559 (98.9)	11 767 (98.9)	1145 (99.2)	1414 (99.4)	594 (98.8)
It was not acceptable for me	134 (0.5)	3 (0.3)	8 (0.6)	15 (0.5)	4 (0.8)	2 (0.4)	4 (0.7)	58 (0.5)	9 (0.8)	8 (0.6)	2 (0.3)
Missing	126 (0.5)	11 (1.0)	11 (0.8)	6 (0.2)	0 (0.0)	0 (0.0)	2 (0.4)	77 (0.6)	1 (0.1)	0 (0.0)	5 (0.8)
Would you recommend Women on Web to other women?											
Yes	25 071 (96.1)	1096 (97.8)	1327 (98.6)	2975 (97.3)	455 (93.6)	450 (95.7)	520 (92.0)	11 560 (97.1)	1131 (97.9)	1183 (83.2)	575 (95.7)
No	826 (3.2)	18 (1.6)	12 (0.9)	58 (1.9)	28 (5.8)	18 (3.8)	33 (5.8)	257 (2.2)	19 (1.6)	237 (16.7)	20 (3.3)
Missing	179 (0.7)	7 (0.6)	7 (0.5)	26 (0.8)	3 (0.6)	2 (0.4)	12 (2.1)	85 (0.7)	5 (0.4)	2 (0.1)	6 (1.0)

*In years.

administer four misoprostol sublingually for 30 minutes, and repeat with two misoprostol every 3 hours until the abortion process starts.[27] However, given that the sample was located in several different countries with varying legal restrictions in abortion access, using self-reported data is the most feasible method.[24] It was not possible to adjust for known confounders, such as gestational age, as this information was not available in our data set.[25] Although WoW limits the availability of the service to women who are <9 to 10 weeks pregnant since last menstrual period at the time they complete the online consultation, between the online consultation and the actual use of the medication, there is a variable time lag, depending on shipping time and any delay in usage after receiving them. However, the majority of the abortions in this data set are expected to have taken place in the first trimester. To our best knowledge, this study provides the largest evaluation so far of the outcome of medical abortion provided by telemedicine. Furthermore, it includes the largest sample of women doing a medical abortion in a wide range of different legal settings. Outcomes are reported in consistency with previous studies for comparability. In addition, we included outcome measures that have never been looked at before, such as financial hardship and pre-existing knowledge about medical abortion.

Interpretation

As illustrated in Table 1, all of the United Nations main geographic regions were represented, with a highly variable frequency of countries. Country representation is also likely to have been affected by language translations and the censorship of the website. When WoW was launched in 2006, it was available in Polish, English, Spanish, French and Portuguese, whereas today it is available in 24 languages.[11,21] The age distribution for the total sample is as expected and in line with a previous report of 'Abortion Worldwide 2017' by the Guttmacher Institute, showing the peak for having an abortion is often around 20–24 years of age, but also common in the early thirties in many countries.[8]

The proportion of the total sample reporting that they knew about medical abortion before using the service was 59.2% and remained almost unchanged between 2009 and 2019. Given the advancements over the past years in use and acceptability among healthcare providers, the dissemination of knowledge about medical abortion by the WHO, local women's rights organisations and other international non-governmental organisations and the media, these results suggest that many women still only learn about medical abortion once they have an unwanted pregnancy, which has also been suggested previously.[28]

Our findings concerning the outcome of the medical abortion treatment are in line with previously published research. A recent systematic review of outcomes of

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Table 3. Changes in the use and outcome of medical abortion between 2009 and 2019

Predictor	Having a complete abortion		Having a surgical intervention		Knowing about medical abortion		Having difficulty to find money for donation	
	n = 25 956		*n* = 25 884		*n* = 25 931		*n* = 25 994	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Year 2009 ref								
2010	1.20 (1.01–1.43)	**0.041**	0.85 (0.71–1.02)	0.087	0.95 (0.84–1.08)	0.430	0.87 (0.76–0.99)	**0.031**
2011	1.22 (1.02–1.45)	**0.029**	0.88 (0.73–1.05)	0.159	1.09 (0.95–1.23)	0.212	0.96 (0.84–1.09)	0.515
2012	1.57 (1.31–1.88)	**<0.001**	0.69 (0.57–0.83)	**<0.001**	1.00 (0.88–1.14)	0.954	1.42 (1.25–1.61)	**<0.001**
2013	1.41 (1.19–1.68)	**<0.001**	0.76 (0.64–0.92)	**0.004**	1.04 (0.92–1.18)	0.525	1.40 (1.23–1.58)	**<0.001**
2014	1.36 (1.10–1.67)	**0.004**	0.76 (0.61–0.94)	**0.012**	1.06 (0.92–1.23)	0.409	1.55 (1.34–1.80)	**<0.001**
2015	1.45 (1.19–1.76)	**<0.001**	0.68 (0.56–0.84)	**<0.001**	1.01 (0.88–1.15)	0.928	1.50 (1.31–1.73)	**<0.001**
2016	1.50 (1.24–1.82)	**<0.001**	0.68 (0.56–0.84)	**<0.001**	1.15 (1.01–1.32)	0.041	1.35 (1.18–1.55)	**<0.001**
2017	1.79 (1.47–2.19)	**<0.001**	0.54 (0.44–0.67)	**<0.001**	1.08 (0.94–1.23)	0.277	1.37 (1.19–1.57)	**<0.001**
2018	1.97 (1.63–2.38)	**<0.001**	0.49 (0.40–0.60)	**<0.001**	0.98 (0.87–1.12)	0.800	1.14 (1.00–1.30)	**0.045**
2019	1.92 (1.59–2.31)	**<0.001**	0.49 (0.40–0.60)	**<0.001**	1.09 (0.96–1.24)	0.196	1.24 (1.09–1.42)	**<0.001**
Age	1.00 (1.00–1.01)	0.28	1.00 (0.99–1.01)	0.86	1.01 (1.00–1.01)	**<0.001**	0.95 (0.76–0.99)	**<0.001**

P-value in bold indicates statistical significance.

medical abortion through telemedicine reported a range of 0–1.9% for continuing pregnancy, 93.8–96.4% for complete abortion, 0.9–19.3% for surgical intervention and 0–0.7% for blood transfusion.[14] Our findings are also in line with reported complete abortion rates for in-clinic medical abortion treatment.[19] The slightly higher rate in surgical interventions in our study compared with other studies might be explained by the fact that almost half of women were living in Poland and the surgical intervention rate in this study was highest in Poland (13.2%) and Brazil (17.2%). High intervention rates in Poland and Brazil have also been reported in previous studies.[29–31] It has been suggested that this is caused by differences in local clinical practices and economic incentives, rather than treatment efficacy or gestational length.[31] We found an overall increase in the rate of complete abortion and a decrease in surgical interventions between 2009 and 2019. This may be caused by a combination of factors, such as a rise of medical treatment of incomplete abortion with the administration of repeat doses of misoprostol, improved training of health professionals and increased knowledge about the medical abortion process by women, as in countries with restricted abortion laws a decrease of follow-up visits after the medical abortion is likely to result in a decrease in surgical interventions.[31,32] Previous research has found a decreasing trend in gestational age at the time of abortion in countries with liberal abortion laws, which could lead to higher efficacy.[33]

These findings are particularly pertinent and relevant in the current situation of the coronavirus disease 2019 global pandemic, where measures implemented to prevent the spread of disease have hampered access to safe abortion care. Telemedical abortion care, which has been primarily outside the medical institutions, is now being further integrated, for example, the United Kingdom has permitted telemedical abortions.[34] This further highlights the potential and feasibility of telemedicine services to provide safe abortion access worldwide during the coronavirus disease 2019 pandemic and beyond.

Conclusion

The purpose of the current study was to evaluate the use and outcome in the telemedical provision of medical abortion over the past 10 years. We identified several promising trends over the past 10 years, including increasing rates of complete abortion and a decrease in surgical interventions. As indicated by a high rate of complete abortion, high acceptability, low rate of ongoing pregnancy and complications such as bleeding needing a blood transfusion, the study adds to the growing body of research suggesting that online telemedical counselling and provision and self-managed medical abortion are safe, effective and highly acceptable methods for women around the world. The varying surgical intervention rates between the different countries suggest that local post-abortion care can be improved and further research is needed to gain a better understanding of the different local post-abortion practices, especially in countries with a higher surgical intervention rate. While being of a descriptive nature, findings also suggest that there is

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an unmet need for information about medical abortion provided by telemedicine.

Disclosure of interests

HN and IO have none to declare. JW is supported by a Wellcome Institutional Strategic Support Fund award (204796/Z/16/Z) outside the submitted work and declares that publishing research benefits his career. KGD has served as an ad hoc speaker and/or member of advisory boards for Exelgyn, Campus Pharma, HRA Pharma, MSD/Merck, Bayer AG, Exeltis, Mithra, Natural Cycles, Gedeon Richter and Azanta, and her clinic has received support for clinical trials from MSD/Merk, Bayer AG, Myovant, and Removaid outside the submitted work. RG is the founder and director of Women on Web. Completed disclosure of interests forms are available to view online as supporting information.

Contribution to authorship

HN was responsible for the conception, planning, carrying out, analysing and writing up of the work. JW was responsible for analysing and editing. OI was responsible for conception, planning and editing. KGD was responsible for conception and editing. RG was responsible for the conception, planning and writing up of the work.

Details of ethics approval

Ethical approval was given by the Karolinska Institutet (Dnr 2020-05406). During the original data collection, participants gave informed consent to their data being used for research purposes. All data were completely anonymised.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. ■

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Nurse versus physician-provision of early medical abortion in Mexico: a randomized controlled non-inferiority trial

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Objective To examine the effectiveness, safety, and acceptability of nurse provision of early medical abortion compared to physicians at three facilities in Mexico City.

Methods We conducted a randomized non-inferiority trial on the provision of medical abortion and contraceptive counselling by physicians or nurses. The participants were pregnant women seeking abortion at a gestational duration of 70 days or less. The medical abortion regimen was 200 mg of oral mifepristone taken on-site followed by 800 µg of misoprostol self–administered buccally at home 24 hours later. Women were instructed to return to the clinic for follow-up 7–15 days later. We did an intention-to-treat analysis for risk differences between physicians' and nurses' provision for completion and the need for surgical intervention.

Findings Of 1017 eligible women, 884 women were included in the intention-to-treat analysis, 450 in the physician-provision arm and 434 in the nurse-provision arm. Women who completed medical abortion, without the need for surgical intervention, were 98.4% (443/450) for physicians' provision and 97.9% (425/434) for nurses' provision. The risk difference between the group was 0.5% (95% confidence interval, CI: −1.2% to 2.3%). There were no differences between providers for examined gestational duration or women's contraceptive method uptake. Both types of providers were rated by the women as highly acceptable.

Conclusion Nurses' provision of medical abortion is as safe, acceptable and effective as provision by physicians in this setting. Authorizing nurses to provide medical abortion can help to meet the demand for safe abortion services.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

In Mexico City, early elective abortion to terminate pregnancy was legalized in April 2007.[1–3] Up to June 2013, 100 000 abortions have been provided by trained physicians in Ministry of Health hospitals and clinics.[4] In 2009, it was estimated that 13.5% (16 475/122 455) of all abortions in Mexico City were safe and legal and provided by the public sector.[5] Even though some safe and legal abortions are done in private facilities,[6] most abortions are done outside sanctioned facilities and are potentially unsafe.[7] Despite Mexico City's efforts to expand services and increase the availability of the mifepristone-misoprostol regimen for medical abortion, patient demand is outpacing service capacity. Furthermore, conscientious objections from trained physicians[8] have further restricted service capacity.

To expand the capacity of the health workforce, task-shifting has been proven to be an important strategy.[9] Evidence from low-resource settings suggests that trained, mid-level providers can administer medical abortion with similar outcomes as physicians.[10–14]

In Mexico, nurses tend to have a subordinate role compared to physicians and have traditionally been excluded from decision-making.[15] Approximately one-third of the Mexico City Ministry of Health personnel are physicians and one-third are nurses.[16] Authorizing nurses to provide medical abortion could increase the potential capacity for provision of this service and help to address increasing demand.

We aimed to assess the effectiveness, safety and acceptability of nurses' versus physicians' provision of early medical abortion in facilities of the Mexico City Ministry of Health.

Methods

We conducted a randomized controlled non-inferiority trial between November 2012 and January 2013 at two Mexico City Ministry of Health abortion clinics and one hospital. Mean numbers of both medical and surgical abortions performed weekly are 137 and 27 at the clinics and 48 at the hospital, representing 50% of legal abortion provision in Mexico City, a city of 8 851 080 people.[17]

We assumed that physicians and nurses would achieve a 95% completion rate for medical abortions, based on a previous randomized controlled trial[11] and a meta-analysis on medical abortion efficacy which found successful medical abortion rates using the mifepristone-misoprostol regimen between 91% to 96% depending on gestational duration.[18] We assumed a 5% non-inferiority margin based on cost-effectiveness and clinical differences – such as the ability of nurses and physicians to determine gestational duration, screen for early medical abortion and determine incomplete abortion.[19] We used the PASS software version 11 (NCSS, LCC, Kaysville, United States of America) to determine that a sample size of 800 (400 per arm) would be sufficient to detect non-inferiority with 90% power and a one-sided significance level of 0.025, assuming 15% loss to follow-up per arm.

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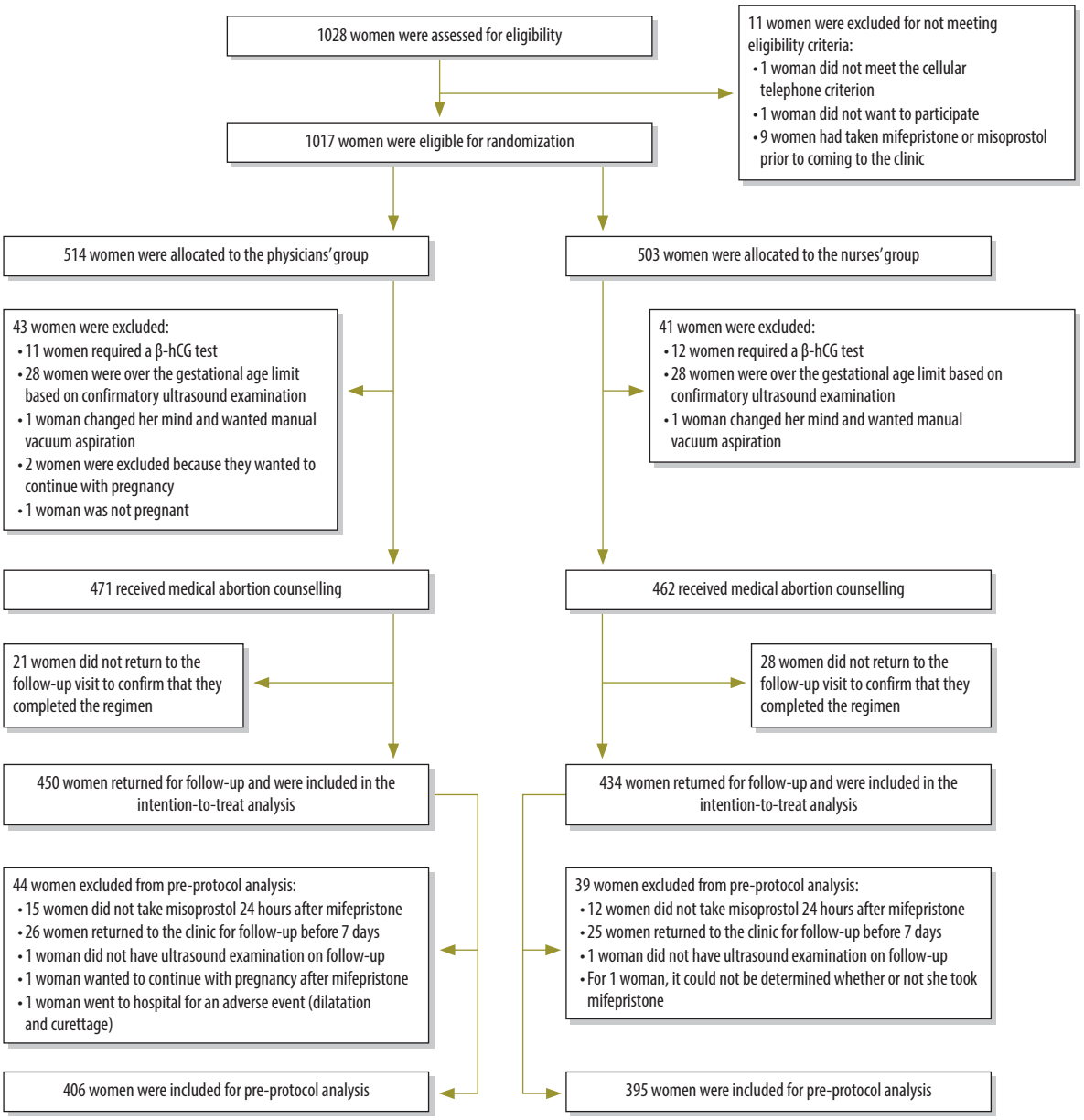
The study protocol was approved by the Mexico City Ministry of Health and Mexico's National Institute of Public Health institutional review boards. Ethical approval was obtained from the World Health Organization's (WHO's) ethics review committee. We invited experts in medical abortion, nursing, ultrasound training and health systems to participate in a scientific advisory and data safety monitoring committee.

The Mexico City Ministry of Health granted temporary permission for nurses to administer medical abortion for study purposes and providers were recruited from existing Ministry of Health personnel. We only recruited physicians who had recently joined clinic staff and who had never provided medical abortion or had only previously managed medical abortion under supervision to minimize unfair comparison between physicians with previous experience and nurses with no experience.

Physicians and nurses received separately one and a half weeks of training on medical abortion management. The training was provided by a certified ultrasonographer and one of the authors. To reach a professional level of ultrasound skill,[20,21] all physicians and nurses received 20 hours of abdominal and transvaginal ultrasound training using a Hitachi SSD-3500SX console.[22] The providers were certified by experienced obstetricians to have achieved required competency. At each site, an experienced obstetrician – not part of the study – was made available for providers to consult as needed.

Women visiting the facilities for an abortion were shown to a private space and screened for eligibility by a nurse participating in the study. Women were invited to participate if they: wanted a

Fig. 1. **Randomized clinical trial profile of women undergoing first-trimester medical abortion provided by nurses or physicians in Mexico City, 2012–2013**



hCG: human chorionic gonadotropin.

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medical abortion, were aged 18 years or older, reported a last menstrual period of less than 70 days previously and were willing to provide contact information for follow-up. They were excluded if they had a history of allergy to mifepristone or misoprostol, chronic systemic corticosteroid use, chronic adrenal failure, coagulopathy or current therapy with anticoagulants, inherited porphyria, chronic medical conditions including pre-existing heart, severe hepatic or renal disease and severe anaemia. They were also excluded if they had previously received a medical abortion as part of the Mexico City legal abortion programme. All women were given an opportunity to ask questions before providing written consent. Participants could voluntarily withdraw from the study at any time and for any reason without change to the care they received. Before randomization, enrolled participants provided contact and sociodemographic information via a structured interview.

We generated a list of consecutive identification numbers and randomly allocated a physician or a nurse that should provide medical abortion to each number using R 3.1.2 software for Windows (R Foundation for Statistical Computing, Vienna, Austria). As women were recruited, they were assigned an identification number. Allocation was concealed in a sealed envelope, which was only opened once the participant was considered eligible and consented to enrol.

All enrolled women received clinical care and medical abortion at their first visit. This included a vaginal and pelvic exam, and an abdominal ultrasound to confirm intrauterine pregnancy and gestational duration. According to Mexico City Ministry of Health guidelines, providers must confirm gestational duration via abdominal ultrasound. Providers followed the guidelines' standard of care regarding ultrasound image interpretation.[22] Women with an inserted intrauterine device (IUD) that could not be removed before administering mifepristone were excluded from the study. If providers could not confirm gestational duration or intrauterine pregnancy, women were referred to another facility for a β-hCG (human chorionic gonadotropin) fraction test. Since we could not ensure their return to the study, they were excluded.

We used the medical abortion regimen recommended by Mexico City Ministry of Health,[23] which differs from WHO's recommendation.[24] Pregnant women with a gestational duration determined as less than 70 days were given 200 mg of oral mifepristone under supervision followed by instructions to self–administer four tablets of misoprostol (200 µg each) buccally at home, 24 hours later.

All women received misoprostol, instructions for administration and contraceptive method counselling from their assigned provider. The study followed the standard of care in counselling and providers offered a mix of different contraceptive methods. Participants were also given an instruction card for contacting a study representative in the event of any questions or concerns and a pamphlet explaining expected side-effects and symptoms that may warrant prompt medical attention – such as

Table 1. **Characteristics of women undergoing medical abortion provided by nurses or physicians in Mexico City, 2012–2013**

Characteristic	No. (%)		
	Physicians' group (*n* = 514)	Nurses' group (*n* = 503)	Total (*n* = 1017)
Age in years, mean (SD)	25.7 (6.0)	26.3 (6.3)	26.0 (6.2)
≤ 19	60 (11.7)	51 (10.1)	111 (10.9)
20–29	337 (65.6)	312 (62.0)	649 (63.8)
30–39	99 (19.3)	119 (23.7)	218 (21.4)
≥ 40	18 (3.5)	21 (4.2)	39 (3.8)
Marital Status			
Single	276 (53.7)	266 (52.9)	542 (53.3)
Married or cohabiting	208 (40.5)	203 (40.4)	411 (40.4)
Separated, divorced, widowed	30 (5.8)	34 (6.8)	64 (6.3)
Education			
No education	0 (0.0)	2 (0.4)	2 (0.2)
At least some primary	38 (7.4)	27 (5.4)	65 (6.4)
At least some junior high school	140 (27.2)	142 (28.2)	282 (27.7)
At least some high school or technical school	204 (39.7)	195 (38.8)	399 (39.2)
At least some university	132 (25.7)	137 (27.2)	269 (26.5)
Occupation[a]			
Student	122 (23.7)	127 (25.3)	249 (24.5)
At home	152 (29.6)	139 (27.7)	291 (28.6)
Employed	165 (32.1)	172 (34.3)	337 (33.2)
Other	75 (14.6)	64 (12.8)	139 (13.7)

SD: standard deviation.
[a] One participant did not provide a response in the nurses' group.
Note: For some characteristics the percentage does not add up to 100 due to rounding.

Table 2. **Assessment of gestational duration of women undergoing medical abortion provided by nurses or physicians in Mexico City, 2012–2013**

Characteristic	Physicians' group (*n* = 514)	Nurses' group (*n* = 503)	Total (*n* = 1017)	*P*
No. of women reporting last menstrual period, (%)	464 (90.3)	451 (89.7)	915 (90)	
Duration of gestation from last menstrual period in days, mean (SD)	51.8 (14)	53.2 (16.8)	52.5 (16.1)	0.136
No. of women with ultrasound assessment, (%)	501 (97.5)	489 (97.2)	990 (97.3)	
Duration of gestation determined by ultrasound in days, mean (SD)	49.7 (13.3)	49.7 (14)	49.7 (13.3)	0.914

SD: standard deviation.

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heavy bleeding, fever, headache and abnormal vaginal discharge. Women were instructed to return to the clinic for follow-up 7–15 days later.

At the follow-up visit, providers confirmed completed abortion based on a clinical symptoms checklist, bleeding history and ultrasound results. If the provider determined that the woman had an ongoing pregnancy or incomplete abortion –such as continued bleeding, tissue residue or cramps – participants were offered an additional 800 µg of misoprostol administered at the clinic or hospital, according to Mexico City Ministry of Health practice.[25] If women requested a manual vacuum aspiration or the provider felt it was warranted – due to remaining fetal tissue, persistent gestational sac or continuation of pregnancy – it was provided on-site by an obstetrician who was not part of the study. Participants who chose to take an additional 800 µg of misoprostol were instructed to return in 7–15 days. If these women still did not have a complete abortion at the second follow-up, a vacuum aspiration was performed on-site, that day.

During follow-up, providers asked participants if they had chosen a post-abortion contraceptive method based on the previous counselling. If available, the method was provided; if not, information on where to obtain it was given.

All adverse and serious adverse events were recorded by providers using a review form that had been reviewed by the scientific advisory and data safety monitoring committee. Events were recorded and analysed to allow for safety reporting.

To assess if there were any significant differences between the two study arms, student's *t*-tests and χ^2 tests for two independent samples were used. Non-inferiority was tested using intention-to-treat and per-protocol analysis. A 95% confidence interval (CI) for the difference between the physicians' and nurses' groups in completed abortion rates between study arms was computed and non-inferiority was accepted if this interval lay completely on the left of the non-inferiority 5% margin, that is, if the difference falls within the predefined equivalence range of 5%. Homogeneity of the three study sites was assessed using the Higgins & Thompson index *H*.

Table 3. **Outcomes of medical abortion provided by nurses or physicians in Mexico City, 2012–2013**

Analysis	Physicians' group	Nurses' group	Difference, % (95% CI)
Intention-to-treat			
No. of women	450	434	–
Complete abortion, no. (%)[a]	443 (98.4)	425 (97.9)	0.5 (−1.2 to 2.3)
Per-protocol			
No. of women	406	395	–
Complete abortion, no. (%)[a]	401 (98.8)	386 (97.7)	1.0 (−0.8 to 2.9)

CI: confidence interval.
[a] Without requiring surgical intervention.

Table 4. **Sensitivity analysis of medical abortion provided by nurses or physicians in Mexico City, 2012–2013**

Scenario[a]	Physicians' group		Nurses' group		Difference, % (95% CI)
	N	No. (%) completed abortion[b]	*N*	No. (%) completed abortion[b]	
Scenario 1					
Treated women without observed outcome	21	21 (100.0)	28	22 (78.6)	NA
All treated women	471	464 (98.5)	462	447 (96.8)	1.8 (−0.4 to 3.9)
Scenario 2					
Treated women without observed outcome	21	21 (100.0)	28	20 (71.4)	NA
All treated women	471	464 (98.5)	462	445 (96.3)	2.2 (−0.1 to 4.4)

CI: confidence interval; NA: not applicable.
[a] Based on observed success rates, we assumed a 100% success rate for women lost to follow-up in both scenarios in the physicians' group. For the nurses' group we assumed 78.6% and 71.4% success rates in the first and second scenario, respectively.
[b] Without the need for surgical intervention.

Stratified analysis for potential site effects was not conducted because the complete abortion rate at one site was 100% for both study groups.

We conducted a sensitivity analysis to test two different outcome scenarios for women lost to follow-up. Based on observed success rates, we assumed a 100% success rate for women lost to follow-up in both scenarios in the physicians' group. For the nurses' group we assumed 78.6% and 71.4% success rates in the first and second scenario, respectively.

Once a complete abortion was confirmed and women were given a contraceptive method or information, a study coordinator not linked to clinical care administered a satisfaction survey that the participants completed on-site. An acceptability scale was constructed using responses to the 14 questions. Some answers were binary – yes or no – and others were categorical – e.g. range of satisfaction and expectation levels. We scored the responses for each question using a range between 0 to 1, where the responses with the lowest acceptability received 0 points and responses with the highest acceptability received 1. The points generated for each question were summed to create a provider acceptability score per participant ranging from 0–14. The mean overall acceptability scores for each provider group were compared to determine women's satisfaction.

All analyses were conducted using SPSS version 18.0 (SPSS Inc., Chicago, USA).[26]

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Results

Fifteen providers, seven nurses and eight physicians, participated in the study. There was one male nurse and five male physicians. There was no significant difference in homogeneity between the different study sites ($P = 0.07$).

Of 1028 women approached, eleven were excluded for not meeting eligibility criteria (Fig. 1). Of the eligible women, 503 were randomized to receive medical abortion from nurses and 514 women from physicians. Women in both groups had similar characteristics (Table 1).

In the nurses' group we excluded 12 women who required a β-hCG fraction test to confirm pregnancy and 28 women who had gestational durations longer than 70 days based on abdominal ultrasound examination. One woman was excluded because she changed her mind after randomization and requested manual vacuum aspiration. In the physicians' group, we excluded two women who decided to continue with the pregnancy, 11 who required a β-hCG fraction test and 28 who had gestational durations longer than 70 days based on abdominal ultrasound examination. One woman was excluded when opting for manual vacuum aspiration after randomization and one woman was not pregnant. The number of women excluded and reasons for exclusion were similar in both groups (Fig. 1).

Forty-nine women did not return for follow-up. Attrition was similar in both groups; 6.1% (28) for nurses and 4.5% (21) for physicians (Fig. 1). The characteristics of the women lost to follow-up were similar to those who remained; however, they were more likely to be married or cohabiting (46.9% [23/49] versus 39.5% [349/884]) and be employed (42.9% [21/49] versus 31.8% [281/884]). For the analyses, 434 women remained in the nurses' group and 450 in the physicians' group.

Women had on average a gestational duration of 53 days by last menstrual period and 50 days by ultrasound examination. There was no significant difference in gestational duration assessed by last menstrual period or ultrasound between providers (Table 2).

Successful medical abortions, without need for surgical intervention, were 97.9% (425/434) for nurses and 98.4% (443/450) for physicians – a result within our 5% a priori non-inferiority limit (Table 3). In 14 cases, abortion was completed after manual vacuum aspiration – nine in the nurses' group and five in the physicians' group. Four of the women who eventually underwent manual vacuum aspiration had initially received an additional buccal misoprostol dose at home, but at the second follow-up three still had embryonic tissue and one persistent gestational sac. The analysis also showed that providers administered an additional misoprostol dose in 68 cases. Nurses were sig-

Table 5. **Contraceptive method prescribed for women undergoing medical abortion provided by nurses or physicians in Mexico City, 2012–2013**

Contraceptive method	No. (%)			P[a]
	Physicians' group ($n = 450$)	Nurses' group ($n = 434$)	Total ($n = 884$)	
No. of women prescribed contraceptives[b,c]	444 (98.7)	430 (99.1)	874 (98.9)	ND
Type of contraceptive prescribed[d]				
Contraceptive injection	326 (73.4)	321 (74.7)	647 (74.0)	0.634
Intrauterine device	312 (70.3)	267 (62.1)	579 (66.2)	0.014
Oral contraceptives (estrogen and progestin pills)	296 (66.7)	267 (62.1)	563 (64.4)	0.171
Condom	255 (57.4)	256 (59.5)	511 (58.5)	0.554
Patch	138 (31.1)	147 (34.2)	285 (32.6)	0.315
Implant	118 (26.6)	123 (28.6)	241 (27.6)	0.488
Minipill (progestin only pills)	26 (5.9)	26 (6.0)	52 (5.9)	0.898
Vasectomy	19 (4.3)	22 (5.1)	41 (4.7)	0.548
Female sterilization (tubal ligation)	16 (3.6)	22 (5.1)	38 (4.3)	0.276
No. of women leaving facility with at least one contraceptive method[c]	432 (97.3)	416 (96.7)	848 (97.0)	ND
Type of contraceptive taken[e]				
Contraceptive injection	152 (35.3)	143 (34.4)	295 (34.8)	0.785
Intrauterine device	135 (31.3)	100 (24.0)	235 (27.7)	0.018
Oral contraceptives (estrogen and progestin pills)	68 (15.7)	55 (13.2)	123 (14.5)	0.291
Condom	46 (10.6)	80 (19.2)	126 (14.9)	0.000
Patch	21 (4.9)	21 (5.0)	42 (5.0)	0.906
Implant	10 (2.3)	19 (4.6)	29 (3.4)	0.072
Female sterilization (tubal ligation)	1 (0.2)	0 (0.0)	1 (0.1)	ND
Hormonal emergency contraceptive	0 (0.0)	9 (2.2)	9 (1.1)	ND

ND: not determined.
[a] *P*-values were calculated using χ^2 tests.
[b] Contraceptive counselling took place at first visit.
[c] Information obtained from the acceptability survey.
[d] We had no information on the number of women prescribed hormonal emergency contraceptives.
[e] We had no information on the number of women who chose vasectomies for their partners or minipills.

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nificantly more likely than physicians to administer an extra dose (45 doses versus 23 doses; $P < 0.05$). At one facility, nurses and physicians were more likely to administer an extra dose compared with providers at the other facilities (43 doses in the nurses' group $P < 0.05$; 17 doses in the physicians' group $P = 0.056$).

We conducted pre-protocol analysis excluding women with the following protocol violations: taking misoprostol later than 24 hours following mifepristone administration, returning to the clinic in less than 7 days or later than 15 days after their first visit or women not having an ultrasound examination. For the analysis, 395 women remained in the nurses' group and 406 women in the physicians' group (Fig. 1). The results of successful medical abortion were similar to the intention-to-treat analysis (97.7% [386/395] for nurses and 98.8% [401/406] for physicians; Table 3).

We conducted a sensitivity analysis to assess the robustness of our conclusion of non-inferiority among nurses providing medical abortion in relation to physicians.[27] We calculated two scenarios where we hypothesized the outcome for the women lost to follow-up and our results demonstrated that nurses were not inferior to physicians when providing medical abortion (Table 4).

There was no difference between physicians and nurses in post-abortion contraceptive counselling and method chosen by the women. Eight-hundred and seventy-four (98.9%) women requested and were prescribed a method and 97.0% (848/874) of these women left the clinic with at least one method (Table 5). Physicians were more likely to prescribe IUDs (312 in the physicians' group versus 267 in the nurses' group) and women seen by physicians were more likely to leave with an IUD (135 in physicians' group versus 100 in nurses' group). Women treated by nurses were more likely to leave with condoms and emergency contraception, 46 in physicians' group versus 80 in nurses' group and 0 in physicians' group versus 9 in nurses' group, respectively.

Consultation with an experienced obstetrician was done in 11 cases. Nurses consulted in six cases for administering an additional misoprostol dose, in two cases for manual vacuum aspiration and one case for a persistent gestational sac. Physicians consulted the obstetrician for interpreting ultrasound results in two cases.

On average, participants reported an acceptability score of 13.6/14 for both providers. Women in both groups reported feeling comfortable with their assigned provider (99.0% [430/434] for nurses and 98.7% [444/450] for physicians). Most women (685/884) treated by either provider reported feeling very satisfied with their service (Table 6).

Only one serious adverse event was recorded; a 26-year old woman at eight weeks' gestation randomized to receive care from a physician was hospitalized for 38 hours due to bleeding following misoprostol administration and underwent a surgical abortion under general anaesthesia without further complications.

Discussion

Our findings suggest that nurses were equal to physicians when providing medical abortion. Nurses were trained in ultrasound techniques, interpreted results and successfully managed early medical abortion up to 70 days of gestational duration as effectively as physicians. Compared with another study[11] on the same subject, our study had higher gestational duration limits and women self-administered misoprostol at home.

The efficacy of medical abortion does not depend on who provides the medication, but on providers' ability to correctly determine gestational duration and exclude women over 70 days' gestation. Effective counselling for misoprostol administration at home, appropriate responses to normal and adverse effects and correct clinical decisions during follow-up are also needed. In our study, nurses were twice as likely to prescribe an additional misoprostol dose. This may reflect differences in judgment of abortion completion. Nurses may have been less confident of their skills and therefore may have depended more on ultrasound findings of persistent tissue, which is not always a sign of an incomplete abortion.[28] At one facility, both nurses and physicians were more likely to administer an extra dose compared with providers at the other facilities. This might be explained by the higher caseload at that facility. In high-volume settings, where time is often limited, providers may give an additional misoprostol dose to be on the safe side and to use this dose as a substitute for spending more time obtaining a detailed history to assess abortion completion.

The need for an adequate learning curve for new medical abortion providers to build confidence is documented and should be given careful consideration when translating these research findings to task-shifting in programme settings.[29]

The Mexico City Ministry of Health's guidelines mandate the use of ultrasound to determine gestational duration. While not an explicit objective determination, our findings suggest that where ultrasound is used for pregnancy dating and assessing abortion completion, nurses can manage this skill as well as physicians. These findings support the feasibility of task shifting in Mexico City.

Participants rated the medical abortion services by physicians and nurses as highly acceptable. Moreover, both types of providers were equally effective in offering post-abortion contraceptive counselling and prescribing a method. We hypothesize that differences in methods provided is due to the fact that physicians, and not nurses, routinely fit IUDs. It is possible that nurses felt less confident counselling women about IUDs. In this setting, nurses are typically responsible for providing women with condoms and emergency contraception. Familiarity with these methods is thus a potential explanation for this difference in prescribing behaviour. Because long-acting contraceptive methods such as IUD's are more effective in reducing the likelihood of repeat unplanned pregnancy, nurses should be trained to insert them as part of routine medical care.[30,31]

A study limitation is that both types of providers practiced in the same facilities. The ethics committee of the Mexico City Ministry of Health required nurses to practice in the same facilities as physicians and would not allow the research team to alter service delivery by separating them. However, we took the necessary steps to reduce potential contamination and limited interaction by allocating different examination rooms for each provider type. This prevented them from observing or consulting with each other, although we understand this would not have prevented them from conversing in other locations. We believe these interactions would have been infrequent

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Table 6. **Acceptability survey of women undergoing medical abortion provided by nurses or physicians in Mexico City, 2012–2013**

Question[a]	No. (%)		
	Physicians' group (*n* = 450)	Nurses' group (*n* = 434)	Total (*n* = 884)
Did the provider explain the procedure in a clear and easy way?			
Yes	448 (99.6)	434 (100.0)	882 (99.8)
No	2 (0.4)	0 (0.0)	2 (0.2)
Did the provider give you time to ask questions about the procedure?			
Yes	449 (99.8)	431 (99.3)	880 (99.5)
No	1 (0.2)	3 (0.7)	4 (0.5)
Did the provider discuss the symptoms you may experience during the procedure?			
Yes	447 (99.3)	433 (99.8)	880 (99.5)
No	3 (0.7)	1 (0.2)	4 (0.5)
Did the provider discuss the warning signs that may occur during the procedure?			
Yes	447 (99.3)	433 (99.8)	880 (99.5)
No	3 (0.7)	1 (0.2)	4 (0.5)
Did the provider discuss the return of fertility after the medical abortion procedure?			
Yes	395 (87.8)	394 (90.8)	789 (89.3)
No	55 (12.2)	40 (9.2)	95 (10.7)
Did the provider take action to manage your pain?			
Yes	449 (99.8)	434 (100.0)	883 (99.9)
No	1 (0.2)	0 (0.0)	1 (0.1)
Could the provider have done more to control your pain?			
Could have done more	53 (11.8)	43 (9.9)	96 (10.9)
Did enough	366 (81.3)	348 (80.2)	714 (80.8)
I did not experience pain during the procedure	31 (6.9)	43 (9.9)	74 (8.4)
Did you have confidence in the technical skills of the provider			
Yes	446 (99.1)	427 (98.4)	873 (98.8)
Sometimes	4 (0.9)	4 (0.9)	8 (0.9)
No	0 (0.0)	3 (0.7)	3 (0.3)
Did the provider make you feel comfortable?			
Yes	444 (98.7)	430 (99.1)	874 (98.9)
Sometimes	6 (1.3)	4 (0.9)	10 (1.1)
How satisfied are you with the provider?			
Very satisfied	342 (76.0)	343 (79.0)	685 (77.5)
Satisfied	106 (23.6)	90 (20.7)	196 (22.2)
Dissatisfied	1 (0.2)	1 (0.2)	2 (0.2)
No opinion	1 (0.2)	0 (0.0)	1 (0.1)
Would you recommend your type of provider to a friend if she needed the same procedure?			
Yes	444 (98.7)	427 (98.4)	871 (98.5)
Maybe	5 (1.1)	7 (1.6)	12 (1.4)
No	1 (0.2)	0 (0.0)	1 (0.1)
How was the medical care you received from the provider in this health centre or hospital?			
Better than you expected	431 (95.8)	408 (94.0)	839 (94.9)
As you expected	19 (4.2)	25 (5.8)	44 (5.0)
Do not know	0 (0.0)	1 (0.2)	1 (0.1)

[a] Information regarding type of contraceptive methods prescribed and taken is presented in Table 5.
Note: For some questions the percentage does not add up to 100 due to rounding

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and would not have affected the results. Instead, keeping the providers in the same facilities might have reduced the confounding factors, because different facilities could have had different characteristics – such as availability and type of equipment and operating procedures. Further research should investigate nurses' ability to provide medical abortion in an environment where a back-up physician may not be available.

Our study found that nurses can manage medical abortion care safely, effectively and with a high degree of patient acceptability, which is consistent with the systematic review on non-physician provision of abortion care.[32] Enabling nurses to manage medical abortion in public health facilities or in rural areas, where there is often unmet need and less infrastructure,[33,34] may address the high demand for safe abortion in Mexico. ■

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ملخص

تقديم خدمات الإجهاض الطبي المبكر في المكسيك بواسطة الممرضات مقابل الأطباء: تجربة غير دونية في بيئة خاضعة للمراقبة على نحو عشوائي

الغرض دراسة فعالية ومأمونية ومقبولية تقديم خدمات الإجهاض الطبي المبكر بواسطة الممرضات مقارنة بالأطباء في ثلاثة مرافق في مكسيكو سيتي.

الطريقة أجرينا تجربة غير دونية عشوائية بشأن تقديم خدمات الإجهاض الطبي والاستشارات حول وسائل منع الحمل بواسطة الأطباء أو الممرضات. وكانت المشاركات نساءً حوامل يلتمسن الإجهاض في مدة حملهن التي بلغت 70 يوماً أو أقل. وكان نظام الإجهاض الطبي يتكون من 200 ملغم من ميفيبريستون الفموي الذي يتم تناوله في المرفق ثم 800 ميكروغرام من ميزوبروستول الذي تتناوله المشاركة في الدراسة بنفسها عن طريق الفم في المنزل بعدها بأربع وعشرين ساعة. وتم إرشاد النساء إلى العودة إلى العيادة للمتابعة لمدة تتراوح من 7 إلى 15 يوماً بعدها. وأجرينا تحليل نية العلاج لفروق الاختطار بين تقديم هذه الخدمات بواسطة الأطباء والممرضات بخصوص الاستكمال والحاجة إلى التدخل الجراحي.

النتائج تم إدراج 884 امرأة، من أصل 1017 امرأة مؤهلة، في تحليل نية العلاج وإدراج 450 امرأة في مجموعة تقديم هذه الخدمات بواسطة الأطباء و434 امرأة في مجموعة تقديم هذه الخدمات بواسطة الممرضات. وكانت نسبة النساء اللاتي استكملن الإجهاض الطبي، دون الحاجة إلى التدخل الجراحي 98.4 ٪ (443/450 امرأة) عند تقديم هذه الخدمات بواسطة الأطباء و97.9 ٪ (425/434 امرأة) عند تقديم هذه الخدمات بواسطة الممرضات. وكان فرق الاختطار بين المجموعة 0.5 ٪ (فاصل الثقة 95 ٪: من 1.2 – ٪ إلى 2.3 ٪). ولم توجد فروق بين مقدمي هذه الخدمات بالنسبة لمدة الحمل التي تم دراستها أو استعمال وسائل منع الحمل لدى النساء. وقيّمت النساء كلا نوعي مقدمي هذه الخدمات بوصفهما مقبولين بدرجة عالية.

الاستنتاج تقديم خدمات الإجهاض الطبي بواسطة الممرضات مأمون ومقبول وفعال بنفس قدر مأمونية ومقبولية وفعالية تقديم هذه الخدمات بواسطة الأطباء في هذه البيئة. ومن الممكن أن يساعد السماح للممرضات بتقديم خدمات الإجهاض الطبي في تلبية الطلب على خدمات الإجهاض المأمونة.

摘要

墨西哥护士与医生提供早期药物堕胎对比：随机对照非劣效性试验

目的 对比调查墨西哥城三个医疗设施的护士和医生提供的早期医疗堕胎服务的有效性、安全性和可接受性。

方法 我们对医生或护士提供的药物堕胎和避孕咨询服务进行了随机非劣效试验。参与者是寻求堕胎的 70 天或更短妊娠期孕妇。药物堕胎方案是现场服用 200 毫克口服米非司酮，接着是 24 小时之后在家口服 800 微克的米索前列醇。指导孕妇在后面的 7 – 15 天后回到医院接受检查。我们对医生和护士提供的完成堕胎服务之间的风险差异和外科干预的必要性执行意向性治疗分析。

结果 在 1017 名合格的女性中，有 884 名女性参与意向性治疗分析，其中医生服务组有 450 名，护士服务组有 434 名。完成药物堕胎且无需手术治疗的女性，医生服务组占 98.4%（443/450），护士服务组占 97.9%（425/434）。组之间的风险差异为 0.5%（95% 置信区间：-1.2% 至 2.3%）。经调查的妊娠期持续时间或使用避孕用具方法的提供者之间没有差别。将这两种类型的提供者均被女性评为高度可接受。

结论 在此设置中，护士和医生提供的药物堕胎服务具有同样的安全性、可接受性和有效性。授权护士提供药物堕胎服务有助于满足安全堕胎服务的需求。

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Résumé

Comparaison de l'avortement médical précoce pratiqué par un infirmier et par un médecin au Mexique: un essai de non-infériorité randomisé contrôlé

Objectif Examiner l'efficacité, la sécurité et l'acceptabilité de l'avortement médical précoce pratiqué par un(e) infirmier(ière) par rapport au même acte réalisé par un médecin dans trois établissements de la ville de Mexico.

Méthodes Nous avons mené un essai de non-infériorité randomisé sur l'avortement médical et le conseil en matière de contraception pratiqués par des médecins ou des infirmiers. Les participantes étaient des femmes enceintes souhaitant avorter à un terme de grossesse de 70 jours ou moins. Le protocole de l'avortement médical était de 200 mg de mifépristone administrés sur place par voie orale, suivis de 800 µg de misoprostol auto-administrés par voie orale à la maison 24 heures plus tard. Les femmes avaient reçu comme consigne de revenir à la clinique pour y être suivies 7 à 15 jours plus tard. Nous avons effectué une analyse en intention de traiter pour les différences de risque entre l'avortement médical pratiqué par les médecins et par les infirmiers et le besoin d'une intervention chirurgicale.

Résultats Parmi les 1 017 femmes éligibles, 884 femmes étaient incluses dans l'analyse en intention de traiter, 450 dans l'acte d'avortement pratiqué par un médecin et 434 dans l'acte d'avortement pratiqué par un(e) infirmier(ière). Les femmes qui ont subi un avortement médical sans avoir eu besoin d'une intervention chirurgicale étaient de 98,4% (443/450) pour l'avortement pratiqué par un médecin et de 97,9% (425/434) pour l'avortement pratiqué par un(e) infirmier(ière). La différence de risque entre les groupes était de 0,5% (intervalle de confiance à 95%: de 1,2% à 2,3%). Il n'y avait pas de différence entre les professionnels de santé pour les termes de la grossesse examinés ou la prise de méthode contraceptive des femmes. Par ailleurs, les femmes acceptaient complètement les deux types de professionnels de santé.

Conclusion Dans ce contexte, l'avortement médical pratiqué par les infirmiers est aussi sûr, acceptable et efficace que celui pratiqué par les médecins. Autoriser les infirmiers à pratiquer l'avortement médical peut aider à répondre à la demande en matière de services d'avortement sécurisés.

Резюме

Выполнение раннего медикаментозного аборта фельдшерами и акушерами в Мексике: рандомизированное контролируемое исследование

Цель Изучить эффективность, безопасность и переносимость раннего медикаментозного аборта, выполняемого фельдшерами в сравнении с акушерами, в трех учреждениях Мехико.

Методы Было проведено рандомизированное исследование медикаментозных абортов и консультаций по контрацепции, выполняемых и предоставляемых фельдшерами на предмет их не меньшей эффективности по сравнению с выполнением данных абортов акушерами. В исследовании принимали участие беременные женщины, желающие сделать аборт на сроке беременности до 70 дней. Медикаментозный аборт заключался в приеме в исследовательском центре 200 мг перорального мифепристона с последующим приемом дома 800 мкг буккального мизопростола через 24 часа. Женщины были проинформированы о необходимости посещения клиники через 7-15 дней для проведения последующего наблюдения. Был проведен статистический анализ всех рандомизированных пациентов для определения разности рисков проведения медикаментозного аборта акушерами в сравнении с фельдшерами и необходимости хирургического вмешательства.

Результаты Из 1017 удовлетворяющих критериям включения женщин 884 были включены в статистический анализ, 450 – в группу выполнения аборта акушерами и 434 – в группу выполнения аборта фельдшерами. Согласно результатам исследования 98,4% (443/450) составляли женщины, которым медикаментозный аборт был выполнен акушерами без необходимости проведения хирургического вмешательства, и 97,9% (425/434) – женщины, которым медикаментозный аборт был выполнен фельдшерами. Разность рисков между группами составляла 0,5% (95%-ный доверительный интервал: −1,2-2,3%). Не были выявлены различия между исполнителями абортов в исследованных сроках беременности или методах контрацепции женщин. Оба типа исполнителей абортов были оценены женщинами как "в высшей степени приемлемыми".

Вывод В данных условиях медикаментозный аборт, выполненный фельдшерами, является столь же безопасным, допустимым и эффективным, как и аборт, выполненный акушерами. Допуск фельдшеров к выполнению медикаментозных абортов может помочь удовлетворить потребности в услугах по безопасному проведению абортов.

Resumen

Enfermeros frente a médicos en la asistencia en los abortos con medicamentos tempranos en México: un ensayo de no inferioridad controlado aleatorio

Objetivo Examinar la eficacia, seguridad y aceptabilidad de la actuación de los enfermeros en los abortos con medicamentos en fases tempranas de la gestación en tres centros de Ciudad de México en comparación con la actuación los médicos.

Métodos Se llevó a cabo un ensayo de no inferioridad aleatorio sobre la realización de abortos médicos y asesoramiento anticonceptivo por parte de médicos o enfermeros. Las participantes fueron mujeres embarazadas que buscaban interrumpir una gestación de 70 días o menos. El régimen para el aborto con medicamentos consistió en 200 mg de mifepristona por vía oral, administrados en el centro, seguidos de 800 µg de misoprostol autoadministrados por vía oral en casa 24 horas más tarde. Se indicó a las mujeres que acudieran a la clínica para realizar un seguimiento entre 7 y 15 días más tarde. Se realizó un análisis por intención de tratar de las diferencias de riesgo entre la asistencia de los médicos y los enfermeros para el término y la necesidad de una intervención quirúrgica.

Resultados De 1017 mujeres elegibles, se incluyeron 884 en el análisis por intención de tratar, 450 en el brazo atendido por médicos y 434 en el grupo atendido por enfermeros. De las mujeres que se sometieron al aborto con medicamentos, el 98,4 % (443/450) de las atendidas por

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médicos y el 97,9 % (425/434) de las atendidas por enfermeras no requirieron ninguna intervención quirúrgica. La diferencia de riesgo entre el grupo fue de 0,5 % (intervalo de confianza del 95 %: −1,2 % al 2,3 %). No hubo diferencias entre los proveedores para la duración de la gestación examinada o método anticonceptivo de las mujeres. Las mujeres calificaron ambos proveedores como muy aceptables.

Conclusión Los enfermeros son tan seguros, aceptables y eficaces como los médicos a la hora de asistir un aborto con medicamentos. Autorizar a las enfermeras a realizar abortos con medicamentos puede ayudar a satisfacer la demanda de servicios para un aborto seguro.

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CLINICAL ARTICLE

Efficacy and acceptability of a mifepristone–misoprostol combined regimen for early induced abortion among women in Mexico City

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ABSTRACT

Objective: To evaluate the experience of women receiving mifepristone–misoprostol for early induced abortion in public sector facilities in the Federal District of Mexico City. *Methods:* An open-label prospective study was conducted with 1000 pregnant women who sought induced abortion with a pregnancy of up to 63 days of gestation, as measured from the date of their last menstrual period. The study was conducted in three public sector healthcare facilities: two secondary level hospitals and one primary care clinic. Women ingested 200 mg mifepristone on day 1, followed by 800 μg buccal misoprostol 24 hours later, and they returned for follow-up on day 8. The primary outcome was complete abortion without recourse to surgical intervention. *Results:* A total of 971 women received mifepristone–misoprostol and were included in the analysis for efficacy of treatment. The overall efficacy of the combined medical abortion regimen studied was 97.3% (n = 945); the success rate did not vary significantly by gestational age (95.9%–100%; $P = 0.449$). Most women (n = 922, 95.0%) had a successful induced abortion with only one dose of misoprostol. *Conclusion:* The combined mifepristone and buccal misoprostol regimen was found to be highly effective and acceptable among Mexican women. www.ClinicalTrials.gov: NCT00386282.
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1. Introduction

Elective induced abortion during the first 12 weeks of pregnancy was legalized in April 2007 in the Federal District of Mexico. The new law prompted immediate action from the Secretariat of Health of Mexico City (SSDF) to provide legal induced abortion services in its facilities. Affiliated hospitals relied on dilatation and curettage (D&C) as the primary method of induced abortion, since obstetrician/gynecologists and general surgeons were already skilled in the procedure. The Secretariat recognized the potential of medical abortion technology to help meet the large demand for induced abortion services. To reduce the burden on the limited resources available for surgery, the SSDF started integrating medical methods of induced abortion. As of August 5, 2013, medical abortion accounted for 69% of elective induced abortions in the Secretariat system [1].

Combined regimens of mifepristone and misoprostol remain the preferred method of medical abortion [2–5], but as mifepristone was not registered or available for distribution in Mexico in 2007, a misoprostol-only regimen was introduced initially.

The present article describes an open-label study of mifepristone–misoprostol medical abortion in SSDF facilities in Mexico City, designed to evaluate the efficacy, safety, and acceptability in this setting; to garner data that could be used for local registration of a 200-mg mifepristone product; and to provide training, access, and experience to healthcare providers with the best known medical method of induced abortion before large-scale introduction occurred.

The primary objective was to evaluate the effectiveness of the regimen of 200 mg mifepristone followed by 800 μg buccal misoprostol for induced abortion of pregnancies of up to 63 days of gestation in women seeking induced abortions at SSDF facilities. The efficacy and safety of this medical abortion regimen have been documented in clinical trials and retrospective studies involving over 12 000 women [3,4,6–8]. Moreover, this regimen is the one most commonly used in the USA and is recognized by several health service delivery organizations and international guidance bodies including the National Abortion Federation [9], Planned Parenthood Federation of America (K. Shea, personal communication, May 16, 2012), the Royal College of Obstetricians and Gynaecologists [10], and WHO [5], among others. It was expected

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that the transition for clinical staff to this regimen would be simple as they were already employing an 800-μg buccal misoprostol-only regimen prior to study implementation.

2. Materials and methods

This open-label prospective study evaluated a combined regimen of 200 mg mifepristone followed by 800 μg buccal misoprostol in women with pregnancies of up to 63 days of gestation, as measured from the date of their last menstrual period. The study was conducted between September 28, 2010 and May 31, 2011 in three SSDF public sector healthcare facilities in Mexico City: two secondary level hospitals (Hospital General Enrique Cabrera and Hospital Materno-Infantil Inguarán) and one primary care clinic (Beatriz Velasco de Alemán). The protocol was approved by the Ethics, Biosecurity, and Research Commission of the Secretariat of Health of Mexico City and the Federal Commission for Protection against Sanitary Risks, the national drug regulatory agency.

Women were enrolled in the present study if they were interested in and eligible for medical abortion established in accordance with clinical evaluation and ultrasound exam, if they were willing to undergo surgical completion of abortion if needed, if they were willing to provide an address and/or telephone number for follow-up purposes, if they had access to a telephone and transport in case of an emergency, and if they consented to comply with the study procedures and visit schedule. Exclusion criteria followed labeled contraindications for mifepristone and misoprostol products. Gestational age was assessed from the date of the woman's last menstrual period, clinical evaluation, and ultrasound.

On day 1, participants swallowed one tablet of 200 mg mifepristone (Miffee; Linepharma, France) in the study center. Women were given 800 μg misoprostol (Cytotec; Pfizer, USA) to administer buccally at home 24 to 48 hours after mifepristone ingestion. They were instructed to place two pills in each cheek pouch and hold them in place, swallowing any remaining fragments after 30 minutes. All women were also given four 500-mg tablets of acetaminophen to take for pain as needed; providers were free to prescribe or recommend other medications at their discretion or if the participant requested additional analgesia. Women were advised to call the study team in case of concerns related to their induced abortion at any time. Participants were asked to return to the health center 8 days after study enrollment for a clinical exam and ultrasound as is standard care to determine the status of the abortion. Women with continuing pregnancies underwent suction aspiration. Participants with nonviable pregnancies, such as persistent gestational sac, retained products of conception or bleeding, were offered a second dose of misoprostol, suction aspiration, or expectant management and were scheduled to return a week later for extended follow-up. Study participants who presented again with a persistent nonviable pregnancy at the extended follow-up visit underwent surgical completion. Suction evacuation was performed if the provider deemed it medically necessary, such as for problematic bleeding, or at the woman's request. Women completed an exit interview prior to study discharge, to provide data on adverse effects and treatment acceptability. They rated their experience of pain during treatment using a visual seven-point Likert scale [11] that depicted a series of faces ranging from sad to neutral to happy. Study staff explained to women that each face represented a grade of pain severity, with the happiest face representing no pain and the saddest face representing the worst pain imaginable. The primary outcome of the study was success of the procedure as defined by complete abortion without recourse to surgical intervention for any reason. In addition, secondary outcomes included adverse effects experienced and method acceptability.

The sample size was calculated based on the published efficacy of 96% of the study regimen [9]. A comparable success rate was expected and thus it was determined that a sample of 500 participants would suffice to document 95% efficacy with a 95% confidence interval of ± 2%. The sample size was increased to account for loss to follow-up (estimated at 15%) and heterogeneity in research sites, personnel, and patient populations. Frequencies and means (with standard deviations) were calculated using SPSS 19.0 (IBM, Armonk, NY, USA) and were evaluated by intention-to-treat analysis. Treatment adherence and abortion status were ascertained at follow-up in the study center or by telephone.

3. Results

One thousand women were enrolled in the study (Table 1). Twenty-nine (2.9%) women did not return for their follow-up visits and could not be reached by telephone by study personnel. Thus, 971 participants were followed up and their results were analyzed for efficacy. Two women were mistakenly enrolled with pregnancies of more than 63 days of gestation as measured from the date of their last menstrual period. In accordance with the intention-to-treat analysis, their outcomes (each had a successful induced abortion with study medications alone) were included in the analysis. The overall efficacy of the combined medical abortion regimen studied was 97.3% (n = 945); the success rate did not vary significantly by gestational age (95.9%–100%; $P = 0.449$) (Table 2). Most women (94.9%, n = 922) had a successful induced abortion with only one dose of misoprostol. There were a total of 26 surgical evacuations (2.7%); the reported reason for the majority of surgical evacuations was bleeding (n = 16, 1.7%). Few women experienced continuing pregnancy (n = 6, 0.6%) or persistent sac (n = 2, 0.2%); an additional two women (0.2%) received surgical intervention for pain.

A total of 858 (88.5%) women reported adverse effects (Fig. 1). Diarrhea and fever/chills were the most commonly reported adverse effects, followed by nausea and vomiting. Fever/chills (n = 86, 8.9%) and diarrhea (n = 76, 7.8%) were most commonly reported by participants as severe. The mean pain score reported was 5.1 (range 1–7).

Of the women who took the study regimen, 38 (3.8%) placed telephone calls to the study team during their participation in the study; of those, the vast majority (n = 34, 89.5%) called only once. Two women (0.2%) made unscheduled visits to the study centers. Seventeen study participants (1.7%) visited other health facilities, primarily for bleeding or pain or a combination of the two (n = 13), followed by anxiety (n = 2), and fainting or tachycardia (n = 2). Twelve women treated in non-study facilities underwent D&C, three were verbally reassured and received no additional treatment, and two women were offered but refused D&C and did not report any adverse effects. There were no serious complications as defined by any occurrence that was unexpected, serious, and related to the induced abortion.

Almost all women (n = 915, 94.4%) reported they were satisfied with their treatment, and most participants (n = 778, 80.3%) reported that the adverse effects were acceptable (Table 3). Women were able to report up to two positive and two negative aspects of the treatment. The most commonly mentioned positive aspects of the medical abortion procedure were the rapidity of the treatment (n = 410/1118, 36.7%) and its efficacy (n = 279/1118, 25.0%). About one-third of women (n = 337, 34.8%) did not report any negative aspect of treatment. Cramps and pain were reported as the worst aspect of this treatment

Table 1
Characteristics of women undergoing medical abortion in Mexico City (n = 1000).[a]

Characteristic	Data
Age, y	25.4 (13–45)
Gravidity	2.3 (1–7)
Women reporting any previous induced abortion	97 (9.7)
Women reporting any previous medical abortion	74 (7.4)
Gestational age in days	
<49	569 (56.9)
50–56	252 (25.2)
57–63	177 (17.7)
>64	2 (0.2)

[a] Values are given as mean (range) or number (percentage).

Table 2
Treatment efficacy by gestational age in days.[a,b]

	<49 (n = 551)	50–56 (n = 247)	57–63 (n = 171)	>64 (n = 2)	Total (n = 971)
Success	540 (98.0)	239 (96.8)	164 (95.9)	2 (100)	945 (97.3)
Surgical evacuation	11 (2.0)	8 (3.2)	7 (4.1)	--	26 (2.7)
Reason for evacuation					
Continuing pregnancy	3 (0.6)	1 (0.4)	2 (1.2)	--	6 (0.6)
Persistent sac	--	1 (0.4)	1 (0.6)	--	2 (0.2)
Bleeding	6 (1.1)	6 (2.4)	4 (2.3)	--	16 (1.7)
Other[c]	2 (0.4)	--	--	--	2 (0.2)

[a] Values are given as number (percentage).
[b] Does not include women lost to follow-up (n = 29).
[c] Reason indicated was pain.

(n = 380/1054, 36.1%), with 46.0% (n = 446) noting that the pain was greater than expected (Table 4). Even so, 88.8% (n = 860) of all women reported they would have another medical abortion in the future if the situation arose. The vast majority of women (n = 700, 72.2%) perceived that bleeding was less than or as expected (Table 4).

4. Discussion

The effectiveness and acceptability of the medical abortion regimen used in the present study were consistent with those reported in the published literature [6,7]. Adverse effects were also comparable for most measures with those reported in other studies that used the same regimen [3,6]. Although women who undergo medical abortion are typically highly satisfied with the treatment and would recommend it to others, pain is often cited as the worst feature of the procedure, no matter what regimen of pain control is used [12]. This was also true for women in the present study. Women's analgesic use was not documented, however, so it was not possible to associate it with pain scores. Notwithstanding, the high level of pain reported on the visual analog scale and the relatively high proportion of women who reported pain being greater than they expected indicates that there may be room for improved pain management. There is little consensus about the most efficacious pain relief regimen for first-trimester medical abortion and research is continuing to inform service delivery practice on pain management [13].

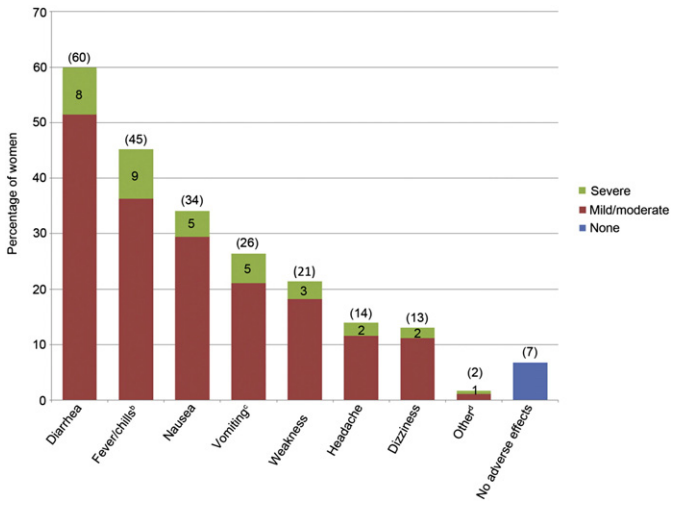

Fig. 1. Adverse effects and degree of severity reported by participants at follow-up (n = 969).[a]
[a]Two participants did not complete the exit interview.
[b]Missing level of severity for 1 participant.
[c]Missing level of severity for 1 participant.
[d]Other reported adverse effects included: anxiety/irritability/depression, dry throat, rash, hypotension, flu, difficulty breathing, hands fell asleep, and hunger.

The high level of satisfaction with the treatment reported by women in the present study is also strongly consistent with the published literature. Previous research has explored the acceptability of medical abortion by women, especially relating to aspects such as increased privacy and autonomy, and the less invasive nature of the procedure compared with surgical alternatives [14]. Satisfaction with these aspects of medical abortion treatment appears to be almost universal and has been reported for diverse populations [12]. Research has also documented that satisfaction is highly correlated with induced abortion success, which were both high in the present study [12].

It is possible that patient satisfaction may also be influenced by provider acceptability of medical methods. Within the first year of the legal induced abortion program in Mexico City providers made a swift transition to medical abortion. A qualitative study reported that healthcare professionals believed medical abortion resulted in a decrease in workload and possibly fewer conscientious objectors [15]. The very low number of calls and unscheduled visits to the study sites in the present study may reflect women's preparedness for what was to occur and their level of trust in the services. This phenomenon may also be indicative of the confidence that the study team had in the method, since these clinical providers and counselors already had previous experience with administering misoprostol-only regimens.

A mifepristone product was registered in Mexico in March 2011 and has been used in Secretariat facilities since December 2011. The mifepristone product currently available is relatively costly, however, the total cost of the drugs for the mifepristone and misoprostol regimen and misoprostol-only regimen previously used by the SSDF are essentially equivalent because of the high cost of misoprostol in Mexico. In reality, the combined regimen is less expensive than misoprostol-only regimens, however, as the method is more effective and therefore saves personnel and other treatment costs associated with aspirations for failed misoprostol-only procedures. In May 2013, a second mifepristone product was registered and it is hoped that this additional product will help to reduce costs further. Registration of additional mifepristone products can reduce the cost of mifepristone and thus increase access in both public and private sectors. Ideally,

Table 3
Acceptability of adverse effects and satisfaction with method of induced abortion (n = 969).[a]

	No. (%)
Adverse effects	
Acceptable	778 (80.3)
Neutral	146 (15.1)
Unacceptable	32 (3.3)
Don't know	13 (1.3)
Satisfaction with treatment	
Satisfactory	915 (94.4)
Neutral	27 (2.8)
Unsatisfactory	27 (2.8)

[a] Two participants did not complete the exit interview.

Table 4
Levels of pain and bleeding during treatment compared with women's expectations (n = 969).[a]

	Pain	Bleeding
	No. (%)	No. (%)
Less than expected	255 (26.3)	296 (30.5)
As expected	261 (26.9)	404 (41.7)
More than expected	446 (46.0)	262 (27.0)
Don't know	7 (0. 7)	7 (0.7)

[a] Two participants did not complete the exit interview.

combined mifepristone and misoprostol medical abortion regimens should be offered in all settings.

Since study completion, the SSDF has adapted its mifepristone abortion protocol to include recent documented innovations including home administration of mifepristone [16] and outpatient induced abortions with the same regimen during the first 10 weeks of pregnancy [17].

The liberalization of the induced abortion law in the Federal District of Mexico has created an unusual situation that has implications for all Mexican citizens. Any woman is legally allowed to receive an abortion in Mexico City, although limitations still exist for those who cannot afford the journey or the cost of services. Notwithstanding, for many women the ability to obtain safe and legal induced abortion reduces the risk of complications (including sepsis, perforated uterus, damaged cervix, death, among others) more often associated with the restricted legal context that exists in the rest of the country. The rapidity with which a medical abortion protocol was introduced into public sector services is a groundbreaking example for the region, benefitting the health system and women alike. The introduction of a medical abortion protocol has helped the Secretariat meet a growing demand that could not easily be accommodated by surgical abortion alone and has relieved the burden on the limited number of induced abortion providers operating during the first year after legalization. The present study helped prepare public health sector providers to transition from a misoprostol-only regimen to a combined regimen once mifepristone was registered and available on the market. Now more than two years since mifepristone was made available in Mexico, the gold standard of treatment using a combined regimen of mifepristone and misoprostol is firmly established as the primary method for induced abortion of early pregnancy.

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Conflict of interest

The authors have no conflicts of interest.

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Original research article

Feasibility of telephone follow-up after medical abortion☆

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Abstract

Background: This study was conducted to assess the feasibility of using telephone calls combined with high-sensitivity urine pregnancy testing as a primary method of follow-up after medical abortion.
Methods: We enrolled 139 women up to 63 days of gestation to receive mifepristone 200 mg orally and misoprostol 800 mcg vaginally or buccally, per their choice. Participants were contacted by phone one week after mifepristone administration and interviewed using standardized questions. If the subject or clinician thought the pregnancy was not expelled, the subject returned for an ultrasound examination. Otherwise, subjects performed high-sensitivity home urine pregnancy testing 30 days after the mifepristone and were called within 3 days of the test. Those with positive pregnancy tests returned for an ultrasound examination. Those with negative tests required no further follow-up.
Results: Six of the 139 (4.3%, 95% CI 1.6–9.1%) subjects presented prior to Phone Call 1 for an in-person visit. All 133 (100%, 95% CI 97.8–100%) subjects eligible for their first telephone follow-up were contacted. Eight of the 133 (6.1%, 95% CI 2.6–11.5%) women were asked to return for evaluation and all did so (100%, 95% CI 63.1–100%). Eight of the 133 women eligible for the 30 day phone call presented for an interim visit prior to the call. After 30 days, 116 of the 117 (99.1%, 95% CI 97.5–100%) eligible subjects were contacted. One subject was not reached for the day 30 phone call. Twenty-seven of the 116 (23.3%, 95% CI 15.6–31.0%) subjects had a positive pregnancy test and required follow-up. Two of these subjects (7.4%, 95% CI 1.0–24.2%) did not return for in-person follow-up. Two of the 116 (1.7%, 95% CI 0.2–6.1%) subjects had inconclusive pregnancy tests and were asked to return for follow-up. One of these subjects (50%, 95% CI 1.2–98.7%) did not return. Complete follow-up was achieved in 135 of the 139 subjects (97.1%, 95% CI 94.3–99.9%). None of the 26 women evaluated for a positive or inconclusive pregnancy test had a gestational sac or continuing pregnancy.
Conclusion: Telephone follow-up combined with urine pregnancy testing after medical abortion is a feasible alternative to routine ultrasonography or serial serum hCG measurements.
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Keywords: Medical abortion; Telephone follow-up; Urine pregnancy test; Mifepristone; Misoprostol

1. Introduction

The Food and Drug Administration guidelines for medical abortion with mifepristone and misoprostol recommend a pelvic examination approximately 14 days after medication administration to evaluate for complete expulsion and assess for complications [1]. Several studies have attempted to expedite follow-up after medical abortion through the use of vaginal ultrasonography [2,3], serial serum human chorionic gonadotropin (hCG) levels [4] and high- or low-sensitivity urine pregnancy testing [5].

With vaginal ultrasonography, investigators in the United States demonstrated that the follow-up examination can occur within the first week after treatment and accurately predicts clinical outcome [6]. The majority of clinicians providing medical abortion in the United States

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confirm completion by vaginal ultrasound [7,8]. With serum β-hCG evaluations, levels drop 60–66% from pretreatment levels within 24 h after misoprostol administration [9,10], and 80% by Days 6–18 [4]. Low levels of circulating β-hCG, however, can persist for a month or longer [11,12]. More importantly, both ultrasonography and serum hCG testing incur costs and require the patient to follow-up in-person for an evaluation. With urine pregnancy testing, both high-sensitivity (detection threshold 25–50 mIU/mL hCG) and low-sensitivity urine pregnancy testing (detection threshold 2000 mIU/mL hCG) have been evaluated at 7 and 14 days following medical abortion treatment [5]. More than 60% of both types of tests were still positive at 2 weeks. Although urine testing could be performed at home, the clinical utility to confirm expulsion shortly after treatment is limited.

Pymar et al. [13] first evaluated history alone as a predictor of medical abortion completion. In 40 women undergoing medical abortion with mifepristone and misoprostol up to 49 days gestation, clinicians accurately predicted pregnancy expulsion 95% of the time based on history alone. This prediction was confirmed using transvaginal ultrasonography. The ability of history alone to accurately predict pregnancy expulsion was confirmed in a planned secondary analysis of a large medical abortion study [14]. In 931 women who attended a follow-up visit 1 week after medical abortion, the clinician and subject both felt the pregnancy had expelled 95% of the time. Vaginal ultrasound confirmed passage of the gestational sac in 99.1% of those subjects in which pregnancy expulsion was predicted.

Thus, it appears that the ability of history alone to predict expulsion of the gestational sac is 95% in women treated with an effective medical abortion regimen. The ability of history alone to predict complete medical abortion is higher than that seen with urine pregnancy testing. However, these assessments were made in a setting where in-person follow-up still occurred and ultrasonography was going to be performed regardless of the responses of the patient and clinician regarding expulsion. With proper education at the time of mifepristone administration, women may recognize and understand if expulsion has occurred. If clinicians can reliably assess medical abortion outcome without a physical examination or sonography, re-evaluation of guidelines for medical abortion follow-up care would be indicated. This study was designed to evaluate whether a system of early follow-up by telephone to triage who requires in-person evaluation in combination with self-administered high-sensitivity urine pregnancy testing at 30 days is an accurate and feasible alternative to current clinical practice. If telephone follow-up after medical abortion is a feasible option it has the potential to increase access to medical abortion, particularly for women that have to travel long distances for abortion services. As a secondary objective, we offered women the choice of vaginally or buccally administered misoprostol to assess their preferences. Both options are widely used and are highly effective [2,15–17]. To our knowledge, no published studies have allowed women to choose the route of misoprostol administration.

2. Materials and methods

This prospective cohort study was performed at the University of Pittsburgh Center for Family Planning Research after receiving approval from the University of Pittsburgh Institutional Review Board. Healthy women 18 years old or older, up to 63 days of gestation, and desiring medical abortion were recruited from the community. Participants needed to be willing to comply with the visit schedules and undergo surgical abortion (suction curettage), if indicated. Potential subjects were excluded from the study if they were currently breastfeeding or had any of the following: no working telephone; a pregnancy with an intrauterine device in utero; ultrasound evidence of possible early pregnancy failure; a known clotting defect or receiving anticoagulants; a hemoglobin less than 10 g/dL; cardiovascular disease, including angina, arrhythmia, valvular disease, or cardiac failure; a contraindication to mifepristone, including adrenal disease or chronic systemic corticosteroid use; a contraindication to misoprostol, including glaucoma, sickle cell anemia, poorly controlled seizure disorder, allergy to prostaglandins; or had previously participated in this trial.

After obtaining written informed consent, the medical history and demographic information were reviewed. Subjects were asked to give every telephone number at which they could be contacted. They were asked to identify the telephone number they considered their primary telephone, and whether that telephone was a land line, a cellular telephone with a contract, or a prepaid cellular telephone (no contract). Subjects had blood drawn for hemoglobin and blood type, and underwent a pelvic examination and transvaginal ultrasonography to confirm gestational age of the pregnancy. The methods used to confirm gestational age have been previously described [15].

In accordance with the Pennsylvania Abortion Control Act, mifepristone administration was scheduled at least 24 h after abortion consent was obtained. Subjects were contacted between the screening visit and medication administration to confirm a working telephone number. A maximum of three attempts to contact the subjects at each telephone number was made. Women were excluded from the study if they could not be contacted.

On study Day 1, all subjects swallowed 200 mg of mifepristone. They were given the choice of self-administering 800 mcg of misoprostol vaginally or buccally. They were given an informational sheet which described the differences in timing and side effects between the two routes of administration based on the available literature (Appendix A) [16–18]. Women using vaginal misoprostol

were instructed to insert all four 200-mcg tablets as high up as possible into the vagina beginning anytime she chose up to 72 h after the mifepristone. Those selecting buccal misoprostol were instructed to place all four 200-mcg tablets in the buccal pouch (two on each side) from 24–72 h after use of the mifepristone and hold the tablets buccally for 30 min, after which the remaining tablets should be swallowed.

All subjects were given a prescription for 20 tablets of codeine (30 mg) or oxycodone (5 mg). They were instructed to take ibuprofen 800 mg or acetaminophen 1000 mg initially for pain and to add the narcotic medication as needed. Rh-immune globulin was given to all Rh-negative subjects. Sure-Vue™ urine pregnancy tests (Fisher HealthCare, Houston, TX) (sensitivity 25 mIU/mL) with instructions were given to all subjects, and all received contraception counseling. Women choosing oral, transdermal or vaginal hormonal contraception were given a prescription, and those choosing injectable, implantable or intrauterine contraception were given referral information. Subjects were given written instructions regarding pain medication use and bleeding parameters. Women were advised to contact the research office if they had any questions or if they experienced vaginal bleeding exceeding two soaked sanitary pads per hour for 2 consecutive hours, fever greater than 100°F, or other severe side effects.

Subjects were scheduled to be called by a clinician on study Day 8 (±2 days), 7 days after taking mifepristone. Up to three attempts at each telephone number were made to contact subjects. The subjects were asked how and when they used the misoprostol, and to provide a general description of what happened after using the misoprostol. In addition, they were asked a standardized set of questions for the clinician to use to assess for expulsion:

1. Did you have cramping and bleeding heavier than a period?
2. Did you pass clots or tissue?
3. What was the highest number of pads you soaked per hour?
4. Do you still feel pregnant now?
5. Do you think you passed the pregnancy?

If the subject or the clinician did not think the pregnancy had passed, the subject was asked to return to the research office within 7 days. An endovaginal ultrasound was performed to determine if the gestational sac was present within the uterus. If the gestational sac was absent, the subject was considered to have completed the study, and she was instructed to begin her contraceptive method or to schedule an appointment for intrauterine or implantable contraception. Women who wanted injectable contraception received the injection at that visit. If the gestational sac was present without a continuing pregnancy, she was given the option of an additional dose of vaginal misoprostol or dilation and curettage (D&C). If she chose an additional dose of misoprostol, she returned in one week for another ultrasound. A D&C was recommended for all women with a continuing pregnancy, defined as embryonic cardiac motion on ultrasound.

If both the clinician and the subject believed that the pregnancy had passed, the subject was instructed to begin her contraceptive method if applicable, or to schedule an appointment for injectable, implantable, or intrauterine contraception. The subject was told to perform the provided urine pregnancy test on study Day 30. She was told that she would be called within 3 days of taking the test, and the date and approximate time was scheduled. She was instructed to call at any time with problems or concerns.

All eligible participants were contacted by telephone as scheduled; if not initially reached, at least three attempts were made. The medical abortion was considered complete in participants with a negative urine pregnancy test, and no return visit was needed. Participants with a positive urine pregnancy test were scheduled for a return visit within 7 days of the telephone call. At the return visit, the urine pregnancy test was repeated with the Sure-Vue™ high sensitivity (sensitivity 25 mIU/mL) and the Clarity™ low sensitivity (Diagnostic Test Group, Boca Raton, FL, USA) (sensitivity 2000 mIU/mL) test. An endovaginal ultrasound was performed and the abortion considered complete in those subjects without a gestational sac visualized on ultrasound. If a gestational sac was present, the subject was offered an additional dose of misoprostol or D&C. Those subjects desiring an additional dose of misoprostol returned in one week for an ultrasound. The medical abortion was considered complete in those subjects choosing D&C. A D&C was recommended for all women with a continuing pregnancy.

At the final contact, either by telephone or in-person, subjects were asked if they would have preferred to take the misoprostol by a different route. The number of phone calls and length of the phone call each subject made to the research office was documented to gain insight into the amount of additional administrative time telephone follow-up may require.

The primary outcome of the study was successful follow-up per study protocol, defined as successful contact with subjects and in-person follow-up for those women asked to return to the office. For sample size estimation, we considered a 90% follow-up rate to be acceptable for this initial study of feasibility. To ensure a 95% confidence interval of no more than 5% (a lower 95% confidence interval of 85%), 139 subjects would be required with an alpha of .05 and beta of .2. We assumed that approximately 10% of subjects that screened for the study would not enroll, yielding a final sample estimate of 157 subjects. Statistical analysis was performed using Stata 10 (Stata, College Station, TX, USA; www.stata.com). Descriptive statistics and comparisons were calculated using chi-square and Fisher's Exact tests. The sensitivity, specificity, positive

and negative predictive value of the phone screen to predict pregnancy expulsion was calculated.

3. Results

Between March and October 2008, 157 subjects were screened and 139 subjects were enrolled in the study. Of the 18 screen failures only 2 subjects (11%, 95% CI 13.8–34.7%) were withdrawn because they did not have a working telephone. The remainder decided to continue the pregnancy, had hemoglobin levels less than 10 mg/dL or did not return to receive medications after screening. The characteristics of enrolled subjects are listed in Table 1.

Fig. 1 depicts the flow of the study. Six subjects returned to the office prior to Phone Call 1 for an interim visit and were not eligible for the first scheduled telephone call. All (100%, 95% CI 97.2–100.0) of the remaining 133 subjects were reached by telephone as scheduled, and all 8 subjects who were asked to return for a visit for unsure expulsion did so.

Table 1
Subject characteristics; n=139, data presented as n (%) or median (range)

Age, years	25 (18–41)
Marital status	
Single	119 (85.6)
Married	10 (7.2)
Divorced or separated	10 (7.2)
Race	
White	60 (43.2)
Black	71 (51.1)
Other	8 (5.8)
Prior vaginal delivery	78 (56.1)
Prior cesarean delivery	27 (19.4)
Prior surgical abortion	54 (38.9)
Prior medical abortion	18 (13.0)
Income in dollars/year	
<10,000	33 (23.7)
10,000-20,000	37 (26.6)
20,000-30,000	33 (23.7)
>30,000	36 (25.8)
Education	
Less than high school	16 (11.5)
Completed high school	48 (34.5)
Some college or trade school	57 (41.1)
College or more	18 (13.0)
Telephone service	
Home phone	23 (16.6)
Cell phone with contract	70 (50.4)
Pre-paid cell phone[a]	46 (33.1)
Gestational age at time of medical abortion (days)	
≤35	1 (0.7)
35–42	14 (10.1)
43–49	50 (36.0)
50–56	65 (46.8)
57–63	9 (6.5)

[a] A cellular telephone without an annual contract and minutes can be added to the phone as needed.

Eight subjects had an interim visit prior to Phone Call 2. Of the 117 subjects eligible to be contacted for the second scheduled phone call, 99.1% (95% CI 95.3–100.0) were contacted, with only one subject lost to follow-up. The pregnancy test results were negative in 87 (75%, 95% CI 66.1–82.6) women; 27 (23.3%, 95% CI 16.0–32.0) had a positive test, and 2 (1.7%, 95% CI 0.2–6.1) had problems reading the test. These latter 29 subjects all denied any ongoing pregnancy symptoms but, per protocol, were asked to return for an in-person visit. Of the 26 subjects that presented for this visit, none had a retained gestational sac or required D&C. The manufacturer of the Clarity™ low-sensitivity test discontinued production during the study, and only the first 15 subjects who returned after Phone Call 2 received the low-sensitivity test. Only one of the 15 was positive (6.7%, 95% CI 0.2–31.9). The repeat high-sensitivity pregnancy test was still positive in 21 subjects (80.8%, 95% CI 60.6–93.4). Of subjects completing Phone Call 2, 19.5% (95% CI 12.6–28.0) would have preferred to return for an ultrasound one week after medication to confirm pregnancy expulsion.

Successful follow-up per study protocol was achieved in 97.1% (95% CI 92.8–99.2) of subjects. A total of four subjects did not complete all follow-up (2.9%, 95% CI .08–7.2). One subject was never contacted by Phone Call 2, two subjects had a positive pregnancy test and one had an inconclusive test. None of these three returned for the in-person visit. Of the 135 women who completed follow-up, 64.4% (95% CI 55.8–72.5) never required an in-person visit.

Eight (6.7%, 95% CI 3.1–12.3%) D&C procedures were performed. Fig. 1 outlines the indications for the D&C procedures. Three subjects were diagnosed with a pelvic infection (2.2%, 95% CI 0.5–6.4%), with one requiring hospital admission and intravenous antibiotics. Two subjects (1.4%, 95% CI 0.2–5.2%) required blood transfusion for symptomatic anemia, one of whom underwent a D&C for bleeding. There were 4 continuing pregnancies (3.0%, 95% CI 0.8–7.4%); one was diagnosed prior to Phone Call 1, two were diagnosed at the follow-up visit after Phone Call 1, and the fourth was diagnosed at an interim visit prior to Phone Call 2.

The prediction by the subject and clinician that the pregnancy had been expelled had a sensitivity of 95.9%, specificity of 50.0%, positive predictive value of 97.5%, and negative predictive value of 37.5%. For this calculation, medical abortion was considered complete if there was ultrasound confirmation of pregnancy expulsion, or a negative high-sensitivity pregnancy test at Day 30. There were 129 subjects included in this analysis; the four subjects lost to follow-up were not included. The number of subjects without follow-up was too low to assess variables (such as type of telephone service or level of education) that were predictive of no follow-up. Fifty-two (37.4%, 95% CI 29.3–46.0) women contacted the research office for unscheduled calls; 57.6% (95% CI 43.2–71.2) called only once, while 42.3% (95% CI 28.7–56.8) called two or more times. The

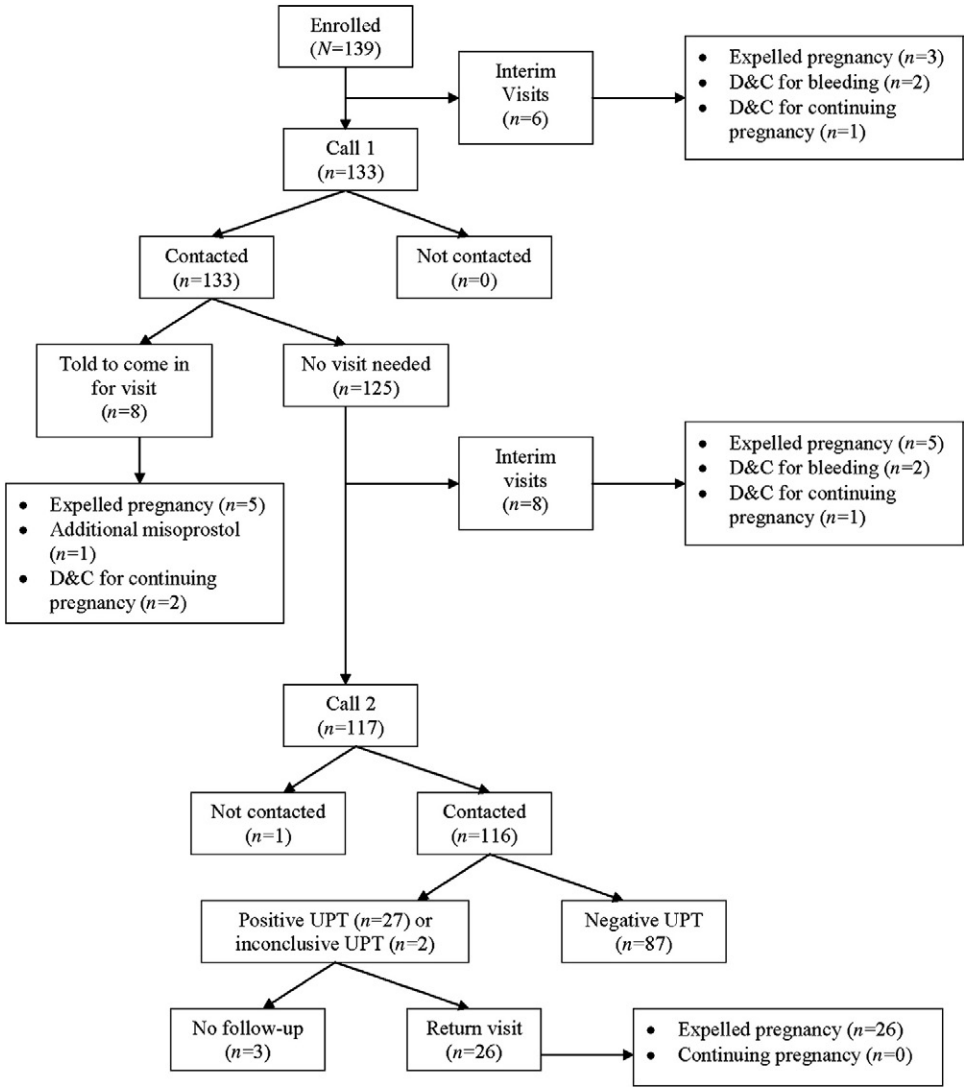

Fig. 1. Study flow. Call 1 scheduled 7±2 days after mifepristone use. Call 2 scheduled within 3 days of Day 30 pregnancy test. UPT, urine pregnancy test.

maximum number of phone calls by one subject was six calls. The mean length of each phone call was 2.5 min (95% CI 1.7–3.3, range 2–27 min).

Almost all women (94.2%, 95% CI 89.0–97.4%) chose vaginal misoprostol, with 74% using misoprostol within 6 h of mifepristone administration (Table 2). Only six women chose buccal misoprostol. When asked at the end of the study if they would choose to take misoprostol the same way, 96.4% (95% CI 91.8–98.8) of subjects would choose the same misoprostol route.

Table 2
Timing of misoprostol use (*n*, %)

Time since mifepristone (h)	Vaginal misoprostol *n*=127	Buccal misoprostol *n*=6
0–<2	32 (25.2)	0
2–<4	46 (36.2)	0
4–<6	16 (12.6)	0
6–<12	14 (11.0)	0
12–<24	9 (7.1)	0
≥24	10 (7.9)	6

4. Discussion

The primary aim of our study was to determine if it is possible to reach women by telephone, and based on a standardized set of questions, determine if an in-person visit is indicated. The intention of these standardized questions is to predict pregnancy expulsion so as to make appropriate recommendations to women about whether or not they should return to the office. In reality, the goal is to ensure that this method of follow-up avoided missing any continuing pregnancies by the final follow-up 30 days after treatment. Only 3% of women did not follow all instructions for follow-up. Given that complete loss to follow-up rates is at least 2%

in studies and clinical practice [19,20], our data show that it is very feasible to use the telephone as a primary method of follow-up after medical abortion.

The high sensitivity and positive predictive value of the standardized question set are reassuring such that when the clinician and subject both believe the pregnancy has passed, they are almost always correct. These results are not unlike those found in previous studies when questions have been used to assess medical abortion success [13,14]. This study was not powered to detect which questions were most predictive of pregnancy expulsion, and this information may warrant additional research. Importantly, all women who did not require a return visit after the phone screen but had problems such as bleeding or continuing pregnancy symptoms presented to the office on their own.

A prior evaluation of high-sensitivity urine pregnancy testing used the test within 2 weeks of treatment to confirm pregnancy expulsion [5], essentially using high and low-sensitivity urine pregnancy tests as a screening tool to diagnose successful medical abortion. In our study, we were using medical history as the screening tool, not the high-sensitivity urine pregnancy test. We only used the pregnancy test to rule out continuing pregnancies. While 25% of the high-sensitivity urine pregnancy tests were positive or inconclusive, none of those subjects that followed up for a positive pregnancy test had a continuing pregnancy. All four subjects with a continuing pregnancy presented on their own to the office prior to Phone Call 2, with only one continuing pregnancy being diagnosed between Phone Call 1 and Phone Call 2. While performing the urine pregnancy test 4 weeks after medication administration increases the number of women that must return for evaluation, it ensures that continuing pregnancies are diagnosed and that a D&C can be performed within the first trimester. We selected high-sensitivity urine pregnancy tests because they are available over the counter. If this method of follow-up is adopted, women could theoretically purchase their urine pregnancy tests in the pharmacy after receiving medical abortion medications.

In all medical abortion studies and in clinical practice, some women are lost to follow-up. The percentage of women with incomplete follow-up in our study was similar to the percentage of women that do not follow-up with the standard medical abortion follow-up protocol. It is impossible to know which women undergoing medical abortion will have a continuing pregnancy and/or will be lost to follow-up. Our data indicate that women with a continuing pregnancy develop pregnancy symptoms and schedule a follow-up visit.

Our 3% continuing pregnancy rate is somewhat higher than the 0–1% cited in other medical abortion studies [16,18,21]. Unlike these other trials, we did not allow an additional dose of misoprostol for subjects with continuing pregnancies. One of the four continuing pregnancies was diagnosed before Day 7 in a subject who presented for worsening pregnancy symptoms. It is still possible that she may have aborted prior to Phone Call 1 had she not had the D&C. All of the subjects with continuing pregnancies used vaginal misoprostol within 3 h of the mifepristone, and three of the four subjects had a gestation of 61 days. These factors may have contributed to the high continuing pregnancy rate.

This is the first published study that allowed women to select which route of misoprostol administration they would prefer. Women overwhelmingly chose vaginal misoprostol. While we did not specifically ask the reason they chose this route, 91.4% of subjects choosing the vaginal route used the misoprostol within 24 h after mifepristone administration. We infer that the ability to use the misoprostol sooner and thereby complete the medical abortion sooner is the reason the vaginal route of misoprostol was selected. While familiarity with a route can also be a contributing factor, only 13% of women had experienced a prior medical abortion, so this reason is unlikely in this case. Although some investigators have implied that women prefer an oral route, our findings suggest that, when all factors are considered, women may prefer the route that allows them to complete the abortion as quickly as possible [3].

We have found that telephone screening in combination with high-sensitivity urine pregnancy testing is feasible and believe that this method of medical abortion follow-up can be offered as an alternative to in-person evaluations for select patients. In our study, only one third of the subjects were required to return for a visit. Some women will feel more comfortable having a return visit and confirming pregnancy expulsion, while others find this additional visit inconvenient and would prefer telephone follow-up. Still, continued quality assessment will be required if such a program is implemented to determine if our findings are generalizable to other providers and settings. We are confident based on our data that women are very self-aware, and if they are having symptoms or problems after a medical abortion, they will return to the office for a visit despite the type of follow-up. This method of medical abortion follow-up provides women with more choices.

Acknowledgments

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Appendix A. MEDICAL ABORTION with MIFEPRISTONE and MISOPROSTOL

Comparing misoprostol use options

Buccal=between your cheek and gums

Vaginal=in your vagina

	Buccal	Vaginal
MIFEPRISTONE	Swallow the tablet right away in the doctor's office	Swallow the tablet right away in the doctor's office

Appendix A (*continued*)

	Buccal	Vaginal
How you will use the MISOPROSTOL	Place all 4 of the tablets between your cheek and gum and allow them to dissolve for 30 minutes. After that time, you should swallow the rest of the tablets.	Place all 4 tablets in vagina
When you can use MISOPROSTOL	1-3 days later (whatever time works best for you)	Any time after you use the mifepristone, up to 3 days later (whatever time works best for you)
Where you will use the MISOPROSTOL	At home	In the office if you insert the pills immediately. At home if you use the pills later.
Chance of side effects	Nausea: 8 in 10 Vomiting: 5 in 10 Diarrhea: 4 in 10	Nausea: 4 in 10 Vomiting: 3 in 10 Diarrhea: 3 in 10
Likelihood of needing pain medication	Moderate to high	Moderate to high
Chance of needing a surgical abortion (because medicines didn't work)	4 out of 100	3 out of 100

Based on information from:

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- Creinin MD, Schreiber CA, Bednarek P, Lintu H, Wagner MS, Meyn L. Mifepristone and misoprostol administered simultaneously compared with 24 hours apart for abortion. Obstet Gynecol 2007;109:885–94.
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opinions of partners, family members, friends, and later co-workers, especially with respect to later abortion and funding restrictions.

Conclusions: The NAF Hotline serves an important and transformative role in the lives of those who work for it. However, the NAF Hotline has the potential to play a much stronger role in shaping hearts and minds and social movement building in the US. Exploring ways to facilitate NAF Hotliners' engagement in ethical storytelling and advocacy appears warranted.

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Transcutaneous electrical nerve stimulation (TENS) for pain control during first-trimester abortion: A single-blinded randomized controlled trial

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Introduction: High-frequency, high-intensity transcutaneous electrical nerve stimulation (TENS), pulsating electrical currents that activate underlying nerves, is an inexpensive and non-invasive pain control approach. We sought to compare TENS to intravenous sedation (IV) for pain control in first-trimester surgical abortion.

Method: We conducted a non-inferiority, single-blinded, randomized controlled trial of participants undergoing surgical abortion up to 11 weeks' gestation. Participants received TENS (electrodes parallel to the spinal cord at the T10-L1 and S2-S4 levels) or IV (100mcg fentanyl and 1mg versed). Providers administered the IV sedation and research staff administered the TENS and were therefore not blinded. The primary outcome was self-reported pain with aspiration (visual analogue scale, VAS 100mm, 0 "no pain" and 100 "worst pain imaginable"). Non-inferiority limit was defined as 15mm. We also assessed participant demographics and blinding.

Results: A total of 109 participants were enrolled (55 TENS, 54 IV) between January 2018 and October 2019. Participants had a mean gestational age of 56-days across groups (p = 0.88); groups were similar with regard to age, race and ethnicity, parity, and BMI. Nine (16%) in the TENS group were given IV sedation and excluded from the per-protocol analysis. 100 participants were included in the per-protocol analysis (46 TENS, 54 IV). Mean reported VAS for aspiration was 64.78 mm (SD24.16) and 60.35mm (SD26.06) in the TENS and IV groups, respectively, with a mean difference of 4.43mm (95% CI −5.6 to 14.47). One IV group participant received additional IV medications (2%). Post-procedure, in both groups the majority of participants identified their correct assignment (p = 0.96); one in five in both groups incorrectly identified their assignment (21.7%, n = 10 TENS; 22.2%, n = 12 IV). Intention-to-treat analysis (n = 109) yielded non-inferior results for the primary outcome.

Conclusions: TENS for pain control during first-trimester surgical abortion is non-inferior to IV sedation with respect to the primary outcome of pain with aspiration. TENS could be a pain control option for patients without access to IV sedation or for those who are ineligible to receive IV sedation due to additional cost, lack of sedation provider or restrictions, including the need for a designated driver. Expanding pain control options improves quality of care and access to abortion.

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Advanced practice clinicians and medication abortion safety: A 10-year Retrospective Review

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Introduction: Expanding the pool of trained, competent medication abortion providers is critical to filling gaps in access to safe abortion across the U.S. Despite a compelling public health argument for advanced practice clinicians (APCs) as abortion providers and the recent label change to mifepristone, 34 states currently mandate that clinicians providing medication abortion must be physicians.

Method: We performed a retrospective observational cohort study of medication abortion and clinician personnel data from the electronic medical record (EMR), quality management incident tracking, and human resources records at a large, urban-based sexual and reproductive health care provider between January 2009 and December 2018 to describe medication abortion outcomes when provided by APCs. We calculated descriptive statistics to assess overall abortion outcomes and complications. In order to assess complications by provider years of experience, we ran a negative binomial regression on total complications, using an offset term of the natural log of the total number of procedures with follow up to estimate a rate ratio.

Results: A total of 59,189 patients initiated medication abortion during the observation period under the supervision of 47 APCs. Among the 37,909 (64%) patients who completed follow up, outcomes included: 98.4% complete abortion, 1.1% failed abortion, 0.4% incomplete abortion, and 0.1% ectopic pregnancy. There were no meaningful differences in characteristics among patients who completed or failed to complete follow-up. 246 (0.6%) patients experienced complications requiring in-clinic management, ED referral, or hospital admission. .Most common interventions included aspiration (n = 112), blood transfusion (n = 36), and/or IV fluids (n = 34). We found no association between provider years of experience and complication rates (RR = 1.00, 95% CI 0.97, 1.04), restricting analyses to providers for whom there was follow-up data on at least 60% of cases in a given year.

Conclusions: Outcomes of medication abortion provided by APCs in our study are well within published benchmarks for medication abortion effectiveness (95–99%) and safety (<1% complications) when managed by physicians. Restricting provision to physicians serves only to impede access by excluding a large group of competent clinicians from offering this service.

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Certainty and Intention in Pregnancy Decision-making: an exploratory study

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Introduction: Abortion is often characterized as an inherently difficult decision, despite previous research finding high levels of



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The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal

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REPRODUCTIVE HEALTH matters

FEATURE

The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal

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Abstract: *Medical abortion was introduced in Nepal in 2009, but rural women's access to medical abortion services remained limited. We conducted a district-level operations research study to assess the effectiveness of training 13 auxiliary nurse-midwives as medical abortion providers, and 120 female community health volunteers as communicators and referral agents for expanding access to medical abortion for rural women. Interviews with service providers and women who received medical abortion were undertaken and service statistics were analysed. Compared to a neighbouring district with no intervention, there was a significant increase in the intervention area in community health volunteers' knowledge of the legal conditions for abortion, the advantages and disadvantages of medical abortion, safe places for an abortion, medical abortion drugs, correct gestational age for home use of medical abortion, and carrying out a urine pregnancy test. In a one-year period in 2011–12, the community health volunteers did pregnancy tests for 584 women and referred 114 women to the auxiliary nurse-midwives for abortion; 307 women in the intervention area received medical abortion services from auxiliary nurse-midwives. There were no complications that required referral to a higher-level facility except for one incomplete abortion. Almost all women who opted for medical abortion were happy with the services provided. The study demonstrated that auxiliary nurse-midwives can independently and confidently provide medical abortion safely and effectively at the sub-health post level, and community health volunteers are effective change agents in informing women about medical abortion.*
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Keywords: medical abortion, auxiliary nurse-midwives, female community health volunteers, outreach health centres, Nepal

The abortion law was reformed in Nepal in September 2002 to improve the health status and condition of women. The law allows abortion up to 12 weeks of pregnancy at the request of the woman, up to 18 weeks if the pregnancy results from rape or incest, and at any time during pregnancy on the advice of a medical practitioner, if the physical or mental health or life of the woman is at risk, or the fetus is impaired or has a condition incompatible with life.[1] Previous laws did not allow abortion under any circumstances and many women who had had an abortion were imprisoned.[2] The introduction of legal abortion has been characterized by a committed effort by the Ministry of Health and Population and non-governmental organizations to rapidly scale up access to safe abortion. Manual vacuum aspiration services became available in 2004; second-trimester procedures were introduced in 2007; and senior nurses who had prior training in post-abortion care began providing services in 2008.[2] Manual vacuum aspiration was the only safe abortion method used until 2009 in Nepal. In line with the Safe Abortion Service Directives 2065 B.S. (2008), the Government of Nepal introduced medical abortion on a pilot basis in six districts through 32 accredited comprehensive abortion care centres for a period of one year in 2009, with a 96.1% success rate. The experience gained encouraged the Government to scale up medical

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abortion services in all accredited abortion clinics throughout the 75 districts of the country in a phased manner. However, medical abortion services are still limited to a relatively small number of accredited government and non-governmental centres, including selected primary health centres and health posts. No sub-health post was approved for medical abortion provision before this study.

Despite these efforts, knowledge and use of medical abortion has been discouragingly low. An evaluation study of medical abortion services in the six pilot districts, carried out by the Center for Research on Environment Health and Population Activities (CREPHA) in 2009, showed that only 15% of 1,093 married women of reproductive age had heard about medical abortion.[3] Government records from the six pilot districts revealed that of the women who had had an abortion in that period, only 6.1% had opted for medical abortion.[3] The study also found a number of other barriers:

- no full-time counsellor at the government facilities to provide information on medical abortion that would enable women to make an informed choice;
- negative attitudes on the part of providers towards medical abortion;
- a policy that barred women living more than two hours' distance from the health facility from using medical abortion;
- low confidence in medical abortion efficacy among the providers; and
- the requirement of repeat visits to the clinic.[3]

The findings contributed to elimination of the policy that stipulated that women living more than two hours from a health facility could not use medical abortion, and also helped provide a choice for women of home or clinic use of misoprostol.

Although medical abortion provision in recent years in Nepal has been expanding, restrictions on certification of facilities and provider provision remain in place. Rural women's access to medical abortion services remains limited due to the government's reluctance to expand the services to outreach health centres, particularly at the sub-health post level (the lowest level of health facility in the government health system) through auxiliary nurse-midwives.

Previous research in Nepal had demonstrated that medical abortion provision by doctors, nurses and auxiliary nurse-midwives is acceptable and feasible.[4,5] More recently, a World Health Organization study by CREHPA showed that mid-level providers could provide medical abortion from certified facilities with the same safety and effectiveness as doctors.[6] These findings were in line with research elsewhere indicating that non-clinicians can safely provide first-trimester abortion.[6–8]

Medical abortion has the potential to expand women's access to safe abortion in Nepal by overcoming the need for a skilled provider in a clinic setting, as needed with aspiration abortion.[8–10] It also increases affordability and privacy.[11,12] Most importantly, it offers the opportunity to decentralize provision of services away from traditional hospital and clinic settings.[13]

Increasing the utilization of medical abortion requires knowledge and motivation. Studies conducted elsewhere have shown that training and advocacy at different levels of the health system, use of mass communication channels, and mobilisation of community-based groups have been effective in increasing utilisation of contraception, HIV and child health services.[14,15] The grapevine is also very effective in spreading the word about misoprostol all over the world, in spite of laws against abortion and in the absence of formal information. However, the effectiveness of using community-based volunteers in increasing awareness about medical abortion and establishing referral systems in rural areas in countries like Nepal has not been studied.

The female community health volunteer programme in Nepal was introduced by the Ministry of Health and Population in 1988. Currently, over 50,000 women serve as an important source of information for communities in nearly all rural areas. They enjoy high respect and acceptability because they play an important role in contributing to key public health programmes, including family planning, maternity care, child health, vitamin A supplementation, deworming and immunization coverage.[15,16] However, they have not been trained or involved in providing information or referral for safe abortion care, including medical abortion.

This study, in two western districts of Nepal in 2011 and 2012, assessed the effectiveness of training 13 auxiliary nurse-midwives based in health posts and sub-health posts to provide medical abortion independently, and 100 female community health volunteers as communicators and referral agents for expanding medical abortion access to rural women.

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Data and methods

The study employed a non-equivalent comparison group design that compared the effect of training auxiliary nurse-midwives to provide medical abortion and female community health volunteers in the intervention group (Rupendehi district) against a similar, but not necessarily equivalent, comparison group located in the neighbouring district (Kailali). Rupendehi has 69 village development committees and two urban municipalities, two hospitals, five primary health care centres, six health posts and 57 sub-health posts. Prior to the implementation of the study, only two government hospitals, three NGO-managed clinics and three private clinics located in Rupendehi were offering medical as well as aspiration abortion services. The present study selected one primary health care centre, five health posts and two sub-health posts (approved as a birthing centre with the presence of at least one auxiliary nurse-midwife) and 120 female community health volunteers from 10 village development committees in the intervention district in consultation with the district health officials and stakeholders. The selection of the intervention area was based on the criteria that no outreach health centre was providing medical abortion services and that the district health officials were supportive of the study. In the comparison area, two primary health care centres and two health posts that had been offering medical abortion services since January 2009 and 96 female community health volunteers from ten village development committees were selected in consultation with district health officials. Both areas were very similar in terms of socio-economic and demographic indicators.

The interventions were carried out at two levels. At the community level, 120 female community health volunteers (a minimum of ten female community health volunteers per village development committee) were trained to communicate information about prevention of unintended pregnancy, abortion law and rights, safe (government-approved) health centres for abortion and legal abortion services, health consequences of unsafe abortion, safety and efficacy of medical abortion, importance of post-abortion/post-partum contraception, availability of medical abortion at health and sub-health posts through trained auxiliary nurse-midwives, and women's choice of place for misoprostol use (either self-administration at home or at the clinic). They were also trained to perform a urine pregnancy test and check eligibility criteria for women asking for medical abortion at health and sub-health posts. After training, the women were given ten sets of urine pregnancy test kits each so that they could maintain this skill and sustain this service by charging women a small amount (US$ 0.26) for a pregnancy test. They were also issued with special referral cards to give to women with a positive test result, either for antenatal care or abortion. Women receiving referral cards for abortion were later visited at home by the same female community health volunteer who had given them a referral card, to find out the outcome of the referral and for post-abortion or post-partum family planning advice.

All 13 auxiliary nurse-midwives working in the eight study health centres and who were already certified as skilled birth attendants were given comprehensive training on providing medical abortion, women's choice on misoprostol use either self-administered at home or in the clinic, management of minor complications and identification of complications requiring immediate referral. The training was conducted by three national trainers at the government's National Health Training Centre, following the national medical abortion training protocol, whose requirements included three days' training at the main Maternity Hospital in Kathmandu. All trained auxiliary nurse-midwives received government approval before starting medical abortion services in their health facilities.

In addition, the district health office supplied 300 sachets of medical abortion tablets (mifepristone 200 mg x 1 and misoprostol 200mcg x 4 in the same pack) and 300 copies of the self-assessment card to be used by women to the eight outreach health centres. No intervention was implemented in the comparison area.

The core study protocol and research instruments were approved by the Nepal Health Research Council (national ethical approval body) and the World Health Organization's Research Ethics Review Committees. Participants (female community health volunteers, women, and auxiliary nurse-midwives) involved in the study were fully informed about the nature of the study, research objectives, and confidentiality of the data. Participants' written consent (thumbprint if not literate) was obtained regarding their participation in the study. Confidentiality of information was ensured by removing personal identification from the data and by securing access to all data and information.

GBP-PET00675

We analyzed matched (paired data) pre- and post-intervention individual interviews with 110 female community health volunteers in the intervention area and similar interview data (but no intervention) with 79 female community health volunteers in the comparison area. Data at baseline and post-intervention were collected. The female community health volunteers were mainly asked about knowledge of existing abortion law, abortion-seeking behaviour of women in their communities, and their own knowledge and perceptions of medical abortion, involvement in urine pregnancy tests, referrals and providing abortion. Similarly, auxiliary nurse-midwives were asked about their training and skills on abortion, number of women whose abortions they managed, management of complications, and their knowledge and perceptions of medical abortion.

After the intervention, we also carried out semi-structured interviews with 13 auxiliary nurse-midwives (nine in the intervention area and four in the comparison area) who provided medical abortion services. Additionally, we carried out 241 exit interviews with women (124 in the intervention area and 117 in the comparison area) who had received medical abortion services from the 12 study facilities (eight in the intervention area and four in the comparison area) over a four-month period.

Interviews with women who had abortions were carried out between the sixth and tenth month of the intervention period. Along with their socio-demographic characteristics, women were asked what they knew about abortion clinics, abortion law, abortion experiences, and contraceptive counselling and use. Eight trained research assistants (four in the intervention area and four in the comparison area), stationed for four months at the study facilities, conducted the exit interviews. We also analyzed the 12 months of service statistics data maintained by the study health facilities.

As the female community health volunteers' interview data were matched, McNemar tests were used to examine whether the difference in knowledge of, and perception about, medical abortion and referral practices between pre-and post-intervention was greater in the intervention area than in the comparison area. Exit interview data were also compared to examine the differences in women's perceptions of medical abortion services intervention and the Chi-square test of association was also used to test whether the differences were independent.

Profile of study participants

Female community health workers

The mean age of female community health volunteers was slightly higher in the intervention area than in the comparison area (40.1 and 35.6 years, respectively) (Table 1). Their ages ranged from 18–60 years, with the great majority over age 25. A higher percentage were illiterate in the intervention area than in the comparison area. On average, they had served more than 13 years as community health volunteers (range 1–23 years).

Women who had a medical abortion during the study

The socio-demographic characteristics of the women who received medical abortion services and were interviewed (124 in the intervention area and 117 in comparison area) ranged in age from 15–53 years. A slightly higher percentage of women in the intervention than in the comparison area had never attended school (26.6% vs 21.4%). Over 70% of women in both areas had had at least two children.

Table 1. Profile of female community health volunteers, baseline interviews, June 2011

Characteristics	Intervention area n=110	Comparison area n=79
Mean age in years (standard deviation)	40.1 (8.8)	35.5 (7.7)
Education[ns]		
No education	16	2
Non-formal education and primary	51	51
Primary to secondary	37	22
Above secondary	6	4
Mean years of schooling (SD)	4.4 (3.9)	3.4 (3.8)
Years experience as community volunteers[ns]		
Up to 5 years	20	13
5–10 years	9	8
10–15 years	17	34
15+ years	64	24
Mean years of experience (standard deviation)	13.3 (5.7)	12.7 (5.8)

Chi square-test * p< 0.05, ** p< 0.01 and *** p<0.001; ns = not statistically significant

Auxiliary nurse-midwives

Six out of nine auxiliary nurse-midwives who were interviewed in the intervention area were working at health posts, two at sub-health posts and one at a primary health care centre. Most of these auxiliary nurse-midwives had been working at these health centres for more than a year. In the comparison area, all four auxiliary nurse-midwives interviewed were working in the health posts for more than a year.

Findings

Female community health volunteers' knowledge of medical abortion

Table 2 shows a significant increase in female community health volunteers' knowledge about the legal conditions of abortion, government-approved health facilities for abortion, medical abortion medications and the correct gestational age for medical abortion at baseline and post-intervention in the intervention area as compared to the comparison area. For example, in the intervention area, knowledge about the legal grounds for abortion increased from 66% at baseline to 100% post-intervention, while remaining the same in the comparison area. Knowledge of the names of approved medical abortion drugs also increased from 1% at baseline to 97% post-intervention. Similarly, there was a sharp increase in knowledge about the upper time limit for home use of medical abortion (≤9 weeks) in the intervention area from 2% at baseline to 69% post-intervention.

There was also a significant increase in knowledge and use of urine pregnancy test kits, particularly in the intervention area. The comparison group also showed a significant increase in knowledge of medical abortion medications, correct gestation period and performing a urine pregnancy test, although the magnitude of change was lower than in the intervention group. Increases observed in the comparison area may reflect improvements as in other parts of the country.

Table 3 shows the changes in female community health volunteers' knowledge about the advantages and disadvantages of medical abortion between baseline and post-intervention. This included a significantly increased percentage at post-intervention who believed that medical abortion was safe (low risk), is an alternative to MVA, allows abortion to happen as a natural process, and ensures privacy, whether at home during the abortion process or in that nobody from her family knows about her abortion if in the clinic. Similar changes, particularly that they believe medical abortion is safe, requires no aspiration procedure and causes no physical trauma was also observed in the comparison area but the magnitude of changes was much lower than in the intervention area. For example, at baseline, about 12% of the female community health volunteers in the intervention group and 15% in the comparison group mentioned

Table 2. Increased knowledge and practice on abortion among female community health volunteers, baseline and post-intervention (%)

	Intervention area (n=110)		Comparison area (n=79)	
	Baseline	Post-intervention	Baseline	Post-intervention
Knows about legal grounds for abortion	66.3	100.0*	93.7	91.1^{ns}
Knows about safe (government-approved) places for abortion	89.1	100.0*	100.0	100.0^{ns}
Heard of medical abortion tablets	0.9	97.3*	13.9	31.6**
Knows upper gestation age for home use of medical abortion	1.8	69.1*	29.1	44.3***
Has had training on doing urine pregnancy tests	1.8	100.0*	30.4	97.5*
Has performed urine pregnancy tests	1.8	95.5*	22.8	68.4*

p-values from McNemar-test: * p< 0.05, ** p< 0.01 and *** p<0.001. ns = non-significant

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Table 3. Increases in female community volunteer's knowledge about advantages and disadvantages of medical abortion (%)

	Intervention area (n=110)		Comparison area (n=79)	
Advantages of medical abortion	**Baseline**	**Post-intervention**	**Baseline**	**Post-intervention**
Low risk procedure/safer	11.8	81.8*	15.2	55.7*
No aspiration procedure required	20.0	77.3*	29.1	48.3**
Natural process	8.2	61.8*	16.5	12.7ns
Can be taken at home	10.0	38.2*	11.4	5.1ns
Privacy	5.5	36.4*	1.3	5.1ns
Others (e.g. easy procedure, lower cost, easy access)	13.6	7.3ns	13.9	8.1ns
Don't know any	59.1	1.8*	54.4	21.5*

a Percentage total may exceed 100 due to multiple responses.
p-values from McNemar-test: * p< 0.05, ** p< 0.01 and *** p<0.001. ns = non-significant

that one of the advantage of medical abortion was that it is a low risk method. At the post-intervention survey, these percentages increased by 70 percentage points in the intervention group and 39 percentage points in the comparison group. The percentage of female community health volunteers who reported lack of knowledge about the advantages of medical abortion significantly fell from 59% at baseline to 2% post-intervention in the intervention area.

In the post-intervention phase, in both the intervention and comparison areas, more of the female community health volunteers knew that there was a risk of incomplete abortion for a small minority of women and an even smaller risk of heavy bleeding. Changes in their knowledge of disadvantages of medical abortion – including issues related to pain, side effects from the misoprostol, and longer duration of the process than with aspiration abortion – were insignificant. This means that further information needs to be provided in future training.

Contribution of female community health volunteers and changes in practice due to the study

In the 12 months of the study, 584 urine pregnancy tests were performed by the female community health volunteers in the intervention area, of which 323 were positive. Of these 323 women, 209 were referred to antenatal care services (their pregnancies were desired) and the remaining 114 women opted for an abortion (108 for medical abortion and 6 for manual vacuum aspiration). Female community health volunteers referred the women opting for an abortion to the nearest health centres and issued 108 of them with referral cards for the medical abortion service. Of the 108 women referred, 80 actually attended the referral health centres, and all of the 80 had a medical abortion. The remaining 28 women either changed their minds and continued the pregnancy or were turned away from the abortion services due to higher gestational age (more than 9 weeks)* or had medical contraindications to abortion such as signs and symptoms of heart disease, for example, high blood pressure.

The female community health volunteers were asked where they referred women for abortion most often both at baseline and post-intervention interviews. Responses (Table 4) show that referral of women to health and sub-health posts increased significantly in the intervention area as compared to the comparison area. At baseline, almost none of the volunteers in the intervention area and 25% of those in the comparison area said they referred women opting for abortion to health and sub-health posts. Post-intervention, these percentages increased by 80 percentage points in the intervention area though only 5 percentage points in the comparison area. Similarly, referral to the primary health care centres also increased

*We do not know what happened to this group of women, but as a result of this happening we are exploring this problem in a new research collaboration.

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Table 4. Place of referral for abortion by female community health volunteers at baseline and post-intervention (%)

	Intervention area (n=110)		Comparison area (n=79)	
Place of referral for abortion	Baseline	Post-intervention	Baseline	Post-intervention
No referral	27.3	0.0*	7.6	6.3^{ns}
Governmental hospital	22.7	0.0*	10.1	6.3^{ns}
Primary health care centres	4.5	18.2*	45.6	48.1^{ns}
Health/sub-health posts	0.9	81.0*	24.1	30.4^{ns}
Private clinic	7.3	0.0^{ns}	3.8	2.5^{ns}
Pharmacy	37.3	0.9*	8.9	6.3^{ns}

p-values from McNemar-test: * p< 0.05, ** p< 0.01 and *** p<0.001. ns= non-significant

significantly in the intervention area at the post-intervention survey compared to the baseline (from 4.5% to 18.2%), whereas there was no significant change in the comparison area (from 45.6% to 48.1%). Referral to a pharmacy for abortion, which is not legal in Nepal, was reduced significantly in the intervention area (from 37.3% at baseline to 0.9% post-intervention) whereas in the comparison group the percentage (from 8.9% to 6.3%) did not change significantly.

Number of medical abortions and abortion success rate

Service statistics showed that 307 women in the intervention area and 289 women in the comparison area had received medical abortion services from auxiliary nurse-midwives in the one-year study period. Of the 307 women, there were five incomplete abortions (1.6%), four of which were treated with manual vacuum aspiration by the auxiliary nurse-midwives. Only one woman was referred to the nearest zonal hospital because it was a Saturday, and the outreach health centre was closed. Of the 289 women in the comparison area, there were seven incomplete abortions (2.4%), five of which were treated with manual vacuum aspiration and two were referred to the district hospitals. The difference in the number of incomplete abortions between the two areas was not statistically significant.

Confidence of auxiliary nurse-midwives providing medical abortion services

Interviews with the auxiliary nurse-midwives participating in this study in the intervention area revealed that all nine of them were confident about providing medical abortion independently, and they also expressed a strong desire to receive training in manual vacuum aspiration and additional skills, particularly in management of complications and clinical assessment. Auxiliary nurse-midwives working in the comparison area expressed similar views and interests.

"Initially I used to get worried about women who received medical abortion from me. I had to make frequent calls to them regarding their condition. I felt relieved only after they informed me that they were fine as the pills had worked well. Now I am more confident than before. I have provided medical abortion to a lot of women. So far none of these women has experienced incomplete abortion or a complication with medical abortion. I now realize that we are as capable of providing medical abortion as any other providers." (ANM working at sub-health post, intervention area)

"I feel that I have provided medical abortion services to many women successfully. My confidence to provide medical abortion service has increased over this period, and I think the government should train us [auxiliary nurse-midwives] to provide manual vacuum aspiration services also." (ANM working at health post, intervention area)

Women's experiences of medical abortion care from an auxiliary nurse-midwife

We conducted 241 exit interviews with women (124 in the intervention area and 117 in the comparison area) who received medical abortion care from an auxiliary nurse-midwife at one of the 12 outreach health facilities (eight in the intervention area

and four in the comparison area). We learned that 96% of the women in the intervention area and 89% of the women in the comparison area reported that the services met their expectations (Table 5). About 97% of women in both intervention and comparison areas reported a complete abortion. The women reported only typical and well-known, short-term side effects such as nausea, vomiting, diarrhoea, abdominal pain, chills and fever.

In the intervention area, 82.3% of women opting for medical abortion chose self-administration of misoprostol at home, compared to 42.7% in the comparison area. The two main reasons for choosing home administration were: saving the time required to stay at the facility, followed by privacy and convenience. Those women who chose the clinic for misoprostol administration said they were scared, or felt safer and had more confidence at the clinic than at home. Almost all the women (96.8% in the intervention area and 97.4% in the comparison area) felt that they had received enough information about medical abortion from the counsellors/providers. Confidentiality, not requiring aspiration, less pain and less cost were perceived as the main advantages of medical abortion. In addition, all the women from both areas reported that they would recommend to their friends or others to attend the facility they visited for medical abortion services.

Discussion and conclusions

In this study, 307 women in the intervention area received medical abortion services from auxiliary nurse-midwives in a one-year period and had no complications that required referral to higher level facility except for one incomplete abortion. Auxiliary nurse-midwives showed that they were capable and interested in providing a good quality medical abortion service safely and effectively at outreach health facilities without the presence of physicians, and were confident of their ability to do so, with very limited clinical resources. This confidence was underpinned by the evidence, in that almost all abortions were complete, no serious adverse events were recorded, and women reported only typical and well-known, short-term side effects. Furthermore, interviews showed that the women who had had a medical abortion were happy with the service they had received and were willing to recommend this service to friends and other women.

Our study also found that female community health volunteers were capable of providing information to women and referrals to auxiliary

Table 5. Experiences of women who received medical abortion care at study sites: exit interviews (%)

Characteristics	Intervention area (n=110)	Comparison area (n=79)
Were the abortion services as expected?		
Yes	96.0	88.9
No	4.0	11.1
Did the provider give enough information about medical abortion?		
Yes	96.8	97.4
No	3.2	2.6
Was the abortion complete?		
Yes	96.8	97.4
Too soon, don't know yet	3.2	2.6
Place of misoprostol administration		
Home	82.3	42.7
Clinic	17.7	57.3
Reasons for choosing home administration[a]	(n=102)	(n=50)
Privacy being at home	67.6	36.0
Easy	62.7	60.0
No need to visit the facility	19.6	16.0
Time saving	69.6	32.0
Felt capable of inserting pills herself	24.5	60.0
Other	1.0	22.0
Reasons for choosing clinic[a]	(n=22)	(n=67)
Safety	68.2	40.3
Scared of self-administration	63.6	82.1
Privacy (confidential: no one from her family will know about her abortion)	63.6	13.4
Proximity	40.9	34.3
Not confident about self-administration	13.6	40.3
Perceived advantages of medical abortion[a]	(n=124)	(n=117)
More confidential	55.6	17.9
Does not involve aspiration	50.8	48.7
Inexpensive	41.1	47.0
Less pain	45.2	28.2
Less bleeding	13.7	11.1
Fewer side effects	26.6	21.4
Low risk procedure	27.4	3.4
Shorter stay in facility	4.8	24.8
No advantages	3.2	13.7
Whether or not she would recommend this facility for medical abortion services to a friend or anyone else	(n=124)	(n=117)
Yes	100.0	99.1
No	0.0	0.9

a % total may exceed 100 due to multiple responses.

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nurse-midwives with the aim of increasing access to medical abortion services among rural women. We therefore recommend that female community health volunteers should continue to play this role both for medical abortion and for manual vacuum aspiration, urine pregnancy tests, post-abortion/delivery contraceptive counselling and follow-up.

The safety, efficacy and acceptability of medical abortion provided by auxiliary nurse-midwives is now well established in Nepal,[6] and this study establishes it even further. To our knowledge, this is the first study to assess the possibility of introducing medical abortion services at the sub-health post level in Nepal.

There is no policy restriction on sub-health posts (if already approved as a birthing centre*) applying for government certification for providing abortion services. However, as of June 2013, no sub-health post (except for the ones in this study, who have continued to provide medical abortion services) had been accredited for providing medical abortion services in Nepal.

On the basis of our findings, we encourage the government to consider accrediting sub-health posts with a trained auxiliary nurse-midwife for medical abortion services in a phased manner, in order to increase access to medical abortion services for rural women. We also encourage the government to support scale-up of training for both female community health volunteers and auxiliary nurse-midwives.

*Only birthing centres will have the post of auxiliary nurse-midwives so as to make this possible.

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Résumé

L'avortement médicamenteux a été introduit en 2009 au Népal, mais l'accès des femmes rurales aux services est demeuré limité. Nous avons étudié les opérations au niveau d'un district pour évaluer l'efficacité de la formation de 13 infirmières sages-femmes auxiliaires comme prestataires de l'avortement médicamenteux, et de 120 femmes comme bénévoles de santé communautaire et agents d'orientation pour élargir l'accès des femmes rurales à l'avortement médicamenteux. Des entretiens ont été organisés avec des prestataires de service et des femmes ayant mené un avortement médicamenteux, et des statistiques de service ont été analysées. Par comparaison avec un district voisin où aucune intervention n'avait été réalisée, dans la zone d'intervention, on a constaté une hausse sensible de la connaissance des bénévoles de santé communautaire sur les conditions juridiques de l'avortement, les avantages et les inconvénients de l'avortement médicamenteux, les lieux sûrs pour l'avortement, les médicaments abortifs, l'âge gestationnel correct pour pratiquer un avortement médicamenteux à domicile et la réalisation d'un test de grossesse urinaire. Sur une période d'un an en 2011-2012, les bénévoles de santé communautaire ont effectué un test de grossesse pour 584 femmes et adressé 114 femmes qui voulaient avorter aux infirmières sages-femmes auxiliaires ; les infirmières sages-femmes auxiliaires ont prêté des services d'avortement médicamenteux pour 307 femmes dans la zone d'intervention. Aucune complication n'a exigé l'aiguillage vers un centre plus spécialisé, à l'exception d'un avortement incomplet. Presque toutes les femmes qui avaient opté pour l'avortement médicamenteux étaient satisfaites des services obtenus. L'étude a montré que les infirmières sages-femmes auxiliaires peuvent pratiquer efficacement, indépendamment et en confiance des avortements médicamenteux en toute sécurité au niveau des sous-centres de santé, et que les bénévoles de santé communautaire sont de précieux agents de changement pour renseigner les femmes sur l'avortement médicamenteux.

Resumen

Los servicios de aborto con medicamentos fueron introducidos en Nepal en 2009, pero el acceso de las mujeres rurales a dichos servicios continu,ó siendo limitado. Realizamos un estudio de investigación operativa a nivel de distrito para evaluar la eficacia de capacitar a 13 enfermeras-obstetras auxiliares como prestadoras de servicios de aborto con medicamentos, y 120 voluntarias comunitarias en salud como comunicadoras y agentes de referencia para ampliar el acceso de las mujeres rurales a dichos servicios. Se realizaron entrevistas con prestadores de servicios y mujeres que recibieron servicios de aborto con medicamentos y se analizaron las estadísticas de los servicios. Comparado con un distrito aledaño donde no hubo intervención, en la zona de la intervención se vio un considerable aumento en los conocimientos de las voluntarias comunitarias respecto a las condiciones para un aborto legal, las ventajas y desventajas del aborto con medicamentos, lugares seguros para tener un aborto, fármacos para inducir el aborto, edad gestacional correcta para el uso domiciliario de los medicamentos para inducir el aborto, y realizar una prueba de embarazo en la orina. En el plazo de un año, 2011-12, las voluntarias comunitarias en salud realizaron pruebas de embarazo en 584 mujeres y refirieron a 114 mujeres a enfermeras-obstetras auxiliares para aborto; 307 mujeres en la zona de la intervención recibieron servicios de aborto con medicamentos de enfermeras-obstetras auxiliares. No hubo complicaciones que necesitaron referencia a una unidad de salud de mayor nivel, excepto un aborto incompleto. Casi todas las mujeres que optaron por tener un aborto con medicamentos estuvieron contentas con los servicios que recibieron. El estudio demostró que las enfermeras-obstetras auxiliares pueden proporcionar servicios de aborto con medicamentos de manera independiente, confiada, segura y eficaz, en un nivel inferior al puesto de salud, y las voluntarias comunitarias en salud son agentes de cambio eficientes para informar a las mujeres acerca del aborto con medicamentos.

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JAMA | Original Investigation

Comparison of No-Test Telehealth and In-Person Medication Abortion

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IMPORTANCE In the US, access to medication abortion using history-based (no-test) eligibility assessment, including through telehealth and mailing of mifepristone, has grown rapidly. Additional evidence on the effectiveness and safety of these models is needed.

OBJECTIVE To evaluate whether medication abortion with no-test eligibility assessment and mailing of medications is as effective as in-person care with ultrasonography and safe overall.

DESIGN, SETTING, AND PARTICIPANTS Prospective, observational study with noninferiority analysis. Sites included 4 abortion-providing organizations in Colorado, Illinois, Maryland, Minnesota, Virginia, and Washington from May 2021 to March 2023. Eligible patients were seeking medication abortion up to and including 70 days' gestation, spoke English or Spanish, and were aged 15 years or older.

EXPOSURE Study groups reflected the model of care selected by the patient and clinicians and included: (1) no-test (telehealth) eligibility assessment and mailing of medications (no-test + mail) (n = 228); (2) no-test eligibility assessment and pickup of medications (no-test + pickup) (n = 119); or (3) in-person with ultrasonography (n = 238).

MAIN OUTCOMES AND MEASURES Effectiveness, defined as a complete abortion without the need for repeating the mifepristone and misoprostol regimen or a follow-up procedure, and safety, defined as an abortion-related serious adverse event, including overnight hospital admission, surgery, or blood transfusion. Outcomes were derived from patient surveys and medical records. Primary analysis focused on the comparison of the no-test + mail group with the in-person with ultrasonography group.

RESULTS The mean age of the participants (N = 585) was 27.3 years; most identified as non-Hispanic White (48.6%) or non-Hispanic Black (28.1%). Median (IQR) gestational duration was 45 days (39-53) and comparable between study groups (P = .30). Outcome data were available for 91.8% of participants. Overall effectiveness was 94.4% (95% CI, 90.7%-99.2%) in the no-test + mail group and 93.3% (95% CI, 88.3%-98.2%) in the in-person with ultrasonography group in adjusted models (adjusted risk difference, 1.2 [95% CI, −4.1 to 6.4]), meeting the prespecified 5% noninferiority margin. Serious adverse events included overnight hospitalization (n = 4), blood transfusion (n = 2), and emergency surgery (n = 1) and were reported by 1.1% (95% CI, 0.4%-2.4%) of participants, with 3 in the no-test + mail group, 3 in the in-person with ultrasonography group, and none in the no-test + pickup group.

CONCLUSIONS AND RELEVANCE This prospective, observational study found that medication abortion obtained following no-test telehealth screening and mailing of medications was associated with similar rates of complete abortion compared with in-person care with ultrasonography and met prespecified criteria for noninferiority, with a low prevalence of adverse events.

Multimedia

Supplemental content

CME Quiz at jamacmelookup.com

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Medication abortion with mifepristone and misoprostol was first approved by the US Food and Drug Administration (FDA) in 2000 and is currently approved for use through 70 days' gestation in pregnancy.[1] In 2023, medication abortion accounted for 63% of abortions in the US, an increase from 53% in 2020 and 31% in 2014.[2-4] Multiple studies have firmly established the safety and effectiveness of the mifepristone and misoprostol regimen for medication abortion; the incidence of major complications or serious adverse events (SAEs) is less than 0.5% and overall effectiveness in ending the pregnancy without the need for a follow-up procedure is 95% to 97%.[5-10]

In recent years, access to various medication abortion models has expanded rapidly, including telehealth or virtual eligibility assessment and counseling, mailing medications directly to patients, and, in some instances, forgoing the requirement for an in-person ultrasonography or physical examination to establish location and duration of pregnancy prior to provision of medication abortion.[11] The FDA's removal of the in-person dispensing requirement for mifepristone, which had long been part of the drug's Risk Evaluation and Mitigation Strategy, facilitated this expansion. Emerging research evaluating the safety and effectiveness of telehealth and in-person, no-test models[12-14] builds on prior evidence demonstrating that provision of medication abortion by telemedicine (with ultrasonography and/or physical examination) has a comparable safety and effectiveness profile to in-person provision.[15-19] A 2022 retrospective cohort study of 2379 pregnant people accessing medication abortion using history-based (no-test) eligibility assessment in the US reported 94.5% effectiveness in ending the pregnancy and rate of SAEs of 0.42%.[20] Similarly, a large, retrospective cohort study of over 50 000 patients receiving medication abortion in the UK reported effectiveness rates of 98% to 99%, with no difference between those accessing care with and without routine pretreatment ultrasonography.[21]

Further evidence on the effectiveness and safety of telehealth and in-person, no-test (without ultrasonography or physical examination) medication abortion informs expansion of these models to all pregnant people seeking abortion, particularly those now living in the 21 states where abortion is banned or heavily restricted[22] or the 6 states where abortion remains legal but telehealth or mailing of medications is banned.[23] The present study compares the effectiveness and safety of medication abortion provided using 2 models of no-test, telehealth abortion care (mailed or pickup medications) with in-person care with ultrasonography.

Key Points

Question Is medication abortion provided using no-test eligibility screening and mailing of medications as effective as in-person care with ultrasonography and safe overall?

Findings This prospective, observational study found that medication abortion obtained following no-test telehealth screening and mailing of medications was associated with similar rates of complete abortion compared with in-person care with ultrasonography (94.4% vs 93.3%, respectively) and met the 5% noninferiority margin, with a low prevalence of adverse events.

Meaning The findings suggest that models of medication abortion care that rely on no-test eligibility assessment and mailing medications to patients are an option for individuals considering medication abortion.

Methods

This was an observational, prospective study comparing medication abortion effectiveness and safety using different methods of eligibility assessment (ultrasonography vs no-test) and dispensing of medications (mail vs in-person). The study protocol, including the statistical analysis plan, was published at Open Science Framework in April 2022 prior to initiating any analyses.[24]

Participants and Procedures

Participants were recruited from 4 abortion-providing organizations in 6 states (Colorado, Illinois, Maryland, Minnesota, Virginia, and Washington) between May 2021 and March 2023. We selected organizations that offered direct-to-patient telehealth or other no-test, history-based eligibility screening models that could dispense mifepristone using a mail-order pharmacy and, to allow for an appropriate comparison group, that also offered in-person provision at a facility within the same clinic network and state. One organization had facilities in 3 states and offered telehealth services to patients in those same states through a centralized call center. Thus, there were a total of 6 facilities, 1 in each state (eFigure 1 in Supplement 1). Eligibility was restricted to patients aged 15 years or older (3 facilities) or aged 18 years or older (3 facilities), English or Spanish speakers, seeking and eligible for medication abortion at that facility, and intending to take the medication up to and including 70 days' gestation. Participants were typically approached by facility staff during initial counseling; those interested in participating received a longer description of the study and then completed electronic informed consent and signed a Health Insurance Portability and Accountability Act waiver allowing clinic staff to review the patients' medical records with the study team. Patients then shared contact information for survey follow-up and received a $15 gift card for enrolling.

Data Collection

Study data were obtained from 2 sources. First, participants were asked to complete electronic surveys 1 day, 2 weeks, and 1 month after receiving the medications. Survey links were sent via text or email and included up to 5 reminders. Surveys were designed such that participants with an unclear abortion outcome (eg, who responded "I'm not sure" if the medications worked to end the pregnancy) were sent repeat surveys until an outcome was ascertained or the patient was considered lost to follow-up. Participants were remunerated with gift cards worth $25 for completing the first and third surveys and $15 for completing the second survey.

Clinics abstracted medical record data using a standardized tool[25] 6 weeks after the initial appointment. If care was

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ongoing, clinics continued to abstract clinical data until the outcome of the abortion was known or adverse events (AEs) had resolved. In-depth, follow-up chart review was conducted for all cases with an unclear abortion outcome or potential AE.

Measures

The primary exposure was model of medication abortion care received. There were 3 groups: (1) no-test (telehealth) eligibility assessment by history and mailing of medications (no-test + mail); (2) no-test eligibility assessment (via telehealth or in-person) by history and pickup of medications (no-test + pickup); or (3) in-person assessment with ultrasonography and in-person dispensing of medications (in-person).

The primary outcome was effectiveness of medication abortion defined as a complete abortion without need for procedural abortion or repeating the mifepristone and misoprostol regimen.[26] We relied on a combination of patient self-report (survey) and clinic (chart-abstracted) data to determine effectiveness. Survey questions included patients' self-assessment of whether they "believe[d] that the abortion pills worked to end the pregnancy," had taken a pregnancy test and its result, "had a suction procedure (vacuum aspiration or dilation and curettage [D&C]) to complete the abortion," or had been "given another dose of the first abortion pill (mifepristone)" as part of follow-up care. Chart-abstracted data included the clinician's assessment of the medication abortion outcome at last contact with the patient (complete, incomplete, ongoing pregnancy, unknown), any tests performed to document pregnancy outcome (ie, ultrasonography, physical examination, review of symptoms, urine pregnancy test, serum human chorionic gonadotropin testing), and details on any follow-up care received or reported to the clinic. A flowchart was developed a priori to resolve discordant patient self-report and chart-abstracted outcomes (eFigure 2 in Supplement 1). Clinic staff completing abstraction were not blind to the study group because this information was in the patient's medical record.

A secondary outcome was safety, defined as reporting of any abortion-related SAE. This included overnight hospital admission, surgery, blood transfusion, or death. Surveys assessed whether patients had "go[ne] to a hospital, emergency department, doctor's office, or clinic (other than your regularly scheduled follow-up visit)" since taking the mifepristone and, if so, what type of care they received (including "I was given a blood transfusion" or "I stayed overnight in the hospital"). Chart-abstracted data included any documented care received at an outside facility as well as details on the care received. We searched across all chart-abstracted data fields for a list of terms related to the defined SAEs to ensure all potential cases were identified. All open-ended chart data fields were also reviewed by a physician (D.G.) to determine whether an SAE was reported.

We collected sociodemographic and pregnancy characteristics prespecified as potential confounders, including participants' age, race and ethnicity, gestational duration, parity, and prior abortion. Race and ethnicity data were based on 2 prespecified questions regarding Hispanic, Latine, or Spanish ethnicity (yes or no) and self-reported race (Asian, Black or African American, Middle Eastern or North African, Native American or Other Pacific Islander, White, or other), with the option to select all that apply and/or write in a response. Gestational duration at initial appointment collected by facility staff was estimated using date of last menstrual period for the telehealth groups and ultrasonography for the in-person with ultrasonography group. For race and ethnicity, prior abortion, and parity, we relied on participants' survey responses; when possible, missing responses were completed using medical record data.

Statistical Analysis

We described the distribution of sociodemographic and pregnancy covariates in the study sample overall. We then tested for differences in the distribution of these covariates as well as the proportion with abortion outcome data by study group using bivariable mixed effects linear or multinomial regression models adjusted for clustering of observations by facility as well as standardized mean differences. Although our prespecified statistical analysis plan describes adjusting for clustering by *site*, our subsequent inclusion of facilities from the same organization but located in different states led to a preference for adjustment for clustering at the state and facility level, in the spirit of the prespecified plan. However, to ensure robustness of findings, we also included sensitivity analyses with random effects for organization (n = 4).

Among enrolled participants who took mifepristone or misoprostol and had abortion outcome data available, the unadjusted proportion (with 95% CI) with a complete abortion by study group was calculated. For the primary, prespecified analysis, we examined noninferiority of the telehealth (no-test) with mailed medications care group compared with the in-person care with ultrasonography group. From a logistic mixed effects model with a random effect for facility, we calculated the unadjusted risk difference (and 95% CI) in effectiveness between telehealth (no-test) with mailed medications and in-person care. We then reran the same model with the addition of prespecified confounders, including age and gestational duration, as well as any variables found to differ by study group in bivariable analysis. Telehealth (no-test) with mailed medications care was considered noninferior if the lower side of the 2-sided CI was above −5%, chosen to be consistent with prior research.[27-29] As secondary, prespecified analyses, we then repeated these steps to examine noninferiority of no-test + pickup (vs in-person) and either no-test (vs in-person with ultrasonography) care. We also descriptively examined the proportion (with 95% CI) in each study group that experienced an SAE and, when possible, differences in proportions by study group from adjusted models.

Prespecified analyses focused on a complete-case analysis. However, to ensure robustness of study findings, we repeated our primary, prespecified analysis using multiple imputation by chained equations. We imputed missing data for all covariates and the primary outcome (effectiveness) using all covariates in the original adjusted models as well as receipt of public assistance, educational attainment, and whether they completed a survey. We then used Stata's MI

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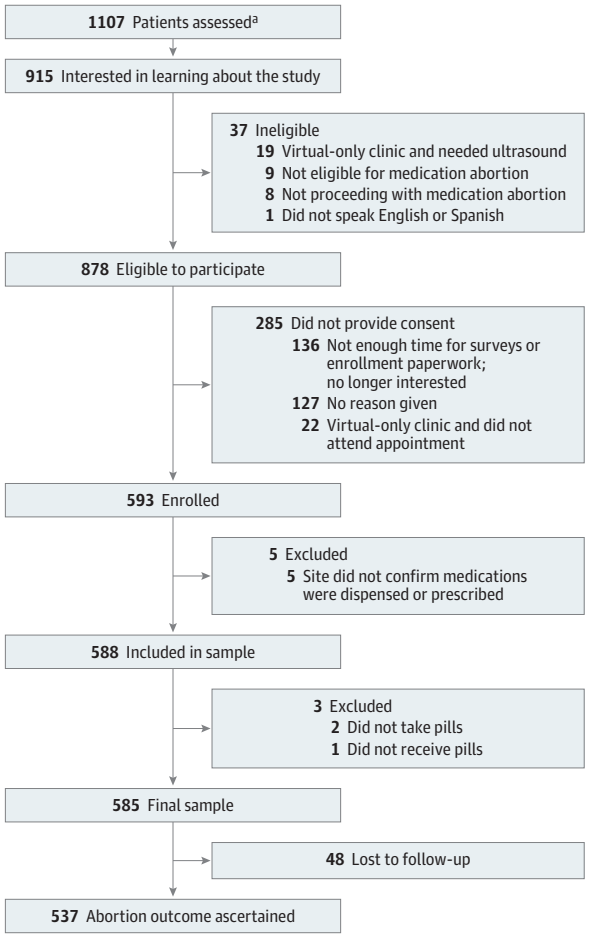
estimate command and a logistic regression model using imputed values and the mimrgns command to estimate the risk difference between study groups (StataCorp). We utilized an inverse probability of treatment-weighted regression adjustment approach to balance covariates between study groups and re-estimate the risk difference. Specifically, logistic regression was used to calculate the propensity score or probability of treatment (telehealth + mail). We then calculated weights as 1/propensity score for the treated group and 1/1-propensity score for the untreated (in-person with ultrasonography) and reran a logistic regression model applying this weight. Finally, to allow for interpretation of marginal, population-level effects, we repeated the primary analysis using a logistic regression model with robust standard errors for facility.

Sample Size

We determined the minimum sample size required to establish noninferiority of telehealth (no-test) with mailed medications care to in-person care for the primary effectiveness outcome. Assuming 20% loss to follow-up, moderate correlation of observations by site (increasing sample size by an additional 15%), and effectiveness of 95%,[7,30] a sample size of 170 participants per study group, or 510 participants overall, gave 80% power with a 1-sided α of .025 to establish noninferiority of telehealth (no-test) with mailed medications care. The study was not powered to detect noninferiority of different models with respect to safety.

All study activities were approved by the University of California San Francisco institutional review board in January 2021 (#20-32514). This manuscript was prepared in accordance with STROBE guidance.[31]

Figure. Study Flowchart



[a]During initial telehealth or in-person appointment.

Results

A total of 1107 patients were approached, of whom 878 were eligible; 588 consented and enrolled (**Figure**). There were no differences in mean age (P = .38), appointment type (P = .72), or gestational duration (P = .51) between those eligible who enrolled vs did not enroll.

Among 588 enrolled patients, 3 were excluded from the analysis because they did not receive (n = 1) or take (n = 1) pills or because they sought emergency care for an ectopic pregnancy *before* picking up the pills (n = 1), resulting in a final sample of 585. Abortion outcome data were available for 537 of 585 (91.8%) of the participants; the proportion with abortion outcome data did not differ by study group (**Table 1**). Further, there were no differences by sociodemographic and pregnancy characteristics in the proportion missing abortion outcome data (eTable 1 in Supplement 1).

Median (IQR) participant age was 26 years (23-31). Nearly one-half (48.6%) were non-Hispanic White, with fewer non-Hispanic Black (28.1%), non-Hispanic other, or multiple races (12.1%) or Hispanic (9.6%). Approximately 4 in 10 participants reported a prior abortion (42.6%). Median (IQR) gestational duration at screening was 45 days (39-53) and did not differ by study group (P = .39). In the no-test + pickup medications study group, two-thirds (66%) completed eligibility assessment virtually and one-third (33%) completed no-test eligibility assessment in-person at a clinic.

Overall, 510 of 537 participants had a complete abortion without a procedure or repeating the mifepristone and misoprostol regimen, for an unadjusted effectiveness rate of 95.0% (95% CI, 92.8%-96.7%). Among the 27 participants classified as having an incomplete abortion, 18 had a follow-up procedure to complete the abortion, 6 reported a positive pregnancy test or uncertainty about whether the pills worked and were then lost to follow-up, 2 had a confirmed or suspected ectopic pregnancy, and 1 reported receiving outside care to complete the abortion to the study clinic. One ectopic pregnancy was confirmed by the patient, who reported to the clinic that they had sought care at an emergency department after taking the medications and had an operation to remove a fallopian tube. The other participant was referred to a hospital for evaluation and treatment of a suspected ectopic pregnancy after reporting no bleeding for more than 24 hours after taking misoprostol.

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Table 1. Sociodemographic and Pregnancy Characteristics by Nonrandomized Study Group

	Study group[a]				Standardized mean difference	
	No-test telehealth + medication by mail (no-test + mail) [n = 228]	No-test + medication pickup (no-test + pickup) [n = 119]	In-person with ultrasonography (in-person + ultrasonography) [n = 238]	*P* value[b]	No-test + mail vs in-person + ultrasonography	No-test + pickup vs in-person + ultrasonography
Age, y						
Mean (SD)	28.3 (6.0)	27.8 (5.7)	26.0 (5.3)		−0.42	−0.33
18 to 19	12 (5.3)	7 (5.9)	11 (4.6)			
20 to 24	58 (25.4)	30 (25.2)	97 (40.8)			
25 to 29	63 (27.6)	38 (31.9)	76 (31.9)	<.01		
30 to 34	57 (25.0)	27 (22.7)	36 (15.1)			
35 to 39	31 (13.6)	13 (10.9)	13 (5.5)			
40 to 43	7 (3.1)	4 (3.4)	5 (2.1)			
Race and ethnicity, No.[c]	n = 222	n = 116	n = 237			
Hispanic	28 (12.6)	8 (6.9)	20 (8.4)			
Non-Hispanic Black	45 (20.3)	37 (31.9)	82 (34.6)	<.01	0.33	0.34
Non-Hispanic other or multiple races	33 (14.9)	6 (5.2)	32 (13.5)			
Non-Hispanic White	116 (52.3)	65 (56.0)	103 (43.5)			
Prior abortion, No.[c]	n = 222	n = 116	n = 236			
No. (%)	99 (44.6)	50 (43.1)	100 (42.4)	.20	0.04	0.01
Nulliparous, No.[c]	n = 223	n = 116	n = 236			
No. (%)	83 (37.2)	52 (44.8)	108 (45.8)	.47	0.17	0.02
Gestational duration at initial appointment, mean (SD), d[d]	46.1 (10.2)	47.0 (8.9)	47.7 (9.8)	.21	0.16	0.08
Abortion outcome reported	204 (89.5)	113 (95.0)	220 (92.4)	.19	0.10	0.10
Gestational duration at initial appointment among those with abortion outcome, d[d]						
No.	n = 219	n = 117	n = 238			
Mean (SD)	46.0 (10.3)	46.8 (8.4)	47.3 (10.1)	.37	−0.03	0.07

[a] N = 585; all values are No. (%) unless otherwise indicated.

[b] *P* value obtained from bivariable mixed effects linear or multinomial regression model adjusted for clustering of observations by facility.

[c] Relies on survey response first and on chart documentation if survey response was missing.

[d] Gestational duration was obtained from self-reported date of last menstrual period for both no-test study groups and from ultrasonography for in-person with ultrasonography group.

Unadjusted effectiveness was 94.1% (95% CI, 90.1%-96.8%) in the in-person group, 95.1% (95% CI, 91.2%-97.6%) in the no-test + mail group, and 96.5% (95% CI, 91.2%-99.0%) in the no-test + pickup group. After adjustment for covariates including age, race and ethnicity, and gestational duration, the risk difference between the in-person and no-test + mail groups was 1.2% (95% CI, −4.1% to 6.4%), above the limit of −5% and indicating noninferiority of telehealth (no-test) with mailed medications care. In this adjusted model, effectiveness was 94.4% (95% CI, 89.6%-99.2%) in the no-test + mail group and 93.3% (95% CI, 88.3%-98.2%) in the in-person group. Similarly, the adjusted risk difference between the in-person and no-test + pickup care groups was 1.7% (95% CI, −4.6% to 8.1%), indicating noninferiority of no-test + medications pickup care. In this adjusted model, effectiveness was 95.0% (95% CI, 88.8%-100.0%) in the no-test + pickup care group and 93.3% (95% CI, 88.8%-97.8%) in the in-person group (**Table 2**).

In sensitivity analyses, rerunning models with imputed missing observations, with application of inverse probability of treatment weights, and with adjustment for clustering of observations by organization (vs facility), results were consistent and demonstrated noninferiority of the no-test model (eTable 2 in Supplement 1).

Overall, 6 of 537 participants experienced an SAE, for a rate of 1.1% (95% CI, 0.4%-2.4%). Events included 4 overnight hospitalizations, 2 blood transfusions, and 1 surgery (for treatment of ectopic pregnancy). The unadjusted rate of SAEs was 1.5% (95% CI, 0.3%-4.2%) in the telehealth + mail group (n = 3) and 1.4% (95% CI, 0.3%-3.9%) in the in-person group (n = 3); no SAEs were reported in the no-test + pickup care group. In adjusted logistic models with robust standard errors for state, the adjusted risk difference between the in-person with ultrasonography and no-test + mail care group was 0.4 (95% CI, −1.0 to 1.7), indicating noninferiority of the no-test + mail model (eTable 3 in Supplement 1).

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Table 2. Noninferiority of Different Models of Care on Effectiveness of Medication Abortion

	Unadjusted risk difference (95% CI)[a]	Adjusted proportion (95% CI) with complete abortion[b] (nonrandomized study groups)			Adjusted risk difference (95% CI)[b,a]
		No-test telehealth + medication by mail	No-test + medication pickup	In-person with ultrasonography	
Unadjusted No. with complete abortion/ No. with abortion outcome data		194/204	109/113	206/220	
In-person with ultrasonography vs no-test telehealth + medication by mail	1.6 (−3.5 to 6.7)	94.4 (89.6 to 99.2)	NA	93.3 (88.3 to 98.2)	1.2 (−4.1 to 6.4)
In-person with ultrasonography vs no-test + medication pickup	1.5 (−4.9 to 7.9)	NA	95.0 (88.8 to 100.0)	93.3 (88.8 to 97.8)	1.7 (−4.6 to 8.1)
In-person with ultrasonography vs any no-test (medication by mail or pickup)	1.5 (−3.1 to 6.1)	94.4 (90.1 to 98.6)[c]		93.2 (88.4 to 98.1)	1.1 (−3.6 to 5.9)

[a] All models include a random effect to account for clustering of observations by facility.

[b] Adjusted for age, race and ethnicity, and gestational duration at time of initial appointment.

[c] Study groups 1 and 2 combined to show contrast with study group 3.

Discussion

In this prospective, observational study of 585 people obtaining medication abortion, it was found that medication abortion following no-test telehealth screening and mail-order pharmacy dispensing of medications was associated with similar rates of complete abortion as in-person care with ultrasonography, met the prespecified threshold for noninferiority, and had a low rate of AEs overall. Further, medication abortion following no-test screening with pickup of medications was also associated with similar outcomes as in-person care with ultrasonography and had low rates of AEs overall. Levels of effectiveness with models of care incorporating telehealth and eligibility assessment in this study were comparable to large 2022 and 2024 studies of no-test telehealth patients.[20,32] This study contributes new evidence pertaining to no-test telehealth models in direct comparison with a concurrent control group of people receiving care from similar facilities through in-person care with ultrasonography. Taken together, these findings indicate that no-test and telehealth models with mailing of medications may be offered as an option to people seeking abortion. Although geographic and logistical barriers have always delayed and complicated pregnant people's access to abortion,[33,34] these barriers have become increasingly problematic following the Supreme Court's June 2022 decision revoking federal protections on abortion.[35,36] Thus, expansion of telehealth and no-test or history-based models offers a safe and effective, as well as urgently needed, way to overcome at least some of the logistical and geographic barriers to accessing abortion.[37]

Study findings may also be used to refute ongoing efforts to further regulate and restrict access to medication abortion, most notably in the *Alliance for Hippocratic Medicine v FDA* case currently before the US Supreme Court. One of the central issues being considered in this case is the quality of the evidence the FDA relied on when it removed the in-person dispensing requirement for mifepristone in 2021.[38] Although the data were robust in 2021 when the FDA performed its review, this current analysis, as well as other research published since then,[20,32] further strengthens the evidence documenting the safety and effectiveness of medication abortion provided using no-test telehealth screening for eligibility and dispensing the medications by mail.

Limitations

This study has limitations. First, approximately 8% of the participants were lost to follow-up and did not complete a survey or have any follow-up contact with the clinic. Although this follow-up rate represents an improvement over prior research that relied only on chart-abstracted outcomes,[12,13,19,20] the possibility that those who were lost to follow-up had worse outcomes remains. Second, only patient-reported outcomes up to 4 weeks after initiation of treatment were collected; it is possible that additional treatment could have been accessed after that point. Third, as an observational study in which patients could select which model of medication abortion care they received, some differences in the sociodemographic and pregnancy characteristics by study group were expected and therefore the study relied on adjustment for these characteristics to account for them in analyses. Reassuringly, differences were not observed in gestational duration by study group, which is likely most strongly correlated with outcomes of safety and effectiveness,[7] and models with imputed data produced comparable findings. However, confounding on unobserved covariates always remains a possibility in observational data. Fourth, this study sample size was not powered to detect noninferiority of, or differences in, safety of different models of care. Although few SAEs (n = 6 [1.1%]), including ectopic pregnancy, were observed, the estimate is qualitatively higher than a large 2022 retrospective study of patients receiving medication abortion through history-based screening, which found that 0.5% experienced an SAE.[20] Inclusion of patient self-reported outcomes, including overnight hospitalization, in defining SAEs likely contributed to this. Notably, the concurrent control group allowed direct comparison of the rate of SAEs between those receiving no-test telehealth medication abortion with mailing of medications vs in-person care with ultrasonography.

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Conclusions

This prospective, observational study found that medication abortion following no-test telehealth screening and mailing of medications was associated with similar rates of abortion completion compared with in-person care with ultrasonography, meeting the prespecified threshold for noninferiority and with a low prevalence of adverse events.

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Concept and design: Ralph, Baba, Biggs, Grossman.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Ralph, Baba.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Ralph, Baba, Biggs.
Obtained funding: Grossman.
Administrative, technical, or material support: Ralph, Baba, McNicholas, Hagstrom Miller, Grossman.
Supervision: Grossman.

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Original Research

The Comparative Safety of Legal Induced Abortion and Childbirth in the United States

Elizabeth G. Raymond, MD, MPH, and David A. Grimes, MD

OBJECTIVE: To assess the safety of abortion compared with childbirth.

METHODS: We estimated mortality rates associated with live births and legal induced abortions in the United States in 1998–2005. We used data from the Centers for Disease Control and Prevention's Pregnancy Mortality Surveillance System, birth certificates, and Guttmacher Institute surveys. In addition, we searched for population-based data comparing the morbidity of abortion and childbirth.

RESULTS: The pregnancy-associated mortality rate among women who delivered live neonates was 8.8 deaths per 100,000 live births. The mortality rate related to induced abortion was 0.6 deaths per 100,000 abortions. In the one recent comparative study of pregnancy morbidity in the United States, pregnancy-related complications were more common with childbirth than with abortion.

CONCLUSION: Legal induced abortion is markedly safer than childbirth. The risk of death associated with childbirth is approximately 14 times higher than that with abortion. Similarly, the overall morbidity associated with childbirth exceeds that with abortion.

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LEVEL OF EVIDENCE: II

See related editorial on page 212.

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Decades of research have demonstrated that legal induced abortion is safe. Mortality and serious acute complications are extremely rare.[1–4] Recently, allegations of later sequelae—breast cancer and mental illness—were refuted.[5,6] However, laws in 22 states in the United States now require that before an abortion is performed, the patient must be given detailed, specific verbal or written information about potential risks. In some cases, this material is misleading or patently wrong.[7]

Health policy and medical practice should be based on the best available evidence. In the past 10 years, the introduction of new abortion methods may have affected the overall safety of the procedure. Notably, mifepristone was approved by the U.S. Food and Drug Administration for medical abortion in 2000; by 2008, approximately 17% of all nonhospital abortions were performed medically rather than surgically.[8] In addition, changes in the risk profile of pregnant women—for example, as a result of growing obesity[9] and an upward shift in the maternal age distribution[10]—as well as the rising cesarean delivery rate[10] may have enhanced the risks of the alternative to abortion, childbirth. The objective of this review is to provide an updated assessment[2] of the safety of abortion relative to delivery.

MATERIALS AND METHODS

We estimated mortality rates associated with live births and legal induced abortions in the United States in 1998–2005 by combining published data from several national data sets. For mortality related to live birth, we divided the number of pregnancy-related deaths among women delivering live neonates as reported by the Centers for Disease Control and Prevention's (CDC) Pregnancy Mortality Surveillance System[11] by the number of live births as reported on birth certificates.[10] The Pregnancy Mortality Surveillance System collects and reviews death certificates and other information from deceased women who were recorded as pregnant within a

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specified time period before death in all 50 states and Washington, DC. To estimate abortion-related mortality, we divided the number of legal abortion-related deaths from the 50 states and Washington, DC, reported by the CDC[12] by the number of legal abortions estimated by the Guttmacher Institute from its annual surveys of all U.S. hospitals, clinics, and physician offices known or suspected to have provided abortion services.[8] We did not calculate confidence intervals around mortality rates because these estimates are derived from the full population.

In addition, we searched PubMed for relevant studies for other population-based comparative data on mortality and morbidity of abortion and childbirth in the United States since 2000. We used the following search strategies: (maternal morbidity [MESH] OR maternal mortality [MESH]) AND pregnancy outcome AND United States [MESH] (73 results); pregnancy outcome AND (maternal morbidity [MESH] OR maternal mortality [MESH]) AND United States [tiab] (49 results); pregnancy outcome AND abortion, induced AND morbidity AND United States [MESH] (94 results). We limited our review to reports that included data on both pregnancy outcomes in a single population with contemporaneous, uniform ascertainment of outcomes.

Because women who choose abortion differ in underlying risk for adverse outcomes from women who opt to continue a pregnancy, we also compared the characteristics of each group. We obtained data about characteristics of U.S. women having abortions and live births in 2008 from the Guttmacher Institute 2008 Abortion Patient survey[13] and from birth certificate data[11] (www.cdc.gov/nchs/data_access/vitalstats/VitalStats_Births.htm. Retrieved 28 May 2011).

RESULTS

Between 1998 and 2005, the pregnancy-associated mortality rate among women known to have delivered live neonates in the United States was 8.8 deaths per 100,000 live births (Table 1). Of all pregnancy-associated deaths of women with known pregnancy outcome, 71% occurred after live births[11]; if 71% of women with unknown pregnancy outcome who died of pregnancy-associated causes are also assumed to have had live births, the mortality estimate increases to 10.4 deaths per 100,000 live births. The mortality rate related to legal induced abortion during that same interval was 0.6 deaths per 100,000 abortions. Thus, according to federal statistics, the risk of death associated with childbirth was approximately 14 times higher than that with abortion.

Table 1. Pregnancy-Related Mortality in Women With Live Births or Legal Induced Abortions in the United States, 1998–2005

	Deaths*	Pregnancies†	Deaths per 100,000 Pregnancies
Live birth		32,347,794	
Known live birth	2,856		8.8
Known live births+71% of pregnancies with unknown outcome	3,352		10.4
Legal abortion	64	10,185,100	0.6

* Number of deaths related to live births from Berg et al[11]; number of deaths related to abortion from Pazol et al.[12]

† Number of live births from Martin et al[10]; number of abortions from Jones et al.[8]

Only one recent study provided comparative data on morbidity associated with various pregnancy outcomes in the United States.[14] Epidemiologists at the CDC examined all International Classification of Diseases, 9th Revision, Clinical Modification diagnoses reported during or within 8 weeks after all 24,481 pregnancies among members of the Kaiser Permanente Northwest Health Maintenance Organization between 1998 and 2001. Of these pregnancies, 16,824 ended in live birth, 4,192 in induced abortion, and the rest in spontaneous abortions, stillbirths, or other outcomes. Common maternal morbidities were defined as conditions either unique to pregnancy or potentially exacerbated by pregnancy that occurred in at least 5% of all pregnancies.

Every complication was more common among women having live births than among those having abortions (Fig. 1). The relative risks of morbidity with live birth compared with abortion were 1.3 for mental health conditions, 1.8 for urinary tract infection, 4.4 for postpartum hemorrhage, 5.2 for obstetric infections, 24 for hypertensive disorders of pregnancy, 25 for antepartum hemorrhage, and 26 for anemia.

In 2008, the median age of women having abortions was younger than that of women having live births, but the proportion of women age 40 years or older was comparable (Table 2). Nearly half of women in each group had no education beyond high school. Patients undergoing abortion were twice as likely to be unmarried or non-Hispanic African American women. Nulliparity was equally common in the two groups.

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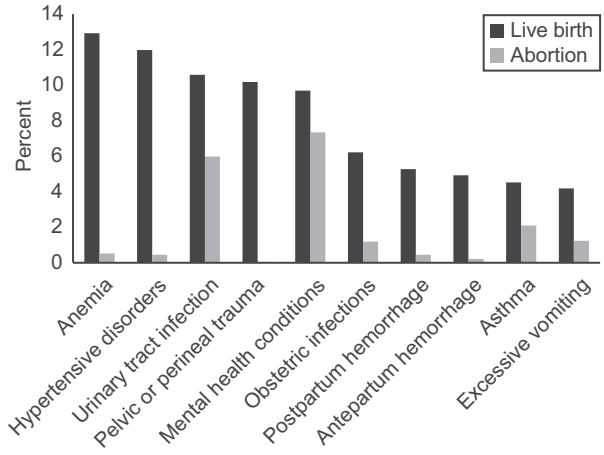

Fig. 1. Common maternal morbidities associated with live birth and abortion, 1998–2001. Common maternal morbidities defined as conditions either unique to pregnancy or potentially exacerbated by pregnancy that occurred in at least 5% of all pregnancies. Data from Bruce FC, Berg CJ, Hornbrook MC, Whitlock EP, Callaghan WM, Bachman DJ, et al. Maternal morbidity rates in a managed care population. Obstet Gynecol 2008;111:1089–95.

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Table 2. Characteristics of Women Having Live Births and Abortions in the United States, 2008

	Live Births*	Abortions†
Age (y)		
Younger than 15	5,764 (0.1)	4,850 (0.4)
15–19	434,758 (10.2)	208,520 (17.2)
20–24	1,052,184 (24.8)	404,920 (33.4)
25–29	1,195,774 (28.2)	295,810 (24.4)
30–34	956,716 (22.5)	163,670 (13.5)
35–39	488,875 (11.5)	99,410 (8.2)
40 or older	113,623 (2.7)	35,160 (2.9)
Total	4,247,694 (100)	1,212,340 (100)
Ethnicity or race		
Hispanic	1,041,239 (24.7)	301,880 (24.9)
Non-Hispanic white	2,267,817 (53.8)	437,660 (36.1)
Non-Hispanic African American	623,029 (14.8)	358,860 (29.6)
Non-Hispanic other	282,783 (6.7)	113,960 (9.4)
Total	4,214,868 (100)	1,212,360 (100)
Marital status		
Married	2,521,128 (59.4)	179,430 (14.8)
Unmarried	1,726,566 (40.6)	1,032,930 (85.2)
Total	4,247,694 (100)	1,212,360 (100)
Education among women aged 20 y and older		
Less than high school	435,462 (18.1)	122,870 (12.3)
High school or GED	630,970 (26.2)	282,710 (28.3)
Some college	685,206 (28.4)	394,590 (39.5)
College graduate	659,044 (27.3)	198,800 (19.9)
Total	2,410,682 (100)	998,970 (100)
Number of prior births		
0	1,703,921 (40.4)	474,030 (39.1)
1	1,330,540 (31.5)	321,270 (26.5)
2 or more	1,186,657 (28.1)	418,260 (34.5)
Total	4,221,118 (100)	1,213,560 (100)

GED, high school equivalency certification.
Data are n (%).
* Data on live births from Martin[10] and the National Center for Health Statistics. Numbers with unknown status are excluded from the table.
† Data on abortion from Jones et al.[13]

DISCUSSION

Legal abortion in the United States remains much safer than childbirth. The difference in risk of death is approximately 14-fold. Abortion also is associated with substantially less pregnancy-related morbidity. These results are consistent with prior analyses of national data.[2] Indeed, the relative safety of abortion has increased substantially since the first decade after nationwide legalization, when child birth-related mortality was approximately seven times the mortality related to abortion.[15] Although we could not find data that allowed comparable calculations of mortality or morbidity associated with surgical and medical abortion, Danco Laboratories, the distributor of mifepristone in the United States, has identified only 11 pregnancy-related deaths among the estimated 1.6 million women who have used the drug in the United States since 2000, which is a mortality rate of 0.7 per 100,000 users (Abigail Long, Danco Laboratories, LLC, personal communication). Clearly, the growing use of medical regimens has not increased relative abortion risk overall.

The disparity between abortion and childbirth safety is not surprising. Pregnancies ending in abortion are substantially shorter than those ending in childbirth and thus entail less time for pregnancy-related problems to occur. Many dangerous pregnancy-related complications such as pregnancy-induced hypertension and placental abnormalities manifest themselves in late pregnancy; early abortion avoids these hazards. Moreover, in the United States in 2008, one third of births occurred by cesarean delivery, an abdominal operation with substantial morbidity.[10,16]

These results may underestimate the relative safety of choosing abortion over continuing a pregnancy for two reasons. First, our comparison was limited to live

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births; we omitted other pregnancy outcomes: spontaneous abortion, stillbirths, ectopic pregnancies, and gestational trophoblastic disease. The number of pregnancies ending in these outcomes was not available. Stillbirths and ectopic pregnancies are associated with higher risks of death than is live birth.[2] We likely therefore underestimated the mortality associated with opting for pregnancy continuation.

Second, patients undergoing abortion appear to be at higher underlying risk than women who opt for delivery. Women who had abortions were more likely to be African American or unmarried, demographic characteristics strongly associated with increased mortality.[11,17] In addition, because comorbidities are sometimes the motivation for abortion, the underlying medical risk of patients undergoing abortion may be higher than that of other pregnant women. Women in good health may be more likely to choose to continue their pregnancies than those who are ill (selection bias termed the "healthy mother" effect[18]). Thus, mortality among patients undergoing abortion may overestimate the mortality risk of the procedure itself.

This study has both strengths and weaknesses. Strengths include the use of the most recent CDC statistics on pregnancy-related mortality for the entire country. Similarly, the cohort study of morbidity had uniform, contemporaneous ascertainment of outcomes in a large health maintenance organization. We systematically reviewed the past decade of PubMed publications for relevant data. Weaknesses include the likely underreporting of deaths, possibly differential by pregnancy outcome (abortion or childbirth).[19] The analytic rules used by the original researchers to handle incomplete or inconsistent data on women's characteristics may have led to errors. Our assessment of women's underlying risk was necessarily incomplete. Moreover, both abortion and childbirth can cause mortality and morbidity long after the end of the pregnancy; these cases are not included in our analysis. However, these weaknesses are unlikely to account for the large differences in mortality and morbidity found in this analysis.

Pregnant women considering their options deserve accurate information about comparative risks. Currently, some state laws and policies violate this standard. In Texas, for example, the mandatory 23-page pamphlet, "A Woman's Right-to-Know," lists 12 potential complications of medical abortion with mifepristone and misoprostol, 12 of suction curettage, and 11 of dilation and evacuation. In contrast, the pamphlet names only six potential complications of vaginal delivery and eight of cesarean delivery.[20] To laypersons who have little understanding of medical risk[21] but can count complications, these tallies may imply that abortion has more complications than does childbirth. Similarly, the mortality statistics are presented as fractions with one in the numerator and with large denominators (eg, 8,475). Empiric evidence[22,23] has demonstrated that women with less formal education than a college degree have trouble comparing risks expressed in this manner. Mortality risk should be expressed as number of deaths per 100,000, which is an easier format to understand.[22,23]

Laws that compel exposure of women to such biased material thwart informed choice and contravene the ethical principle of autonomy.[24] Moreover, they put clinicians in the untenable position of having to be complicit in misleading their patients. Since the early 1970s, the public health evidence has been clear and incontrovertible: induced abortion is safer than childbirth.

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Contraception

Review article

First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review☆

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Abstract

Background: The dose of mifepristone approved by most government agencies for medical abortion is 600 mg. Our aim was to summarize extant data on the effectiveness and safety of regimens using the widely recommended lower mifepristone dose, 200 mg, followed by misoprostol in early pregnancy and to explore potential correlates of abortion failure.
Study Design: To identify eligible reports, we searched Medline, reviewed reference lists of published reports, and contacted experts to identify all prospective trials of any design of medical abortion using 200 mg mifepristone followed by misoprostol in women with viable pregnancies up to 63 days' gestation. Two authors independently extracted data from each study. We used logistic regression models to explore associations between 15 characteristics of the trial groups and, separately, the rates of medical abortion failure and of ongoing pregnancy.
Results: We identified 87 trials that collectively included 120 groups of women treated with a regimen of interest. Of the 47,283 treated subjects in these groups, abortion outcome data were reported for 45,528 (96%). Treatment failure occurred in 2,192 (4.8%) of these evaluable subjects. Ongoing pregnancy was reported in 1.1% (499/45,150) of the evaluable subjects in the 117 trial groups reporting this outcome. The risk of medical abortion failure was higher among trial groups in which at least 25% of subjects had gestational age >8 weeks, the specified interval between mifepristone and misoprostol was less than 24 h, the total misoprostol dose was 400 mcg (rather than higher), or the misoprostol was administered by the oral route (rather than by vaginal, buccal, or sublingual routes). Across all trials, 119 evaluable subjects (0.3%) were hospitalized, and 45 (0.1%) received blood transfusions.
Conclusions: Early medical abortion with mifepristone 200 mg followed by misoprostol is highly effective and safe.
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Keywords: Medical abortion; Mifepristone; Misoprostol; Systematic review

1. Introduction

Since mifepristone was introduced in France and China more than two decades ago, medical abortion with this antiprogestin has expanded rapidly throughout the world. Mifepristone is now registered in 50 countries (www.gynuity.org, accessed 14 December 2011). In the United States, about one fifth of all outpatient abortions are performed medically [1], and in several countries in Europe, the proportion exceeds 60% [2,3].

Although medical abortion regimens approved by most government regulatory agencies specify 600 mg mifepristone, in practice, a dose of 200 mg is standard worldwide [4–7]. A prostaglandin, misoprostol, is administered after the mifepristone to enhance success. The dose, route, and timing of administration of misoprostol are not standardized. In the United States, affiliates of Planned Parenthood Federation of America provide 800 mcg buccally 24–48 h after the mifepristone [4]. The International Federation of Obstetricians and Gynaecologists recommends either vaginal, buccal, or sublingual administration [5] as do the World Health Organization [6] and the United Kingdom Royal College of Obstetricians and Gynaecologists [7], which also recommend

☆ E.G.R. and C.S. conducted literature searches and abstracted data. M.A.W. performed statistical analyses. All authors contributed equally to interpretation and manuscript preparation. No authors have any conflicts of interest.

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oral dosing at gestational ages up to 49 days. Lower doses, divided doses, oral administration, and a shorter or longer interval between the two drugs also have been used clinically or evaluated in research studies.

The purpose of this review is to summarize published data on the effectiveness and safety of regimens including 200 mg mifepristone followed by misoprostol for early medical abortion. We also explore whether variation among studies in the frequency of medical abortion failure could be explained by characteristics of the study designs, treatment protocols, or study populations.

2. Materials and methods

We searched Medline using PubMed on 7 July 2011 for studies of medical abortion using mifepristone and misoprostol. Our search strategy was as follows: (abortion OR pregnancy termination OR termination of pregnancy) AND (mifepristone OR RU 486 OR RU-486 OR RU486 OR Mifegyne OR Mifeprex OR Medabon) AND (misoprostol OR prostaglandin). In addition, we reviewed the reference lists of relevant articles, and we contacted experts in the field for information about any published or unpublished trials not discovered in our search.

Two authors (E.G.R., C.S.) independently examined the search results (titles and as necessary abstracts and full publications) and other available information to identify all English language reports of prospective trials that included at least one group of women with viable first trimester pregnancies who were treated with a specified abortion regimen consisting of 200 mg mifepristone followed by misoprostol. These trials included randomized trials, cohort studies, and case series studies. For each group of interest in these reports, the same two authors separately abstracted data, including information about the study design and treatment protocol, the number and characteristics of women treated, and the numbers who had medical abortion failure, medical abortion failure with a diagnosed ongoing (viable) pregnancy, hospitalization, and blood transfusion. We contacted some authors to obtain additional data or to clarify details about the studies. We resolved discrepancies by discussion.

In some reports, the effectiveness analyses excluded subjects who initiated treatment but failed to complete the full prescribed medical abortion regimen. Our analyses included all pregnant women in each trial group who received at least mifepristone and who had a gestational age of 63 days or less, were not known to have an ectopic pregnancy, and had a reported abortion outcome. Most trials defined medical abortion failure as need for surgical intervention to complete the abortion, but a few used other definitions, such as failure to abort within 24 h after the misoprostol [8] and use of additional abortifacient drugs after the initially prescribed regimen [9]. Of necessity, we used the authors' definitions, but when possible, we also included as failures ongoing pregnancies that were continued at the patient's choice after ingestion of mifepristone.

In abstracting data about protocols and study populations, we combined the original authors' categories that were similar but not necessarily identical; for example, in recording gestational age ranges, we considered "<63 days", "≤63 days", "<9 weeks", and "≤9 weeks" all to be equivalent, and we considered subjects who had had no live births to be nulliparous if the report did not describe parity (including both live births and stillbirths). In recording parity and the gestational age distribution, we accepted figures for either the entire enrolled trial population or the analyzed population, as provided by the authors. We used our judgment to resolve internal inconsistencies and to correct frank errors noted in a few reports.

Our analysis considered each group from each trial (regardless of study design) as a separate case-series. We combined data across trial groups to calculate the proportion of subjects who had medical abortion failure and the proportion who had ongoing pregnancy. We used exact Pearson chi-square goodness-of-fit tests, calculated using StatXact, Version 8.0 (Cytel Inc., Cambridge, MA, USA), to assess heterogeneity across trial groups in both outcomes. To explore possible explanations for heterogeneity, we used logistic regression to examine associations between selected characteristics of the trial groups and, separately, medical abortion failure rate and ongoing pregnancy rate. The models controlled for nesting of groups within trial using generalized estimating equations with an independence working correlation matrix. The response for the models was the ratio of the number of events to the number of evaluable patients for each trial group (conducted in SAS, version 9.2, SAS Institute, Cary NC, USA); thus, model results were weighted by trial group sample size. We used "missing" categories to include trial groups with missing predictor data wherever relevant. The models included interaction terms for misoprostol dose and route of first dose. We excluded from both models one trial group of 4 women treated with 200 mcg misoprostol [10]. We excluded from the ongoing pregnancy model 3 trial groups in which ongoing pregnancy was not assessed [11–13], and to allow model convergence, we also excluded 4 groups in which women received misoprostol 600 mcg sublingual [14–17] because no ongoing pregnancies occurred in any groups with that dose/route combination. For one study in which the misoprostol dose was increased from 400 to 800 mcg partway through [18], we estimated the number of women and events in each of the two respective trial groups by assuming that the enrollment rate was constant over the course of the study. In reviewing the results, we focused on associations that were both substantial (odds ratio >1.5 or <0.67) and significant ($p<.05$).

A previously published protocol for this systematic review does not exist.

3. Results

The Medline search yielded 860 citations. Of these, 81 included at least one group of women who were treated with an abortion regimen that used 200 mg mifepristone followed by misoprostol in viable first trimester pregnancy [8–88]. In addition, we became aware of six reports of unpublished trials (M. Pena and S. Raghavan, Gynuity Health Projects, personal communication) that met these criteria.

The 87 trials included 36 randomized trials and 51 prospective cohort or case series studies conducted at 314 sites in 35 countries (Table 1). Sixty-three of the trials were performed between 1994 and 2011; the other 24 reports did not provide dates of data collection. Inclusion criteria for the trials were similar and broad: in general, any woman who requested medical abortion, did not have contraindications to the abortion drugs, and was within a specified gestational age range (determined by ultrasound or clinically) was eligible. Some trials had age restrictions and/or excluded women with multiple gestations.

The 87 trials included 120 groups of women treated with a regimen of interest: 62 trials studied a single such regimen, 18 studied two, six studied three, and one studied four (Appendix). The total prescribed dose of misoprostol in the regimens studied varied from 200–6400 mcg. In most trial groups, the misoprostol was delivered in one administration, but 13 groups received the total dose in divided increments over 1–7 days. Routes of administration included vaginal, oral, buccal and sublingual. The two most commonly studied regimens used 800 mcg misoprostol vaginally or 400 mcg orally. The interval between the mifepristone and the misoprostol ranged from 0 to 72 h. Some protocols required that all subjects receive the misoprostol in the clinic, whereas others allowed most or all women to take the misoprostol at home. In nearly half the groups, the treatment protocol specified that selected subjects who did not abort after the initial treatment should be offered one or more additional doses of misoprostol rather than immediate surgical evacuation.

The timing of the initial follow-up evaluation of abortion success varied from 1–21 days after mifepristone administration. In about half the trial groups, ultrasound was used routinely at the follow-up visit to determine whether the medical abortion regimen resulted in complete abortion and, if not, whether the pregnancy was ongoing. In other groups, outcome assessment, including the diagnosis of ongoing pregnancy, relied primarily or solely on patient symptoms and/or clinical examination. Some trials allowed collection of outcome information by telephone or by review of outside records. No trial had explicit criteria for hospitalization and transfusion of subjects.

The 120 trial groups included a total of 47,283 treated subjects, of whom 45,528 (96%) provided evaluable data for our effectiveness analyses (Table 1). The median proportion of treated subjects with missing outcome data was 1.3% (range 0–19%). The number of evaluable subjects in the 120 groups ranged from 4 to 4,132.

Among all evaluable subjects, 2,192 (4.8%) had medical abortion failure (Table 2). Across trial groups, the proportion with this outcome ranged from 0 to 40% (Fig. 1A). Half the groups had failure rates of 4.8% or less, and more than 90% of the evaluable subjects were in trial groups in which the failure proportion was 8.8% or less.

In 84 trials (117 groups), researchers noted whether or not each patient with medical abortion failure was diagnosed with ongoing pregnancy at the time of the failure ascertainment (Table 2). Of the 45,150 evaluable subjects in these trials, 499 (1.1%) had ongoing pregnancies. Across these groups, the median percentage of subjects with ongoing pregnancies was 0.7%, and 90% of the subjects were in groups in which less than 2.9% of subjects had ongoing pregnancy (Fig. 1B). The 499 ongoing pregnancies constituted 23% of the 1,976 medical abortion failures in these groups.

We found strong evidence of heterogeneity across trial groups in both the proportion of subjects who had medical abortion failure and the proportion who had ongoing pregnancy ($p<.001$ for both outcomes). Logistic regression models included as independent variables all the characteristics listed in Table 2. These models found few associations that were both substantial and significant. After adjustment for other characteristics included in the model, groups in which at least 25% of the women were in the ninth week of pregnancy had higher medical abortion failure rates than groups in which fewer women were so advanced in gestation (OR 1.5; 95% CI 1.1–2.0). Groups instructed to take the misoprostol <23 h after the mifepristone also had higher medical abortion failure rates than other groups (OR 2.1; 95% CI 1.4–3.2). At each total misoprostol dose level, oral administration was associated with higher medical abortion failure rates than each of the other three routes, but no substantial differences were noted among the other routes. Similarly, for each route, 400 mcg misoprostol was associated with higher failure rates than higher doses, although not all of these associations were significant.

Associations of misoprostol dose and route with ongoing pregnancy were mostly consistent with the associations with failure of all types; that is, both the oral route and the 400 mcg dose of misoprostol were generally associated with higher ongoing pregnancy rates than other doses and other routes. Ongoing pregnancy was twice as common in groups in which ultrasound was not routinely used to confirm success than in groups in which it was used in all women (OR 2.0, 95% CI 1.0–3.9). No notable associations were apparent between ongoing pregnancy rates and of any of the other group characteristics, however.

Across all trials, 119 of 45,528 evaluable subjects (0.3%) were hospitalized; of these, 46 hospitalizations (38%) occurred in a single trial [21] which included 4,132 treated women. Most of the hospitalizations were for vaginal bleeding, pelvic pain, or infection; some were for ectopic

Table 1
Characteristics of trial groups, subjects, medical abortion failures and ongoing pregnancies

	Trial groups[a]	Evaluable subjects[a]	Abortion failure		Ongoing pregnancy	
	N=120 (117)	N=45,528 (45,150)	N=2,192		N=499	
	n	*n*	*n*	%[b]	*n*	%[b]
Study design						
Randomized trial	65	22,768	1,172	5.1	230	1.0
Cohort or case-series study	55 (52)	22,760 (22,382)	1,020	4.5	269	1.2
Data collection dates[c]						
Before mifepristone registration	42 (41)	13,859 (13,608)	744	5.4	140	1.0
After mifepristone registration	44 (42)	22,029 (21,902)	864	3.9	245	1.1
Missing	34	9,640	584	6.1	114	1.2
Geographic region						
Europe	31 (30)	10,772 (10,745)	378	3.5	88	0.8
Americas	36	16,598	564	3.4	123	0.7
Other	53 (51)	18,158 (17,807)	1,250	6.9	288	1.6
Number of study sites						
1	59 (57)	12,071 (11,944)	452	3.7	102	0.9
>1	61 (60)	33,457 (33,206)	1,740	5.2	397	1.2
Prescribed interval between mifepristone and misoprostol						
<23 h	11	2,018	108	5.4	20	1.0
23–72 h	109 (106)	43,510 (43,132)	2,084	4.8	479	1.1
Protocol specified additional dose of misoprostol for selected subjects						
No	67 (64)	20,512 (20,134)	1,335	6.5	276	1.4
Yes	53	25,016	857	3.4	223	0.9
Protocol required all subjects to take misoprostol in clinic						
No	56 (55)	24,921 (24,894)	1,132	4.5	306	1.2
Yes	57 (56)	18,007 (17,907)	930	5.2	178	1.0
Not stated	7 (6)	2,600 (2,349)	130	5.0	15	0.6
Minimum scheduled follow-up interval						
<1 week	36	15,343	485	3.2	90	0.6
≥1 week	84 (81)	30,185 (29,807)	1,707	5.7	409	1.4
Protocol required ultrasound to assess failure						
In none or some subjects	51 (50)	26,505 (26,478)	1,472	5.6	365	1.4
In all subjects	64 (63)	18,046 (17,946)	647	3.6	121	0.7
Not stated	5 (4)	977 (726)	73	7.5	13	1.8
% of population who were nulliparous						
>50%	34 (33)	15,522 (15,271)	563	3.6	89	0.6
≤50%	40 (39)	16,378 (16,278)	838	5.1	203	1.2
Missing	46 (45)	13,628 (13,601)	791	5.8	207	1.5
% of population with gestational age >56 days						
>25%	16	8,579	506	5.9	87	1.0
≤25%	84 (82)	33,123 (32,996)	1,506	4.5	380	1.2
Missing	20 (19)	3,826 (3,575)	180	4.7	32	0.9
Misoprostol dose and route[d]						
200 mcg oral	1	4	1	25.0	1	25.0
400 mcg buccal	1	272	8	2.9	4	1.5
400 mcg oral	21	9,299	737	7.9	215	2.3
400 mcg sublingual	10	2,875	126	4.4	30	1.0
400 mcg vaginal	5	1,116	86	7.7	20	1.8
600 mcg oral	9	1,608	132	8.2	22	1.4
600 mcg sublingual	4	540	7	1.3	0	0.0
600 mcg vaginal	1	242	18	7.4	9	3.7
≥800 mcg buccal	6	2,205	71	3.2	16	0.7
≥800 mcg oral	10 (8)	2449 (2,322)	158	6.5	38	1.6
≥800 mcg sublingual	4	1,003	52	5.2	5	0.5
≥800 mcg vaginal	43 (42)	19,210 (18,959)	653	3.4	99	0.5
Varied or missing	5	4,705	143	3.0	40	0.9

[a] Number in all groups (number in groups in which ongoing pregnancy was reported, if different).
[b] Percent of subjects in trial groups reporting outcome.
[c] Dates of mifepristone registration in each country obtained from www.gynuity.org, accessed 17 August 2011. Coded as "before mifepristone registration" if the year that data collection ended was not more than 1 year after the registration year and otherwise as "after" if the data collection started in the year after the registration year or later. This variable is missing for trials conducted in multiple countries and studies that provided insufficient information about dates of data collection.
[d] Total misoprostol dose and route of first dose if multiple doses were administered.

Table 2
Associations between trial and population characteristics and rates of medical abortion failure and ongoing pregnancy[a]

	Medical abortion failure rate		Ongoing pregnancy rate	
	OR	(95% CI)	OR	(95% CI)
Group size: each increase of 500 women	1.0	(0.9–1.1)	1.0	(0.9–1.2)
Study design				
Randomized trial	1.1	(0.9–1.4)	1.2	(0.8–1.9)
Cohort or case-series study	1		1	
Data collection dates[b]				
Before mifepristone registration	1.2	(0.8–1.6)	0.7	(0.3–1.5)
After mifepristone registration	1		1	
Geographic region				
Europe	0.7	(0.4–1.3)	0.6	(0.3–1.3)
Americas	1		1	
Other	1.0	(0.7–1.5)	0.9	(0.4–1.7)
Number of study sites				
1	0.9	(0.7–1.3)	0.8	(0.5–1.2)
>1	1		1	
Prescribed interval between mifepristone and misoprostol				
<23 h	2.1	(1.4–3.2)	1.2	(0.5–2.9)
23-72 h	1		1	
Protocol specified additional dose of misoprostol for selected subjects				
Yes	0.7	(0.5–1.1)	1.1	(0.6–2.0)
No	1		1	
Protocol required all subjects to take misoprostol in clinic				
No	0.9	(0.7–1.2)	1.3	(0.7–2.7)
Yes	1		1	
Minimum scheduled follow-up interval				
<1 week	0.9	(0.7–1.2)	1.4	(0.6–3.0)
≥1 week	1		1	
Protocol required ultrasound to assess failure				
Never or in selected subjects	1.1	(0.7–1.7)	2.0	(1.0–3.9)
In all subjects	1		1	
% of population who were nulliparous				
>50%	1.1	(0.9–1.4)	0.8	(0.5–1.3)
≤50%	1		1	
% of population with gestational age >56 days				
>25%	1.5	(1.1–2.0)	0.9	(0.6–1.6)
≤25%	1		1	
Lost to follow-up %: each 1% increase	0.6	(0.0–25.2)	5.9	(0.0–4,524)
Misoprostol route by dose[c]				
400 mcg				
Sublingual	0.5	(0.4–0.7)	0.5	(0.3–0.7)
Buccal	0.5	(0.3–0.8)	0.5	(0.2–1.0)
Vaginal	0.6	(0.4–1.0)	0.7	(0.4–1.3)
Oral	1		1	
600 mcg				
Sublingual	0.2	(0.1–0.3)	–	
Vaginal	0.5	(0.2–0.9)	4.6	(1.2–18.0)
Oral	1		1	
≥800 mcg				
Sublingual	0.6	(0.4–0.9)	0.3	(0.2–0.6)
Buccal	0.6	(0.4–0.9)	0.3	(0.2–0.6)
Vaginal	0.6	(0.5–0.8)	0.4	(0.3–0.6)
Oral	1		1	
Misoprostol dose by route[c]				
Oral route				
≥800 mcg	0.7	(0.5–0.9)	0.6	(0.3–1.1)
600 mcg	0.9	(0.7–1.3)	0.6	(0.3–1.2)
400 mcg	1		1	
Vaginal route				
≥800 mcg	0.6	(0.4–0.9)	0.3	(0.2–0.6)
600 mcg	0.7	(0.4–1.2)	3.6	(1.2–11.5)
400 mcg	1		1	
Sublingual route				
≥800 mcg	0.8	(0.6–1.1)	0.4	(0.2–0.8)
600 mcg	0.3	(0.2–0.6)	–	
400 mcg	1		1	
Buccal route				
≥800 mcg	0.7	(0.5–1.2)	0.4	(0.2–0.8)
400 mcg	1		1	

[a] Analyses of medical abortion failure used 119 trial groups; analyses of ongoing pregnancy used 112 trial groups (see text).

[b] Dates of mifepristone registration in each country obtained from www.gynuity.org, accessed 17 August 2011. Coded as "before mifepristone registration" if the year that data collection ended was not more than 1 year after the registration year and otherwise as "after" if the data collection started in the year after the registration year or later. This variable is missing for trials conducted in multiple countries and studies that provided insufficient information about dates of data collection.

[c] Total misoprostol dose and route of first dose if multiple doses were administered.

pregnancy or other conditions unrelated to the abortion. Forty-five women (0.1%) received blood transfusions. Hospitalizations and blood transfusions were less common in trials in which women were permitted to take the misoprostol at home (0.15% and 0.08%, respectively) than in trials in which clinic administration was required (0.45% and 0.14%, respectively).

4. Discussion

Medical abortion using mifepristone 200 mg followed by misoprostol in the first 63 days of gestation is remarkably effective and safe. In trials that together included more than 45,000 women conducted in disparate settings over nearly two decades using a variety of regimens and treatment protocols, fewer than 5% of subjects required surgery to complete termination of the pregnancy. The proportion who had ongoing pregnancy at follow-up — the outcome of greatest concern to clinicians — was 1.1%. Serious complications requiring hospitalization or transfusion occurred in less than 0.4% of patients.

Some random variability in results is expected in any collection of research studies. However, our analysis found strong evidence of statistical heterogeneity across trials in both medical abortion failure rates and rates of ongoing pregnancy. This finding indicates that the non-uniformity in these outcomes was due to underlying differences among the studies rather than simply to chance. We identified a few practices that were associated with a lower risk of medical

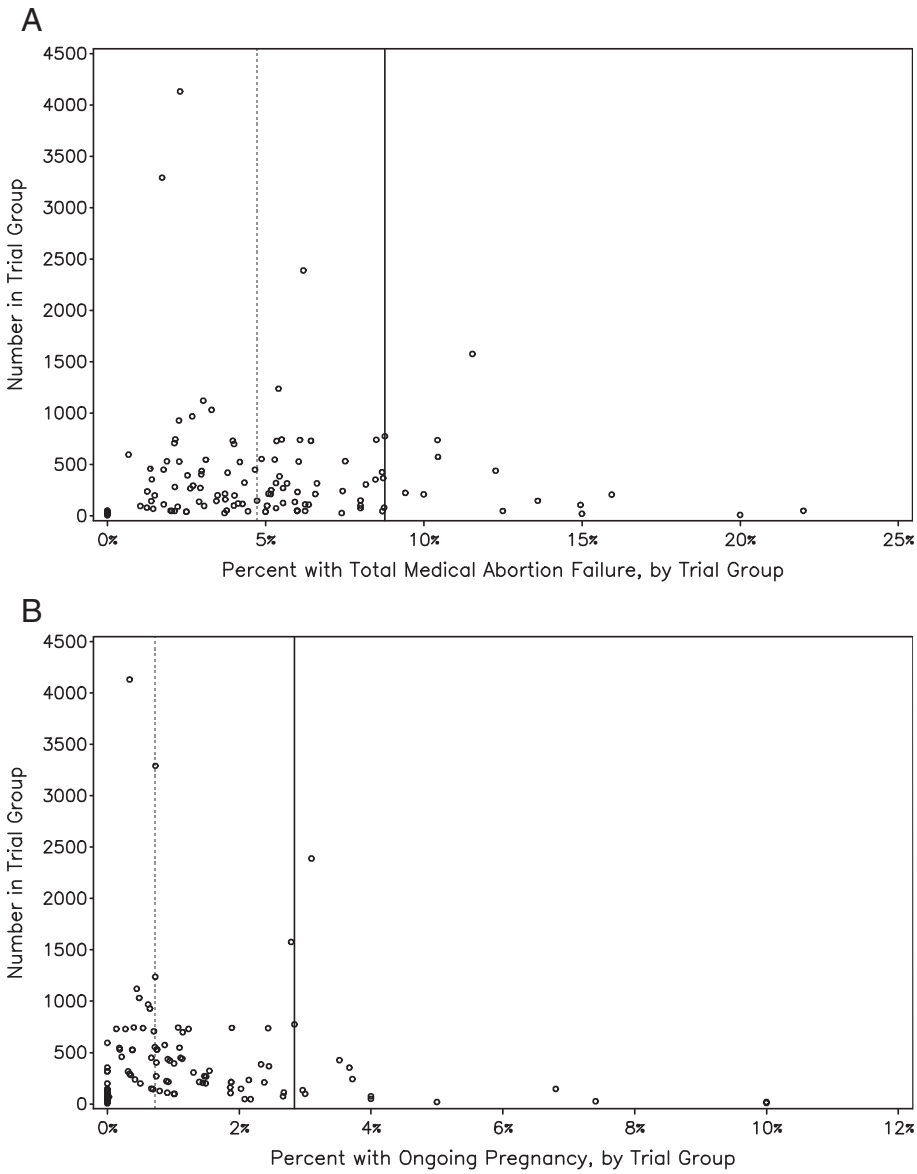

Fig. 1. Size of trial group by percentage of subjects with medical abortion failure and ongoing pregnancy at follow-up assessment. 50% of trial groups are to the left of dashed line; 90% of subjects are to the left of solid line. One group of 4 subjects with one ongoing pregnancy is omitted from both panels; panel A also omits one group of 20 subjects with 8 medical abortion failures. (A) Medical abortion failure. (B) Ongoing pregnancy.

abortion failure: an interval of at least 24 h between the mifepristone and misoprostol, use of misoprostol doses higher than 400 mcg and administration of misoprostol by a buccal, vaginal, or sublingual rather than oral route. The last of these is consistent with the conclusions of a recent Cochrane review of first trimester medical abortion, which included only randomized trials [89]. As cited previously, most current guidelines for medical abortion incorporate these practices.

We also found slightly higher risks of medical abortion failure in groups that had a high proportion (>25%) of women in the 9th week of pregnancy: after adjustment for other factors, these groups overall had a 50% higher odds of medical abortion failure. However, we did not find a higher risk of ongoing pregnancy in these groups. Given the low overall risk of medical abortion failure and the relative ease of treating failure using surgical evacuation (which would have been the treatment for all subjects had medical abortion not been attempted), offering medical abortion to women at this gestational age seems reasonable.

We observed no significant association between abortion failure rates and the timing of the follow-up evaluation. The data thus are inconclusive with respect to the theory that high surgical intervention rates are in part attributable to impatience among providers and patients [90]. Moreover, although routine ultrasound evaluation at follow-up was

associated with a lower risk of diagnosis of ongoing pregnancy, we found no evidence for or against an effect of this practice on overall medical abortion failure rates — that is, the need for surgical intervention. Prompt confirmation of completeness of the abortion and clinical assessment without routine ultrasound may enhance women's satisfaction with the procedure.

We found no evidence that allowing women to take the misoprostol at home increased the rates of abortion failure or serious complications. Most women prefer this option [90], and it is presumably substantially more efficient for the health care system than requiring patients to return to the provider for administration of the prostaglandin. This requirement, which is law in some countries such as the United Kingdom [7], thus is unjustifiable and should be abandoned.

This analysis has some limitations. Our data allowed us to explore heterogeneity across patient populations, not across individual patients; therefore, we may have missed some associations that would have been identified in an individual-level analysis. Missing data on some characteristics of some groups may have affected the direction or strength of associations, and we acknowledge that including "missing" categories for predictor variables would not have been preferred had we analyzed individual-level data [91]. Because none of the 540 women in the four groups that received misoprostol 600 mcg sublingual had ongoing pregnancies, these groups were excluded for technical reasons from our regression analysis of that outcome; this omission may have affected the apparent associations of other factors with ongoing pregnancy. Undetected publication bias is always possible; we attempted to minimize this problem by consulting experts likely to be aware of relevant unpublished studies through their many years of work in this field. We had information on only selected characteristics of the studies, and unmeasured confounding was not controlled by randomization. We evaluated many potential associations without any adjustment for multiple comparisons; however, we fit only a single model for each outcome. In 5 of the 120 trial groups, at least 10% of subjects were lost to follow-up. However, the overall follow-up success was high, and even if we made the extreme assumption that all the subjects who were lost had abortion failures, the overall medical abortion failure rate would still have been low (8.3%).

The large quantity of data presented in this review demonstrates that currently used medical abortion regimens are so effective and safe that additional research aimed at further clinical improvement will have little public health benefit. Future investigations should focus on service delivery issues: increasing access, reducing cost, enhancing patient comfort and ensuring availability of ancillary services such as contraception that can aid women in reaching their reproductive goals.

Acknowledgments

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Reprints will not be available.

Appendix. Selected data from 120 trial groups

Ref	Country	Date	Dose/route	Delay	Treated	Evaluable	Medical abortion failure		Ongoing pregnancy	
					N	N	N	%	N	%
11	Ethiopia	2009	800 mg vag	48	251	251	13	5.2	n/a	n/a
87	USA	2006–2007	800 mg buc	24 to 36	482	421	16	3.8	4	1.0
87	USA	2006–2007	800 mg oral	24 to 36	480	426	37	8.7	15	3.5
86	Nepal	2009–2010	800 mg vag	48	1077	1032	34	3.3	5	0.5
85	Multiple	2003–2005	800 mg vag	48	545	532	40	7.5	4	0.8
85	Multiple	2003–2005	800 mg vag	24	542	529	32	6.0	4	0.8
84	Multiple	2007–2008	400 mg SL	24	751	741	63	8.5	14	1.9
84	Multiple	2007–2008	400 mg vag	24	751	738	77	10.4	18	2.4
84	Multiple	2007–2008	800 mg SL	24	752	739	45	6.1	4	0.5
84	Multiple	2007–2008	800 mg vag	24	751	744	41	5.5	8	1.1
83	Multiple	1998–2000	800 mg oral then 400 mg oral bid×7 d	36 to 48	740	730	47	6.4	9	1.2
83	Multiple	1998–2000	800 mg vag then 400 mg oral bid×7 d	36 to 48	741	731	29	4.0	1	0.1
83	Multiple	1998–2000	800 mg vag	36 to 48	738	729	39	5.3	2	0.3
82	Taiwan	2000	400 mg, route n/a	48	20	20	8	40.0	1	5.0
82	Taiwan	2000	600 mg, route n/a	48	20	20	3	15.0	2	10.0
81	N. Korea	2007–2008	400 mg SL	48	199	199	8	4.0	0	0.0
80	UK	n/a	600 mg oral	48	100	100	8	8.0	3	3.0
79	China	n/a	400 mg vag	48	100	98	3	3.1	1	1.0

(*continued*)

Ref	Country	Date	Dose/route	Delay	Treated	Evaluable	Medical abortion failure		Ongoing pregnancy	
					N	N	N	%	N	%
78	China	n/a	800 mg SL	48	100	99	5	5.1	1	1.0
77	China	n/a	800 mg oral then 400 mg oral bid×7 d	48	50	48	3	6.3	0	0.0
77	China	n/a	800 mg vag then 400 mg oral bid×7 d	48	50	50	3	6.0	2	4.0
77	China	n/a	800 mg vag	48	50	47	1	2.1	0	0.0
76	China	n/a	400 mg vag	48	200	200	3	1.5	1	0.5
75	China	n/a	400 mg vag then 400 mg oral bid×14 d	48	20	20	0	0.0	0	0.0
74	China	n/a	800 mg SL	48	112	112	2	1.8	0	0.0
74	China	n/a	800 mg vag	48	112	112	7	6.3	3	2.7
73	India	n/a	600 mg oral	48	51	50	11	22.0	0	0.0
14	India	n/a	200 mg SL×3 q6h	24	40	40	0	0.0	0	0.0
72	Nepal	2009	600 mg oral	48	50	50	3	6.0	0	0.0
71	USA	2001–2003	400 mg oral	48	376	354	30	8.5	13	3.7
70	Canada	2001	400 mg oral	24 to 48	319	319	17	5.3	0	0.0
70	Canada	2001	600 mg oral	24 to 48	319	317	21	6.6	1	0.3
70	Canada	2001	800 mg vag	24 to 48	318	317	18	5.7	0	0.0
69	USA	n/a	800 mg vag	0	80	80	7	8.8	0	0.0
66	USA	1998–1999	800 mg vag	24	745	708	15	2.1	5	0.7
66	USA	1998–1999	800 mg vag	72	772	699	28	4.0	8	1.1
66	USA	1998–1999	800 mg vag	48	778	745	16	2.1	3	0.4
67	USA	2000	400 mg oral×2 q2h	48	279	270	15	5.6	2	0.7
67	USA	2000	400 mg oral	48	228	223	21	9.4	2	0.9
67	USA	2000	800 mg vag	48	538	528	12	2.3	2	0.4
68	USA	1999–2000	400 mg oral×2 q2h	24	561	548	29	5.3	6	1.1
68	USA	1999–2000	800 mg vag	24	607	596	4	0.7	0	0.0
65	USA	1997–1999	800 mg vag	48	1137	1121	34	3.0	5	0.4
64	USA	1999	800 mg vag	48	30	27	2	7.4	2	7.4
63	USA	1996–1997	800 mg vag	48	933	928	21	2.3	6	0.6
62	China	n/a	600 mg oral	48	149	148	7	4.7	3	2.0
61	Moldova	2005–2006	400 mg oral	24	240	233	14	6.0	5	2.1
61	Moldova	2005–2006	400 mg SL	24	240	238	3	1.3	1	0.4
60	Moldova	2007–2009	400 mg buc	24	277	272	8	2.9	4	1.5
60	Moldova	2007–2009	400 mg SL	24	273	267	7	2.6	4	1.5
59	USA	n/a	800 mg vag	6 to 8	40	40	1	2.5	0	0.0
58	USA	1998–2000	800 mg vag	48	28	28	0	0.0	0	0.0
57	USA	2008	800 mg vag or buc	0 to 72	139	135	8	5.9	4	3.0
10	UK	n/a	200 mg oral	48	4	4	1	25.0	1	25.0
10	UK	n/a	400 mg oral	48	10	10	2	20.0	1	10.0
10	UK	n/a	600 mg oral	48	7	7	0	0.0	0	0.0
56	Vietnam	2001	400 mg oral	48	1601	1577	182	11.5	44	2.8
55	Vietnam	2007–2008	800 mg buc	24	201	201	7	3.5	3	1.5
54	USA	2003	800 mg vag	0	40	40	2	5.0	0	0.0
53	India	2004–2005	400 mg SL	48	149	144	2	1.4	1	0.7
52	USA	2001–2004	800 mg buc	24 to 48	223	216	11	5.1	2	0.9
52	USA	2001–2004	800 mg vag	24 to 48	219	213	14	6.6	4	1.9
51	UK	n/a	600 mg oral	48	110	110	7	6.4	1	0.9
50	USA	2006	800 mg buc	0	120	117	5	4.3	0	0.0
15	Taiwan	2002–2005	600 mg SL	48	356	355	5	1.4	0	0.0
49	Taiwan	2005–2009	600 mg vag	0	254	242	18	7.4	9	3.7
48	Taiwan	2005–2006	800 mg vag	0	90	90	2	2.2	0	0.0
47	Sweden	2004–2007	800 mg vag	36 to 48	395	395	10	2.5	4	1.0
46	Nepal	2007–2008	400 mg oral	48	400	367	32	8.7	9	2.5
45	USA	n/a	800 mg vag	48	125	121	5	4.1	0	0.0
18	Finland	2000–2002	400 or 800 mg vag	24, 48, or 72	1289	1238	67	5.4	9	0.7
16	UK	2002–2003	600 mg SL	36 to 48	49	49	1	2.0	0	0.0
44	UK	2002–2003	600 mg SL then 400 mg SL 3 h later	36 to 48	57	53	0	0.0	0	0.0
44	UK	2002–2003	800 mg vag then 400 mg vag 3 h later	36 to 48	72	69	1	1.4	0	0.0
17	UK	n/a	600 mg SL	36 to 48	96	96	1	1.0	0	0.0
17	UK	n/a	800 mg vag	36 to 48	53	53	2	3.8	0	0.0
43	Tunisia	2000–2001	400 mg oral	48	332	323	14	4.3	5	1.5

(*continued on next page*)

(*continued*)

Ref	Country	Date	Dose/route	Delay	Treated	Evaluable	Medical abortion failure		Ongoing pregnancy	
					N	N	N	%	N	%
42	UK	2003–2005	800 mg vag	6	210	210	21	10.0	5	2.4
42	UK	2003–2005	800 mg vag	36 to 48	215	215	8	3.7	3	1.4
41	India	2009–2010	400 mg vag	0	40	40	2	5.0	0	0.0
41	India	2009–2010	400 mg vag	24	40	40	1	2.5	0	0.0
40	USA	n/a	800 mg vag	6 to 8	80	80	1	1.3	0	0.0
39	Tunisia	2007–2008	400 mg oral	48	126	126	7	5.6	1	0.8
38	Vietnam, Tunisia	1997–1998	400 mg oral	48	315	306	25	8.2	4	1.3
37	UK	n/a	400 mg oral×2 q2h	36 to 48	75	75	6	8.0	3	4.0
37	UK	n/a	800 mg oral	36 to 48	75	75	4	5.3	2	2.7
36	USA	1998–1999	800 mg vag	24, 48, or 72	138	138	4	2.9	0	0.0
8	India	n/a	400 mg oral	24	48	48	6	12.5	1	2.1
8	India	n/a	400 mg SL	24	45	45	2	4.4	0	0.0
35	India	n/a	800 mg vag	48	50	50	1	2.0	0	0.0
34	USA	2004–2006	800 mg vag	0	567	554	27	4.9	4	0.7
34	USA	2004–2006	800 mg vag	23 to 25	561	546	17	3.1	1	0.2
33	USA	2000–2001	800 mg vag	24 to 48	148	145	5	3.4	0	0.0
9	USA	2002–2003	800 mg vag	23 to 25	539	531	10	1.9	1	0.2
9	USA	2002–2003	800 mg vag	6 to 8	539	525	22	4.2	2	0.4
32	India	2004–2005	400 mg oral×2 q3h	48	150	150	12	8.0	1	0.7
32	India	2004–2005	400 mg oral	48	150	147	20	13.6	10	6.8
12	France	2001–2002	400 mg oral×2 q24h	24	30	27	1	3.7	n/a	n/a
31	USA	2005–2007	800 mg vag, oral or buc	6 to 72	4087	3292	57	1.7	24	0.7
30	Nepal	2004–2005	400 mg oral	48	112	107	16	15.0	2	1.9
29	Nepal	2005–2006	800 mg vag	48	50	50	3	6.0	0	0.0
27	Albania	2001–2003	400 mg oral	48	409	404	12	3.0	3	0.7
28	India	2007–2008	400 mg oral	48	599	574	60	10.5	5	0.9
26	Curacao	2009–2010	800 mg buc	24 to 36	304	281	6	2.1	1	0.4
25	Tunisia	1999–2000	400 mg oral	48	222	213	11	5.2	4	1.9
24	India	n/a	600 mg oral	48	450	440	54	12.3	5	1.1
23	UK	n/a	800 mg vag	48	500	459	6	1.3	1	0.2
22	UK	n/a	600 mg oral	48	400	386	21	5.4	9	2.3
21	UK	1994–2001	800 mg vag	36 to 48	4132	4132	95	2.3	14	0.3
13	India	2003–2004	800 mg oral	24	100	100	4	4.0	n/a	n/a
20	Turkey	2004–2005	400 mg oral	48	161	161	6	3.7	3	1.9
20	Turkey	2004–2005	400 mg SL	48	46	46	4	8.7	1	2.2
19	Turkey	2000–2001	400 mg oral	48	208	207	33	15.9	3	1.4
88	multiple	n/a	400 mg oral	48	792	775	68	8.8	22	2.8
U1	Mexico	2010–2011	800 mg buc	24 to 48	998	969	26	2.7	6	0.6
U2	Ukraine	2005–2007	400 mg oral	48	439	436	13	3.0	4	0.9
U3	Uzbekistan	2008–2009	400 mg SL	24	450	450	21	4.7	5	1.1
U4	Moldova	2007	400 mg SL	24	300	295	8	2.7	1	0.3
U5	Vietnam	2006–2008	400 mg oral	48	2400	2389	148	6.2	74	3.1
U6	Ukraine	2007–2009	400 mg SL	24	450	450	8	1.8	3	0.7

n/a: data not available.
Ref indicates reference number. U1-U6 are unpublished studies.
Date indicates dates of data collection.
Dose/route indicates dose and route of misoprostol. SL, sublingual; vag, vaginal; buc, buccal; q, every; h, hours; d, days.
Delay indicates prescribed interval between mifepristone and misoprostol, in hours.
Evaluable indicates number of subjects with known abortion outcome.
Failures indicates number and percent of evaluable subjects with abortion failure.
Ongoing pregnancy indicates number and percent of evaluable subjects with abortion failures that were ongoing pregnancies.

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EXHIBIT B-5

APPENDIX TO PETITIONER GENBIOPRO, INC.'S CITIZEN PETITION DATED JULY 3, 2025[1]

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Original research article

TelAbortion: evaluation of a direct to patient telemedicine abortion service in the United States☆,☆☆,★,★★

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ABSTRACT

Objectives: To evaluate the safety, feasibility, and acceptability of a direct-to-patient telemedicine service that enabled people to obtain medical abortion without visiting an abortion provider in person.
Study design: We offered the service in five states. Each participant had a videoconference with a study clinician and had pre-treatment laboratory tests and ultrasound at facilities of her choice. If the participant was eligible for medical abortion, the clinician sent a package containing mifepristone, misoprostol, and instructions to her by mail. After taking the medications, the participant obtained follow-up tests and had a follow-up consultation with the clinician by telephone or videoconference to evaluate abortion completeness. The analysis was descriptive.
Results: Over 32 months, we conducted 433 study screenings and shipped 248 packages. The median interval between screening and mailing was 7 days (91st percentile 17 days), and no participant took the mifepristone at ≫71 days of gestation. We ascertained abortion outcomes of 190/248 package recipients (77%): 177/190 (93%) had complete abortion without a procedure. Of the 217/248 package recipients who provided meaningful follow-up data (88%), one was hospitalized for postoperative seizure and another for excessive bleeding, and 27 had other unscheduled clinical encounters, 12 of which resulted in no treatment. A total of 159/248 participants who received packages (64%) completed satisfaction questionnaires at study exit; all were satisfied with the service.
Conclusions: This direct-to-patient telemedicine abortion service was safe, effective, efficient, and satisfactory. The model has the potential to increase abortion access by enhancing the reach of providers and by offering people a new option for obtaining care conveniently and privately.

☆ TelAbortion Project Team, 21 May 2019

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Implications: Provision of medical abortion by direct-to-patient telemedicine and mail has the potential to increase abortion access by increasing the reach of providers and by offering people the option of obtaining abortion care without an in-person visit to an abortion provider.

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1. Introduction

Access to abortion is limited for many people in the United States. The number of clinics providing this service declined by 6% between 2011 and 2014 [1], and in 2017, 27 cities with populations of 50,000 or more had no abortion clinic within a 100 mile radius [2]. Even people who live near a clinic may have difficulty attending in person due to scheduling conflicts, long wait times for appointments, the high cost of travel, child care, and lost wages [3], concerns about confidentiality, and anticipated harassment at clinics [4].

In response to this problem, we launched the TelAbortion Project in 2016 to provide medical abortion using telemedicine. Unlike other telemedicine abortion services in our country [5–7], the TelAbortion model does not require the patient to present in person to a facility that provides abortion: rather, she obtains screening tests at laboratories and radiology offices and then communicates with the abortion provider by videoconference. If she is eligible for treatment, the provider dispenses the abortion medications by mail [8]. This direct-to-patient approach has been successfully instituted in international settings [9–15] but has been inhibited in the United States because the restriction on mifepristone distribution imposed by the Food and Drug Administration (FDA) is interpreted as prohibiting mailing [16]. Consequently, we implemented TelAbortion as a research study conducted under an Investigational New Drug application. The specific goals of the study are to assess the safety, acceptability, and feasibility of the service. Here, we provide data from the first 32 months of the project.

2. Methods

To date, the project has been conducted at five institutions: Choices Women's Medical Center in New York, the University of Hawaii (UH), Oregon Health & Science University (OHSU), Maine Family Planning (MFP), and Planned Parenthood Columbia Willamette (PPCW) in Oregon. These sites initiated enrollment in the order listed over 25 months. Choices stopped recruitment in mid-2017 due to slow accrual; the other sites are still enrolling. Each institution offered TelAbortions to people in its home state, and OHSU and MFP also served Washington and New York, respectively. We selected the six study states after confirming that they had no laws prohibiting the service.

We publicized the study using multiple approaches, including a study website (www.telabortion.org), outreach to clinicians, media reports, Google advertising, and strategically placed posters and pamphlets. In addition, sites provided information about the study to people contacting them for abortion appointments.

After a screening consultation with a study coordinator by telephone, each interested person had a "TelEvaluation" by videoconference with a study clinician who provided standard pre-abortion counseling and explained the study procedures, including expected costs. The participant signed the study informed consent form and other documents electronically using commercially available secure software. The clinician recorded relevant demographic and medical information. If the participant had not already had an ultrasound and Rh typing, the clinician assisted her in identifying facilities where she could conveniently obtain those tests and have the results sent to the study clinician. The participant and the clinician agreed on a plan for evaluating abortion outcome using ultrasound, serum HCG tests before and after mifepristone ingestion, or urine pregnancy test.

A person was eligible for medical abortion through the study if she was located in a project state where the study clinician was licensed, if she had no contraindications to medical abortion (intrauterine device in place, chronic adrenal failure, long-term corticosteroid therapy, allergy to mifepristone, misoprostol or other prostaglandin, hemorrhagic disorder, current use of anticoagulant therapy, or inherited porphyria), if her ultrasound showed an intrauterine pregnancy, and if the clinician judged that she would be able to receive and take the mifepristone at ≤70 days of gestation. Choices excluded people with negative Rh blood type because of concerns about ensuring provision of Rh immune globulin. OHSU and PPCW excluded people ≪18 years old and UH excluded people ≪14 years old.

If the participant was eligible and wished to continue with the abortion, the site sent to her by overnight or regular tracked mail a package containing one tablet of mifepristone 200 mg and eight tablets of misoprostol 200 mcg. Analgesics, antibiotics, anti-emetics, and contraceptives were included or prescribed at the discretion of the site clinician. The package also included an instruction sheet that described how to use the medications, expected symptoms and side effects, the follow-up plan, and emergency procedures. The abortifacient regimen was mifepristone 200 mg followed by misoprostol 800 mcg within 48 h administered buccally or vaginally per accepted practices at the sites. The participant was instructed to take the other four misoprostol tablets if no bleeding occurred within 24 h.

The site scheduled a follow-up contact with the study clinician for 7–14 days after the package was mailed. At this contact, the clinician interviewed the participant to assess symptoms, adverse events, and other relevant information. If further care was indicated, the clinician referred her to an appropriate facility. If a participant had not had the planned follow-up tests by 3–4 weeks after mifepristone ingestion, the clinician instructed her to obtain and perform a home urine pregnancy test. Once the clinician determined that the abortion was complete (i.e., she needed no further care related to the abortion), staff administered a satisfaction questionnaire by telephone.

Throughout the study, participants or their insurance were responsible for paying for tests and treatments obtained outside the study site. Initially, the study paid for all care and medications provided directly by the study sites; once we had gained some experience with the service, we amended the protocol to require that participants or their insurance pay standard charges for these services. Because sites initiated enrollment at different times, this amendment affected some participants at UH and all at MFP and PPCW; it was not implemented at Choices or at OHSU as of this analysis. Each participant at every site received $50 after completing the exit interview.

We initially planned to enroll a total of 50 participants, a number determined by funding considerations. When additional support became available we continued the project to obtain more generalizable data.

Sites sent paper data forms to Gynuity Health Projects for entry into a central database. The analysis was descriptive. We counted each enrollment as an independent participant. We defined an adverse event as serious if it was fatal, life-threatening or resulted in hospitalization, transfusion, or significant disability. An unplanned clinical encounter was any visit to a clinician that was not planned before the study package was mailed. We defined meaningful follow-up as ascertainment of ingestion of abortion medications, abortion outcome, or unplanned clinical encounters.

The UH Office of Research Compliance Human Studies Program, OHSU Institutional Review Board, and Advarra Institutional Review

Board all approved the protocol. We registered the study at clinicaltrials.gov (NCT02513043).

3. Results

Between May 2016 and December 2018 (79 site-months), we conducted 433 screenings (Fig. 1), including three with people who had enrolled in a prior pregnancy. Most screened people (187; 43%) had learned about the study from the study clinic itself through the clinic's website or appointments personnel; the rest were referred by other providers, internet searches, the study website, media articles, or friends. Of the 433 people, 363 (84%) scheduled TelEvaluations with study clinicians. Most (322; 89%) cited speed, convenience, lack of local options, or cost as reasons for interest, including 47 (13%) who specifically mentioned cost. Seventy-eight (21%) said that they wanted privacy or to avoid harassment.

A total of 165 people (38%) either declined to schedule TelEvaluations or did not present for the appointment. We ascertained reasons from 98 (59%). The most common were concerns about the logistics or time involved (46%), the decision to have a medical abortion (18%), or cost (14%); 23% were ineligible for medical abortion through the study. In Hawaii, implementation of the protocol amendment for billing had no apparent effect on uptake of TelEvaluations over time.

The 268 participants who had TelEvaluations were diverse (Table 1). In the continental states, 52% of participants lived ≥50 miles from their study site, and 29% lived ≥150 miles distant. Of 59 participants enrolled by OHSU, 27 (46%) lived in Washington state, and one of the 30 participants enrolled by MFP lived in New York. In Hawaii, ≫60% of participants lived on an island without an abortion clinic.

We sent study packages to 248 (93%) of the 268 participants who had TelEvaluations (Fig. 1). Of the other 20, seven miscarried shortly after their TelEvaluations, three decided against abortion, two would not have received the package by 70 days of gestation, seven had other reasons, and one did not provide a reason.

The characteristics of the 248 participants who were sent packages were similar to those of the screened population (Table 1). All met eligibility criteria, and all received the package sent. Of the 207 participants (83%) who reported having taken at least one abortifacient medication (Fig. 1), 187 reported the date of ingestion of mifepristone; all of these participants took that medication on or before 70 days of gestation except two who took it at 71 days.

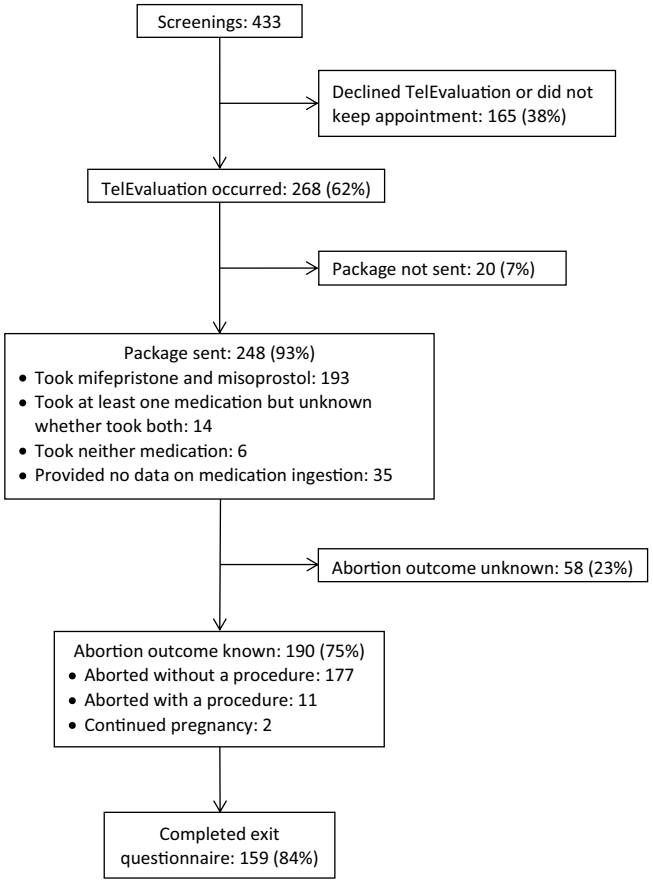

Fig. 1. Flow of participants through TelAbortion study*.

Table 1
Characteristics of TelAbortion study participants who had TelEvaluations, received study packages, and had known abortion outcomes

	Had TelEvaluation N=268		Received study package N=248		Had known abortion outcome N=190	
	n	%	n	%		
Study site						
Choices Women's Medical Center	6	2%	4	2%	4	2%
University of Hawaii	161	60%	151	61%	115	62%
Oregon Health & Science University	59	22%	54	22%	43	23%
Maine Family Planning	30	11%	27	11%	17	9%
Planned Parenthood Columbia Willamette	12	4%	12	5%	6	5%
Age						
15–24 years	66	25%	63	25%	48	25%
25–34 years	144	54%	135	54%	105	55%
35–45 years	58	22%	50	20%	33	19%
Highest level of education completed						
Less than HS	10	4%	8	3%	2	1%
HS/GED	64	24%	61	25%	47	25%
More than HS	174	65%	160	65%	127	67%
Missing	20	7%	19	8%	14	7%
Number of previous pregnancies						
0	67	25%	62	25%	52	27%
1	64	24%	60	24%	42	22%
≫ = 2	137	51%	126	51%	96	51%
Number of previous medical abortions						
0	226	84%	211	85%	165	87%
1	35	13%	33	13%	22	12%
≫ = 2	6	2%	4	2%	3	2%
missing	1	0.4%	0		0	
Rh type						
pos	244	91%	232	94%	178	94%
neg	18	7%	16	6%	12	6%
unknown	6	2%	0		0	
Gestational age at TelEvaluation						
26–35 days	26	10%	26	10%	20	11%
36–63 days	208	78%	202	81%	157	83%
64–69 days	22	8%	20	8%	13	7%
missing	12	4%	0		0	
State of residence						
Hawaii	161	60%	151	61%	117	62%
Oregon	44	16%	41	17%	32	17%
Washington	27	10%	25	10%	20	11%
Maine	29	11%	26	10%	16	9%
New York	7	3%	5	2%	5	3%
Distance of residence from provider (OR, WA, ME, NY)						
1–9 mi	15	14%	14	14%	12	16%
10–49 mi	36	34%	34	35%	22	30%
50–99 mi	15	14%	12	12%	9	12%
100–149 mi	10	9%	9	9%	8	11%
≫ = 150 mi	31	29%	28	29%	22	30%
Hawaiian island of residence						
Oahu	52	32%	49	32%	39	33%
Hawaii	59	37%	53	35%	40	34%
Maui, Molokai, or Lanai	4	2%	4	3%	3	3%
Kauai or Niihau	46	29%	45	30%	35	30%
Study paid for services provided by study site						
yes	141	53%	128	52%	100	53%
no	127	47%	120	48%	90	47%

We were unable to ascertain abortion outcomes for 58 package recipients (23%), and two participants decided to continue their pregnancies and did not take the mifepristone. Of the other 188, 177 (94%), including the three who had previously enrolled, aborted completely without a procedure. All but four of these 177 reported having taken at least one abortifacient medication. Tests used in assessment of completeness included ultrasound in 86 participants (49%), 80% decline in serum HCG concentration in 58 (33%), and urine pregnancy tests in 36 (20%). Five participants (3%) were assessed using only other means. Eleven participants (6%) had uterine evacuation procedures, of whom two had not taken the mifepristone, four had ongoing pregnancies after mifepristone ingestion as reported by the provider, and five had bleeding and/or incomplete abortions.

Eleven of the 16 Rh-negative participants who received packages obtained Rh immune globulin, three opted out of this prophylaxis before package shipment, one did not keep an appointment made for her to receive it, and one did not provide relevant information.

A total of 217 participants had meaningful follow-up after package shipment. Two of these (1%) reported serious adverse events. One was hospitalized because of a seizure after an aspiration performed for bleeding. The second was hospitalized because of severe anemia (hemoglobin of 6.3 g/dl) 7 days after mifepristone ingestion at 56 days of gestation; she was diagnosed with complete abortion but received a transfusion. We judged that neither event would have been averted had the abortion medications been provided in person. Sixteen other participants (7%) attended an emergency department or urgent care center: 14 for bleeding and/or pain, one for dizziness, and one to get Rh immune globulin. Two of these 16 participants had aspirations, one had products of conception manually removed from her cervical os, three received medication for pain and/or nausea, one was treated for a urinary tract infection, and the other nine received no medical treatment. Eleven participants (5%) had clinic or office visits: eight had outpatient aspirations, and three had no reported medical treatment. All 29 participants reported having taken at least one abortifacient medication except one who miscarried without taking it, one who decided to have a uterine evacuation procedure, one who decided to continue the pregnancy, and two who did not provide data on medication ingestion. The proportion of participants with any unscheduled encounter was significantly more common among participants who lived ≥50 miles from the providing study site than among participants who lived closer (18% vs. 6%; p=.01).

Implementation of the service was efficient (Table 2). The median duration of TelEvaluations as recorded in 180 cases was 24 min (range 8–70 min). Nearly all packages (91%) were mailed within 17 days after the participant's initial contact with the study site (median 7 days). Of the 177 participants who had complete medical abortion without a procedure, more than half had their last evaluation test within 17 days after the package was mailed.

The 159 participants who completed the satisfaction questionnaire were highly satisfied with the service (Table 3). The most valued aspects of the service cited by respondents were convenience (77%), privacy (45%), and communication with the study staff (39%). The most disliked aspect of the service, cited by 21%, was inconvenience.

Table 3
Acceptability of TelAbortion to study participants at exit interview.

	N=159	
	n	%
Satisfaction		
Very satisfactory	127	80%
Satisfactory	32	20%
Satisfaction with speaking to provider remotely		
Very satisfactory	135	85%
Satisfactory	22	14%
Unsatisfactory	0	
Very unsatisfactory	1	1%
Don't know	1	1%
Experience getting pre abortion tests		
Easy or very easy	135	85%
Difficult or very difficult	22	14%
Missing	2	1%
Future preference		
TelAbortion	136	86%
In-person abortion	16	10%
No preference	7	4%
Would recommend TelAbortion to a friend		
Yes	152	96%
No	3	2%
Maybe	4	3%

4. Discussion

The TelAbortion Project is the first reported effort in the US to enable people to obtain abortion legally without an in-person visit to an abortion provider. The project has been highly successful. Participants received treatment appropriately and efficiently. Of participants with follow-up, 94% had complete abortion without a procedure, comparable to success rates of medical abortion provided in person [17]. No serious adverse events occurred that would have been avoided by an initial in-person encounter. All participants were satisfied with the service.

The proportion of participants who visited a hospital, emergency department, or urgent care center for abortion-related problems (8%) was higher than the proportion of 4% recently reported in an analysis of nearly 11,319 medical abortion patients in California [18]. Of note, our participants lived much farther from the abortion provider than did the California patients (≥100 miles: 38% in our continental states vs. 2.5% in California [19]), which has been associated with higher use of emergency departments following treatment [20]. In our study, half of these encounters did not entail any medical treatment. Their incidence could possibly be reduced by stronger encouragement to contact the TelAbortion provider for advice before seeking unplanned in-person care.

More than half of the participants lived more than 150 miles from the project sites or on a Hawaiian island without an abortion clinic, suggesting that the TelAbortion option filled an evident need. We were surprised to find, though, that many participants lived quite close: 14% of participants in the four continental states lived less than 10 miles from the site and nearly half within 50 miles. Most of our participants cited convenience or privacy as key reasons for interest in TelAbortion;

Table 2
Intervals between events in TelAbortion process.

	N	Days			
		Minimum	Median	90th percentile	Maximum
Screening to TelEvaluation	248	0	3	8	25
TelEvaluation to package shipment	248	0	2	11	35
Package shipment to package delivery	248	0	1	2	8
Package shipment to mifepristone ingestion*	187	1	2	6	12
Package shipment to final follow-up test†	166	1	16	41	127
Package shipment to exit questionnaire	159	7	24	67	280

†Among participants who aborted without a procedure; excludes 11 for whom date of final follow-up test was unavailable.
* Excludes 19 participants who reported having taken mifepristone but did not provide a date of ingestion.

some specifically mentioned difficulties with scheduling and the importance of having the abortion quickly. Remote provision of the service is well suited to address these issues.

We encountered several challenges in implementing the service. Ensuring that people across entire states are aware of the service requires outreach beyond routine local advertising. Identifying facilities where people can conveniently get pre-abortion tests and retrieving results can be time-consuming. Establishing billing processes for off-label use of mifepristone has been complicated. Connecting people with local sources of Rh immune globulin is also problematic. We expect that these issues will resolve as the service expands.

Our data have some limitations. Most of our participants came from Hawaii, which has unique access barriers due to the absence of abortion providers on most of its islands. We did not ascertain abortion outcomes for 23% of participants treated; our estimates of the proportion with medical abortion failure or complications may thus be underestimated. Interest in TelAbortion may have been influenced by the financial support and compensation provided by the study. Notably, though, at the UH site, which was the only site in this analysis that enrolled people before and after we instituted billing for the service, we found no evidence of a decrease in uptake of or satisfaction with TelAbortion.

We believe that the TelAbortion model has the potential to substantially increase access to abortion in the United States by increasing the reach of providers and by offering a safe and legal option for obtaining the service outside of an established clinical setting. Currently, the FDA's restriction on distribution of mifepristone appears to preclude implementation of TelAbortion except in the context of a research study. However, this restriction is medically unwarranted [16], and advocates are working to convince FDA to withdraw it [21]. Meanwhile, we intend to continue to offer TelAbortion through an expanded study to evaluate its benefits, risks, feasibility, and acceptability in a more diverse population. We plan to examine the potential for simplifications of the study procedures to decrease cost and further enhance convenience, and we hope to explore the potential for the TelAbortion model to reduce out-of-pocket costs, particularly for people who have no insurance coverage for abortion but do have coverage for the required screening and follow-up tests performed outside a facility that provides abortion. We anticipate that our data will ultimately be useful for supporting policy advances at both state and federal levels.

E. Raymond, E. Chong, B. Winikoff, et al., TelAbortion: evaluation of a direct to patient telemedicine abortion Service in the United States

Supplemental Table
Abortion outcome by gestational age on day of mifepristone ingestion, among participants who were sent study packages and provided date of mifepristone ingestion*

	Gestational age on day of mifepristone ingestion						
	≤35 days N=3 n (%)	36-42 days N=12 n (%)	43-49 days N=37 n (%)	50-56 days N=46 n (%)	57-63 days N=45 n (%)	64-70 days N=42 n (%)	71 days N=2 n (%)
Aborted without procedure	3 (100%)	10 (100%)	32 (91%)	43 (98%)	39 (95%)	33 (97%)	2 (100%)
Aborted with procedure for ongoing pregnancy	0	0	1 (3%)	1 (2%)	1 (2%)	1 (3%)	0
Aborted with procedure for bleeding or incomplete abortion	0	0	2 (6%)	0	1 (2%)	0	0
Abortion outcome missing	0	2	2	2	4	8	0

* Table excludes 6 participants who received study packages but did not take mifepristone, 19 who took mifepristone but did not provide a date of ingestion, and 36 who provided no data on mifepristone ingestion. Percents exclude women with missing abortion outcomes.

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Commentary: No-test medication abortion: A sample protocol for increasing access during a pandemic and beyond ☆,☆☆

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1. Introduction

The COVID-19 pandemic is acutely threatening access to essential health services, including abortion [1]. Across all fields of medicine, changes in practice models are occurring rapidly. For patients seeking abortion, urgent modifications of current protocols are needed to ensure that patients can continue to obtain this time-sensitive treatment while limiting transmission of infection by maintaining distance between and among patients and providers. Remote delivery of care, which has recently been endorsed by local, state, and federal authorities as a key epidemic control measure [2], will be indispensable to accommodate patients and staff who are navigating quarantines, stay-at-home directives, lack of transportation, new family or work obligations, or other unavoidable circumstances that impede their ability to go in in person to a health facility.

Fortunately, medication abortion (MA) using mifepristone and misoprostol can address many of these challenges. At present, MA typically entails a visit to a clinician or facility that provides abortion where an ultrasound or pelvic examination and often blood tests are performed to evaluate eligibility before pills are dispensed. Many abortion providers require a follow-up ultrasound or blood test after treatment to confirm abortion completion. However, research and experience have demonstrated that these tests, which inherently involve physical contact between patient and health care worker, are usually unnecessary for safe and effective MA [3–7]. Indeed, over the past 15 years, international organizations have provided mifepristone and misoprostol by mail to tens of thousands of patients screened only by history [8–11]. A prospective study conducted in 2015–2016 in the United States, Mexico, and Moldova provided 406 MAs without screening ultrasound or pelvic examination [12]. No serious adverse events were reported that resulted from the omission of the tests, and participants were highly satisfied.

To assist abortion providers with the current crisis, we present a sample protocol (Box. 1) for providing a "no-test" MA that includes recommendations for patient selection, Rh status evaluation and management, the treatment regimen, and follow-up. Although FDA-imposed restrictions on mifepristone dispensing may require patients to go to the abortion provider or facility to obtain the drug [13], this protocol would enable every other part of the MA process to be implemented without any in-person encounter. The protocol is intended to serve as a guidance; abortion providers should use clinical judgment when adapting it for their practice settings and patient populations. Below we summarize the data that we considered in developing this protocol and our rationales for and comments on selected provisions.

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Sample Protocol for No-Test Medication Abortion

PURPOSE

To enable safe and effective provision of medication abortion without a mandatory pre-treatment ultrasound, pelvic examination or laboratory tests when medically appropriate, given that these tests may be significant barriers to access and, in the setting of a pandemic, may increase transmission of infection to patients and health care workers.

CRITERIA

- Pregnancy confirmed by patient report of urine or serum test or prior ultrasound
- Last menstrual period started ≤77 days before anticipated date of mifepristone ingestion
- Certain of last menstrual period onset date ± 1 week
- None of the following symptoms or risk factors for ectopic pregnancy:
  - Vaginal bleeding or spotting within the past week
  - Unilateral pelvic pain or significant bilateral pelvic pain within the past week
  - Prior ectopic pregnancy
  - Prior permanent contraception or other tubal surgery
  - IUD in uterus at conception or currently
- None of the following contraindications to medication abortion, assessed by history:
  - Hemorrhagic disorder or concurrent anticoagulant therapy
  - Chronic adrenal failure
  - Concurrent long-term systemic corticosteroid therapy
  - Inherited porphyria
  - Allergy to mifepristone, misoprostol, or other prostaglandin
- No strong preference for pre-treatment ultrasound, pelvic examination or laboratory tests

RH TYPING AND ADMINISTRATION OF ANTI-D IMMUNOGLOBULIN

- Not needed if the gestational age on the anticipated mifepristone ingestion date will be <70 days or if the patient reports positive Rh type, wants no future children, or declines anti-D immunoglobulin.
- Should be considered for patients not meeting above criteria

TREATMENT

Provide the following:

- Mifepristone 200 mg orally
- Misoprostol 800 mcg x 2
- Analgesics, antiemetics per health facility protocol
- Patient instruction sheet and health facility emergency contact information
- Two high sensitivity pregnancy tests (HSPTs)

The patient should take mifepristone 200 mg orally followed by misoprostol 800 mcg buccally or vaginally 24-48 hours later. Patients with estimated GA >63 days should take a second dose of misoprostol 800 mcg 4 hours after the first. Patients with estimated GA ≤63 days should take the second dose if no bleeding occurs within the first 24 hours after the first misoprostol dose or if instructed to take it by a clinician. Review the instruction sheet with the patient.

FOLLOW-UP

1. Plan a follow-up contact with the patient one week after dispensing treatment.
2. If the patient reports indicators of continuing or ectopic pregnancy (e.g., any of the symptoms on the instruction sheet), evaluate with ultrasound or serum HCGs.
3. Otherwise, instruct the patient to perform the first HSPT 4 weeks after taking misoprostol (not earlier) and to contact the abortion provider if the result is positive.
4. If the patient has indicators of continuing or ectopic pregnancy, evaluate with ultrasound or serum HCGs
5. If the first HSPT result is positive but the patient has no such indicators, instruct the patient to perform the second HSPT in 1 week.
6. If second HSPT result is also positive, evaluate with ultrasound, serum HCGs, additional urine testing, or uterine aspiration.

Box. 1. Sample protocol for no-test medication abortion.

2. Patient selection

The three key goals of clinical evaluation before MA are (1) to confirm that the gestational age (GA) is within accepted limits for effective and safe outpatient treatment, (2) to identify ectopic pregnancy, and (3) to establish that the patient has no other contraindications to MA.

The sample no-test MA protocol specifies an upper GA limit of 77 days as estimated from the first day of the last menstrual period (LMP). The LMP-based GA should be ≤77 days on the day of mifepristone ingestion, which may be later than the day the drug is dispensed if the patient plans to take the pills home for later use or if the medication is mailed or dispensed to a patient intermediary. The patient should be certain within one week of the LMP onset date.

We chose a 77-day limit because recent data have indicated that outpatient MA is safe and effective through that GA [14,15] and because this limit is consistent with current guidelines of the National Abortion Federation [16] and Planned Parenthood Federation of America (personal communication, Gillian Dean, MD, MPH, Planned Parenthood Federation of America). We note, though, that 2014 guidelines issued by the American College of Obstetricians and Gynecologists (ACOG) and the Society for Family Planning [17] as well as the mifepristone label approved by the US Food and Drug Administration in 2016 specify a 70-day limit. In response to the pandemic, ACOG has recently issued a statement acknowledging that LMP-based gestational dating without ultrasound is acceptable, although no specific GA limit was specified [18].

Regardless of the precise GA limit selected, use of the no-test approach will inevitably result in treatment of some fraction of patients whose true GAs exceed 77 days. Data from studies that compared LMP-based GA estimates to ultrasound-based estimates suggest that this fraction tends to be higher in patient populations that include more patients with advanced GA [19,20] and that it may be reduced by decreasing the LMP-based GA cutoff [19]. Reassuringly, the largest study, which was conducted in the United States in 2005–2007 [21], found that only 31 (1%) of 3012 MA patients who were certain that their LMPs had started ≤77 days prior had GAs > 77 days by ultrasound examination. Furthermore, international studies that included more than 1600 patients treated with mifepristone and one or more misoprostol doses at 13–24 weeks of gestation reported efficacy and safety similar to that expected in earlier gestation: >93% of patients aborted without further intervention, 0.7–4% required transfusion, and no patient required hysterectomy or died [22]. Therefore, we expect that serious adverse health consequences of GA underestimation based on LMP will be rare. Nevertheless, clinicians using the no-test approach to MA should have a plan for managing or referring patients who may need a second trimester procedure to complete the abortion.

When assessing GA, providers may incorporate other historical information reported by the patient that, for simplicity, we do not mention in the sample protocol but that may indicate that the GA is greater than the proposed limit. For example, a patient who reports a positive pregnancy test >7 weeks before presentation is unlikely to have a GA of ≤77 days. The sample protocol does not exclude patients who report menstrual irregularity or recent use of hormonal contraceptives. Although these conditions may signal ovulatory dysfunction, we expect that they would more likely lead to overestimation of GA than to underestimation, which is the primary concern for MA eligibility, and excluding patients with these conditions may therefore unnecessarily limit access by eligible patients.

MA with mifepristone and misoprostol is contraindicated in patients with ectopic pregnancy not because the drugs are dangerous for such patients but because the regimen is not a proven treatment for this condition. The sample no-test protocol excludes patients with significant symptoms of or risk factors for ectopic pregnancy; recent vaginal bleeding or pelvic pain, prior permanent contraception, prior ectopic pregnancy, or intrauterine device in place at conception [23,24]. We do not exclude patients who report prior pelvic inflammatory disease because unconfirmed diagnoses of this condition are associated with only a mildly increased risk [24]. We recognize that the listed criteria will not identify every patient with ectopic pregnancy; an estimated half of all patients with this condition have no risk factors [25]. However, published and emerging data suggest that the incidence of ectopic pregnancy among patients seeking MA is very low, <1% [26,27]. Moreover, substantial data [28–32] and current clinical MA guidelines [16,33] support treatment of patients in whom ectopic pregnancy has not been definitively excluded because the condition can be detected and managed afterwards. Thus, this aspect of the protocol is consistent with the standard of care.

The medical contraindications in the sample protocol are those listed in the FDA-approved mifepristone label. Patient history is sufficient for assessing these conditions.

3. Rh typing and other pre-treatment laboratory testing

Recent research has suggested that the risk of Rh sensitization after early abortion is negligible [34–36]. Consequently, the National Abortion Federation has concluded that forgoing Rh typing and administration of anti-D immunoglobulin is reasonable for Rh-negative patients having aspiration abortion before 56 days of gestation and may be considered for all patients having MA at less than 70 days [16,37]. The sample protocol is consistent with this conclusion. In addition, it specifies that testing is unnecessary for patients who can report a Rh-positive blood type or who are certain that they want no future children after the planned abortion. Any patient may opt out of Rh typing; the recent statement from ACOG notes that Rh testing and RhD immunoglobulin administration should not be a barrier to the provision of medication abortion [18].

Hemoglobin/hematocrit and other laboratory tests are not routinely needed before first-trimester abortion but may be performed as indicated by medical history and patient symptoms [16].

4. Treatment regimen

The sample protocol specifies that patients should receive a standard regimen of mifepristone 200 mg orally and misoprostol 800 mcg vaginally or buccally [16]. In addition, each patient should be provided with an extra dose of misoprostol 800 mcg. Those with estimated GA > 63 days should be instructed to take this second misoprostol dose 4 hours after the first to improve effectiveness [16,38]. Patients with estimated GA < 63 days may be instructed to take the second dose if no bleeding occurs within the first 24 hours after the first dose or to retain it for use if recommended by the provider. Alternatively, all patients may be told to take two misoprostol doses 4 hours apart. Although this specific regimen has not been studied, trials of repeated doses of misoprostol in the first and second trimester suggest that it will be safe [39–43].

5. Scheduled follow-up

The primary goals of follow-up are to confirm absence of continuing pregnancy, to detect ectopic pregnancies not diagnosed before treatment, and to identify complications that need evaluation and treatment. To accomplish these goals, the sample protocol relies on patient symptoms and high sensitivity urine pregnancy tests (HSPTs) that the patient performs at home. This strategy has been validated in several studies [44,45], is consistent with current MA guidelines for follow-up of patients who have documented intrauterine pregnancies [16,17], and is increasingly used by MA providers.

The sample instruction sheet (Box. 2), which includes a list of symptoms that may need in-person evaluation, is derived from studies of symptoms used to assess outcomes in MA patients with intrauterine pregnancies documented by ultrasound [44–47] and from experience in managing patients with ectopic pregnancies. The instruction sheet directs patients to contact the abortion provider if specified symptoms occur or the HSPT result is positive. Research has shown that patients can safely use these tools on their own to recognize when follow-up is needed [48,49], and

Sample Instructions for Patients Receiving No-Test Medication Abortion

1. **Call your abortion provider** if:
   - ☐ You vomit within the first 30 minutes after taking mifepristone.
   - ☐ You have a fever of 100.4°F or higher more than 24 hours after you take the misoprostol.
   - ☐ One week after taking misoprostol, you have any of the following:
     - You have not had cramping and bleeding heavier than a period.
     - Your bleeding is not getting lighter.
     - You do not feel that you passed the pregnancy.
     - Your pregnancy symptoms (such as nausea and breast tenderness) are not resolving.
   - ☐ At any time, you have any of the following:
     - An increase in pain/cramps or bleeding more than 24 hours after taking misoprostol.
     - Severe pain or cramps that don't get better with pain medicine, rest, or heating pads.
     - Enough bleeding to soak 2 maxi pads an hour for more than 2 hours.
     - Dizziness or vomiting lasting more than 2 hours.
     - Weakness, nausea, or diarrhea lasting more than 24 hours.
2. Perform one urine pregnancy test 4 weeks after taking misoprostol (not earlier). **Call your abortion provider if the result is positive or invalid**. Use the second test if instructed to do so by your abortion provider.

Box. 2. Sample instructions for patients receiving no-test medication abortion.

indeed patient-controlled follow-up is widely used for MA follow-up by provider organizations in multiple European countries [50–52]. However, the sample no-test protocol recommends a planned follow-up contact with the provider one week after dispensing the abortifacient medications to confirm absence of symptoms of ongoing or undiagnosed ectopic pregnancy or other potential complications. This contact may be conducted by videoconference, telephone, patient portal, email, text, or other telehealth modalities [53,54].

MA failures are often detectable based on symptoms alone [6,44,47–49]. Nevertheless, the sample no-test protocol recommends a HSPT 4 weeks after misoprostol use to confirm pregnancy termination. Available data indicate that 5–25% of HSPTs performed about a month after MA treatment produce positive results, nearly all of which are "false positives" in patients who no longer have viable pregnancies [44,45]. Therefore, the sample protocol recommends that two HSPTs be provided initially to each patient. The patient should be instructed to contact the provider if the result of the initial 4-week test is positive. If the patient is asymptomatic, a repeat test one week later may be appropriate. If the patient has symptoms of ongoing or ectopic pregnancy or the second HSPT result is positive, further evaluation is indicated. The specific procedures for this evaluation should address the patient's individual clinical situation and may include ultrasound, serial serum HCG levels, additional urine pregnancy testing, or aspiration and tissue examination.

Patients receiving a no-test MA may remain at risk for having ectopic pregnancy until a negative HSPT result is obtained. Therefore, vigilant attention on the part of both provider and patients to symptoms such as increased pelvic or abdominal pain, continued vaginal bleeding, or dizziness is imperative.

6. Counseling

Patients requesting a no-test MA should receive standard pre-abortion counseling about pregnancy options, the risks and benefits of MA, expected results, side effects, and warning signs. In addition, each patient should be explicitly informed that LMP-based dating may underestimate GA, in which case efficacy may be lower than expected, bleeding and cramping may be heavier, and, rarely, fetal tissue may be visible. Moreover, patients should understand that without ultrasound, ectopic pregnancy will not be definitively excluded before treatment. To increase the chance of abortion success and reduce the time to diagnosis of ectopic pregnancy or MA complications, patients should be advised to diligently follow all instructions provided. However, patients should also be advised that serious adverse events of no-test abortion are expected to be rare and that side effects of MA can often be managed remotely. To avoid unnecessary infectious exposure during a pandemic as well as excess cost and inconvenience, patients should contact the abortion provider before seeking in-person care.

7. Conclusion

Although the COVID-19 crisis prompted the development of this sample protocol, we recognize that the pandemic is only one of many longstanding, serious impediments to abortion access in

the United States. Omitting unnecessary use of ultrasound, examination, and laboratory tests before MA can reduce barriers to this essential service by decreasing cost and enhancing convenience and comfort. The no-test approach can enable provision of abortion in new venues and by new categories of providers, and it can facilitate new service delivery models, such as synchronous or asynchronous telehealth, stationary or mobile "mini-clinics", pill pick-up arrangements, or dispensing via lockboxes or, potentially, by mail [7,54]. If the no-test strategy results in earlier treatment, it may increase MA success rates [14,43,55]. Details of the no-test MA protocol will certainly need to be revised as new evidence emerges, but we anticipate that this approach to providing the service will continue to be beneficial for both patients and abortion providers even after the current epidemic resolves.

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Systematic review

Who can provide effective and safe termination of pregnancy care? A systematic review*

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Background Unsafe termination of pregnancy is a major contributor to maternal morbidity and mortality. Task sharing termination of pregnancy services between physicians and mid-level providers, a heterogeneous group of trained healthcare providers, such as nurses, midwives and physician assistants, has become a key strategy to increase access to safe pregnancy termination care.

Objectives To systematically review the evidence to assess whether termination of pregnancy services by nonphysician providers can be performed safely and effectively.

Search strategy We searched the Cochrane Central Register of Controlled Trials, MEDLINE, MEDLINE in process and other nonindexed citations and POPLINE.

Selection criteria We included randomised controlled trials (RCTs), as well as clinical studies, using study designs that compared efficacy, safety and acceptability of termination of pregnancy services by physicians versus other provider groups.

Data collection and analysis Two reviewers independently extracted the data, and we performed a meta-analysis where appropriate using RevMan. Quality assessment of the data used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Main results We identified five controlled studies comprising 8908 women undergoing first-trimester surgical termination of pregnancy (one RCT and three prospective cohort studies) and medical termination of pregnancy (one RCT). The mid-level provider group included midwives, nurses, auxiliary nurse midwives and physician assistants trained in termination of pregnancy services. Safety and efficacy outcomes, including incomplete termination of pregnancy, haemorrhage, injury to the uterus or cervix, did not differ significantly between providers.

Author's conclusions Limited evidence indicates that trained mid-level providers may effectively and safely provide first-trimester surgical and medical termination of pregnancy services. Data are limited by the scarcity of RCTs and biases of the cohort studies.

Keywords Abortion, mid-level providers, midwives, nonphysician providers, nurses, physician assistants, provision, safety, termination of pregnancy.

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Introduction

Multiple barriers may prevent access to safe abortion care (termination of pregnancy or management of miscarriage). Even when legal, access to safe services is often restricted by the lack of trained providers,[1] particularly in nonurban settings. Many countries have policies that limit the provision of services to physicians or physician specialists (obstetrician gynaecologists), thereby limiting the number of available providers and further restricting women's access.

Improving maternal health is one of the eight Millennium Development Goals,[2] and an estimated 13% of all maternal deaths are caused by unsafe termination of pregnancy.[3] Task shifting termination of pregnancy care services to mid-level providers (MLPs), a heterogeneous group of various nonphysician healthcare providers, such as nurses, midwives and physician assistants, has become a key strategy to achieve this goal.[4] Task shifting can broaden the provision of safe termination of pregnancy to the primary care level and thus has the potential to expand access to services.

* The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the World Health Organization or Ipas.

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To assess whether the provision of termination of pregnancy services by providers other than physicians could be performed with similar levels of safety, efficacy and acceptability as when performed by physicians, we undertook a systematic review of this topic.

Methods

The current review has been prepared in accordance with the PRISMA guidelines[5] and included a review protocol.

Criteria for considering studies for this review

Criteria covered the areas of participants, interventions, comparisons, outcomes and study design (PICOS) as outlined below.

Types of study

Randomised controlled trials (RCTs) on this topic were anticipated to be scarce and many of the safety outcomes are rare. In order to increase the evidence base addressing this issue and to increase the generalisability to various settings, we included clinical studies using the following study designs: RCTs, cluster RCTs, nonrandomised cluster-controlled trials, controlled before and after studies, interrupted time series[6] and cohort studies.

Types of participant

Women undergoing medical or surgical termination of pregnancy or receiving treatment for miscarriage at any gestational age of pregnancy.

Types of intervention

Termination of pregnancy or management of a miscarriage provided by either physician providers or MLPs. MLP for this review is defined as any formally trained nonphysician provider, and comprises a heterogeneous group depending on the cadre of provider, country and setting.

Types of outcome measure

The primary outcomes were: (1) efficacy: complete termination of pregnancy; correct assessment of gestational age; (2) safety: complications, their recognition and management. The secondary outcomes were: (1) training needed for competency; (2) acceptability and satisfaction; (3) costs.

Search methods for the identification of studies

Electronic searches

An electronic literature search of the Cochrane Central Register of Controlled Trials (third quarter, 2011), MEDLINE (1946 to October 2011), MEDLINE in process, other nonindexed citations (6 October 2011) and POPLINE (1927 to October 2011) without language preference and using terms that include abortion, termination of pregnancy services and healthcare providers.

Searching other sources

We contacted researchers in the field to seek information on unpublished or ongoing studies that we might have missed or that may have been unavailable with the electronic search. Reference lists of articles retrieved were hand searched.

Data collection and analysis

Selection of studies

The primary reviewer (RMR) evaluated the articles identified from the literature search. A second reviewer (NK) evaluated the articles in question for inclusion and, where needed, additional information was sought from the study's author. Studies under consideration were evaluated based on methodology without consideration of the results. We included studies examining manual vacuum aspiration, electric suction aspiration or dilation and curettage. We considered as medical termination of pregnancy those regimens that used mifepristone/misoprostol, misoprostol alone or methotrexate/misoprostol.

Data extraction and management

Two reviewers (RMR and NK) independently extracted data using standard extraction forms. Data collected included PICOS, funding information and, if applicable, randomisation, allocation and blinding and loss to follow-up. Participant characteristics included number, demographics and gestational age. Discrepancies were resolved by consensus of the reviewers.

Assessment of the risk of bias in the included studies

Two reviewers (RMR and NK) independently graded the quality of the included studies using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system that incorporates in its assessment the study design, limitations, inconsistency, indirectness and imprecision.[7] The quality of evidence was classified into one of four categories: high (further research is very unlikely to change our confidence in the estimates of the effects), moderate (further research is likely to greatly affect our confidence in the estimates of the effects and may change the estimates), low (further research is very likely to greatly affect confidence in the estimates of the effects and is likely to change the estimates) or very low (any estimate of effect is very uncertain).

For RCTs, we assessed bias by:

1 Assigning a quality score for concealment of allocation:[8]
 (a) adequate concealment of allocation;
 (b) unclear whether adequate concealment of allocation;

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(c) inadequate concealment of allocation;
(d) allocation concealment not used.

2 Blinding of participants, clinicians and investigators.
3 Protection against exclusion bias.
4 Appropriate analysis of data.

Any discrepancies between reviewers were addressed by a joint re-evaluation of the original article. Funnel plots were used to assess publication bias.

Measures of treatment effect and assessment of heterogeneity

We used RevMan5.1 software for data analysis. Effects of dichotomous outcomes are presented as risk ratios with a 95% confidence interval, and were considered to be statistically significant if the confidence interval did not include 1.0. We examined for heterogeneity using the I^2 statistic.[9] If $I^2 > 75\%$ (considerable heterogeneity), we used a random effects model in the analysis.

Dealing with missing data

For RCTs, we aimed to use an intention-to-treat analysis. However, in one study,[10] the need for post-randomisation exclusion of women who turned out to be ineligible was part of the study design. We excluded these women from the analysis, but included women who were lost to follow-up after undergoing a termination of pregnancy. Depending on the study and outcome, the denominator of the cohort studies included women who underwent the intervention or only those who were followed up. We did not impute any outcomes, and thereby may have slightly mis-estimated the true proportion of complications. Loss to follow-up was considered in the GRADE assessment.

Data synthesis

Using RevMan5.1 software for data analysis, and consistent with our protocol, we divided the studies into two comparisons.

1 Comparison 1: surgical termination of pregnancy.
2 Comparison 2: medical termination of pregnancy.

Within each comparison, RCTs and prospective cohort studies were considered separately. The only RCT on surgical termination of pregnancy showed significant heterogeneity between the two countries in which it was performed. Therefore, we combined them in a meta-analysis using a random effects model. We summarised but did not perform meta-analyses of the cohort studies because of their heterogeneity and other limitations.

Results

Results of the search

Our search strategy (Appendix S1) identified a total of 806 articles (Figure 1).

Studies were excluded after screening the title and abstract or the full-text article ($n = 41$) based on study design, lacking a comparison group or not assessing the outcomes of interest. Ultimately, we identified five studies that met all inclusion criteria. Of note, we did not identify studies comparing the provision of active miscarriage management or costs of services. Each study investigated only one method of termination of pregnancy; there were no identified studies in which providers chose the method.

Included studies

Five studies with a total of 8908 subjects were included in this review with the following interventions and comparison groups.

Comparison 1: surgical termination of pregnancy. One RCT[11] (2894 women) compared MLPs, mostly midwives and one doctor assistant, with physicians performing surgical termination of pregnancy up to 12 weeks at various clinics in South Africa (mean gestational age, 7.7 weeks) and Vietnam (mean gestational age, 6.1 weeks). Three prospective cohort studies (4910 women) compared MLPs – nurses in India[12] (1089 women) and physician assistants in two US studies[13,14] (3821 women) – with physicians. In the Indian clinics, women with pregnancies up to 10 weeks of gestation (mean gestational age, 8.6 weeks) and, in the USA, up to 15 weeks of gestation (>80% <10 weeks) were included. All studies were conducted in a setting in which emergency care in the case of complications was accessible.

Comparison 2: medical termination of pregnancy. One RCT[10] (1104 women) compared nurses and auxiliary nurse midwives with physicians in several Nepalese hospitals using 200 mg mifepristone, followed by 800 μg vaginal misoprostol 2 days later. Women with pregnancies up to 9 weeks (mean, 6.6 weeks) were included. The study required that the women resided within 90 minutes of the study site to guarantee access to emergency care if needed.

The Indian study[12] compared newly trained MLPs with newly trained physicians. The other studies included previously trained pregnancy termination providers;[10,11,13,14] however, in Warriner et al.,[11] physicians had more years of experience than did MLPs. Table 1 presents the characteristics of the included studies.

Quality of evidence

The quality of evidence of all included studies was graded using the GRADE system.[7] A panel of international experts reviewed and prioritised our proposed outcomes of interest, and the critical outcomes are summarised in Table 1 (for complete GRADE tables, see Tables S1 and S2). We found no serious inconsistency or indirectness among the studies. RCTs were rated as low to moderate quality,

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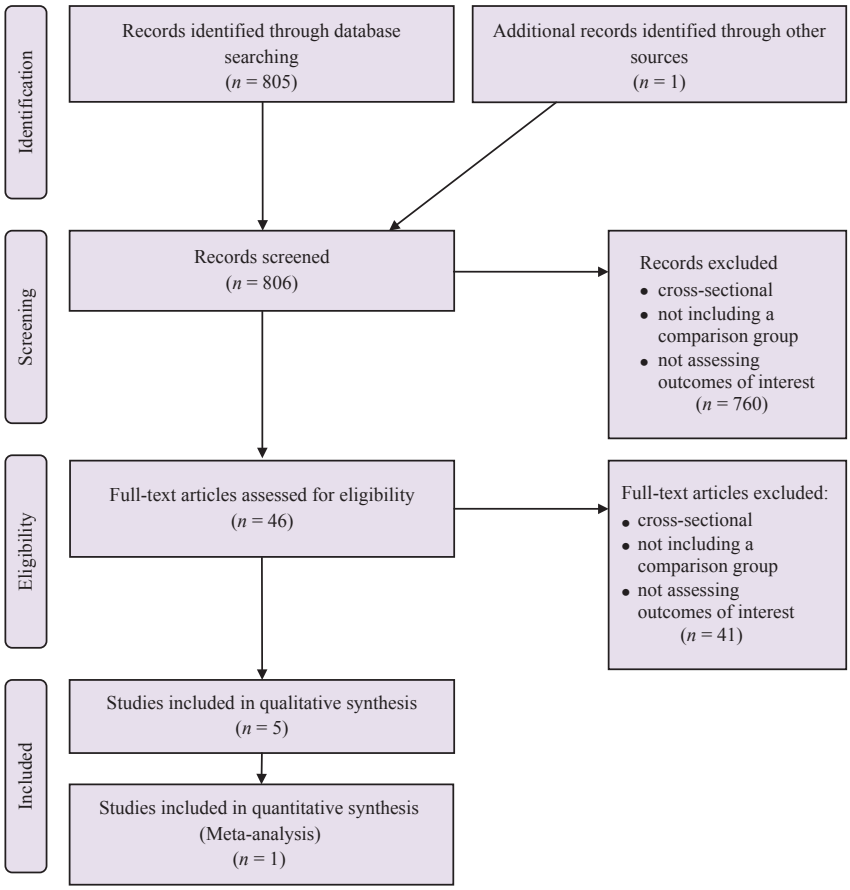

Figure 1. Study selection.

whereas prospective cohort studies ranged from very low to low quality for the outcomes of interest. The most frequent reason for downgrading the evidence was imprecision because of a wide confidence interval (related to the small number of studies or to the heterogeneity of the results[11]) and small number of events (related to the rare occurrence of complications). No studies met the criteria for upgrading. In cohort studies, high loss to follow-up also occurred.

Risk of bias in the included studies

Inclusion and exclusion criteria were clearly defined[10,11] for protection against exclusion bias.

Incomplete data occurred in 3.6% of women with surgical termination of pregnancy,[11] either because they withdrew before the procedure or because they were lost to follow-up after the procedure. In the RCT on medical termination of pregnancy by Warriner et al.,[10] 6.3% of women had incomplete data (including the women who were excluded post-randomisation as they were found to be ineligible based on the provider examination).

We did not find evidence of reporting bias. According to the funnel plots, studies included in this review are symmetrically distributed, indicating that publication bias is unlikely. Published results corroborate observational study results, such as programme evaluations on the safety and efficacy of MLPs providing termination of pregnancy services.

Effects of intervention

Results are stratified by surgical versus medical termination of pregnancy. All effect sizes are presented in Table 1 and in the forest plot of overall complications (Figure 2).

Comparison 1: surgical termination of pregnancy

RCT

None of the safety and efficacy outcomes (overall complications, incomplete abortion necessitating re-aspiration, haemorrhage (>500 ml), injury to the uterus, injury to the cervix or infection) occurred frequently or showed a statistically significant difference between provider groups (Table 1). Among the 2894 women randomised to MLPs (mostly midwives or doctor assistants) and physicians, 18 and 10, respectively, experienced complications [risk ratio (RR), 3.1; 95% confidence interval (95% CI), 0.2–59.3] (Table 1, Figure 2].[11]

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Table 1. Characteristics and findings of the included studies

Reference	Study design	Participants	Country; setting; time of study or data collection	Intervention	Critical outcomes	Number of women analysed: *n* (%)		Effect: RR (95% CI)	Comments
						Mid-level providers (MLPs)	Physicians	MLP versus physician	
Surgical termination of pregnancy (TOP)									
Warriner et al.[11]	Randomised controlled trial, equivalence trial; computer-generated randomisation, sealed opaque envelopes for allocation concealment, no blinding	1160 South African and 1734 Vietnamese women, surgical TOP up to 12 weeks of gestation	South Africa and Vietnam; multicentre (8 urban and peri-urban Marie Stopes International); September 2003–June 2004 South Africa, May–December 2003 Vietnam	1) MLP 2) Physician; manual vacuum aspiration (MVA); 2-week follow-up	Overall complications	18/1453 (1.2)	10/1441 (0.69)	3.1 (0.2–59.3)	Provider experience (MLP/physician): South Africa 4/7 years; Vietnam 7/10 years. 25 providers; MLP: 6 South Africa (2 midwives), 8 Vietnam (1 doctor assistant, 7 midwives). Undergo standardised and government-accredited training in abortion; doctors: 6 South Africa, 5 Vietnam
					Incomplete TOP	16/1453 (1.1)	8/1441 (0.56)	3.0 (0.2–42.0)	
					Haemorrhage, injury to uterus or cervix	0/1453 (0)	0/1441 (0.0)	No estimate	
					Infection	2/1453 (0.1)	1/1331 (0.1)	1.7 (0.2–12.5)	
Freedman et al.[13]	Prospective cohort study (next available provider)	2458 women, surgical TOP up to 12 weeks of gestation	USA; freestanding clinic in Vermont; January 1981–December 1982	1) Physician assistant (PA) 2) Physician (next available provider); MVA or electric vacuum aspiration (EVA); 4-week follow-up	Overall complications	35/1285 (2.7)	36/1173 (3.1)	0.9 (0.6–1.4)	Experienced providers; PAs undergo structures training and a national certification examination, they are state licensed to practice with physician supervision; trainees were excluded; only 94% of all women undergoing a procedure participated in the study (no explanation). Some outcomes are not broken down by provider type
Goldman et al.[14]	Prospective cohort study (PAs and physicians were in different clinics)	1363 women, surgical TOP up to 14 weeks of gestation	USA; 2 freestanding clinics, 1 in New Hampshire (physician providers) and 1 in Vermont (PA providers); July 1996–October 1997	) PA 2) Physician; MVA or EVA; 2-week follow-up	Overall complications	12/546 (2.2)	19/817 (2.33)	1.0 (0.5–1.9)	Experienced providers; PAs undergo structures training and a national certification examination, they are state licensed to practice with physician supervision; 3 PAs and 3 physicians all with minimum of 5 years of experience in surgical abortion; PAs gave routine postoperative 14 days of antibiotics, physicians not; 28.5% loss to follow-up

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Table 1. (continued)

Reference	Study design	Participants	Country; setting; time of study or data collection	Intervention	Critical outcomes	Number of women analysed: *n* (%)		Effect: RR (95% CI)	Comments
						Mid-level providers (MLPs)	Physicians	MLP versus physician	
					Ongoing pregnancy	1/546 (0.2)	0/817 (0.0)	4.5 (0.2–110.0)	
					Incomplete TOP	7/546 (1.3)	3/817 (0.4)	3.5 (0.9–13.4)	
					Haemorrhage	5/546 (0.9)	1/817 (0.1)	7.5 (0.9–63.9)	
					Injury to uterus	1/546 (0.2)	0/817 (0.0)	4.5 (0.2–109.9)	
					Injury to cervix	0/546 (0.0)	0/817 (0.0)	No estimate	
					Infection	2/546 (0.4)	16/817 (2.0)	0.2 (0.04–0.8)	
					Missed ectopic pregnancy	1/546 (0.2)	0/817 (0.0)	4.5 (0.2–110.0)	
Jejeebhoy et al.[12]	Prospective cohort study (just one provider type was assigned to each facility at a given point in time)	1089 women, surgical abortion up to 10 weeks of gestation	India (Bihar and Jhakhand); five clinics of the NGO Janani; July 2009–January 2010	1) Nurses 2) Physicians; clinical exam; MVA; 1-week follow-up with pelvic exam	Overall complications	6/433 (1.4)	4/432 (0.9)	1.5 (0.4–5.3)	Newly trained providers; a 'verifier' repeated all pelvic exams and confirmed appropriate inclusion of woman
					Inaccurate assessment of gestational age	21/555 (3.8)	14/534 (2.6)	1.4 (0.7–2.8)	
					Ongoing pregnancy; haemorrhage; injury to uterus or cervix, infection, missed ectopic pregnancy	0/433 (0.0)	0/432 (0.0)	No estimate	
					Incomplete TOP	5/433 (1.2)	4/432 (0.9)	1.3 (0.3–4.6)	
					Failure to assess complete TOP	3/433 (0.7)	3/432 (0.7)	1.0 (0.2–4.9)	
					Overall acceptability	425/433 (98.2)	422/432 (97.7)	1.0 (0.99–1.02)	
					Acceptability to women of counselling about contraception	433/433 (100)	431/432 (99.8)	1.00 (1.00–1.01)	
Medical termination of pregnancy									
Warriner et al.[10]	Randomised controlled equivalence trial; computer-generated randomisation, sealed opaque envelopes for allocation concealment, no blinding	1104 women, medical abortion up to 9 weeks (63 days) of gestation, no more than 90-minute journey from the study clinic	Nepal; multicentre (5 district hospitals); April 2009–March 2010	1) MLP 2) Physician; counselling; clinical exam; medical abortion with 200 mg oral mifepristone followed by 800 μg vaginal misoprostol 2 days later; 3-hour hospital monitoring after misoprostol; 2-week follow-up	Serious complication requiring blood transfusion or hospitalisation	0/0 (0.0)	0/0 (0.0)	No estimate	Newly trained providers (3-day training course); all providers MVA trained. MLP: 8 staff nurses (3-year degree), 3 auxiliary nurse midwives (18 months of training) all MVA trained; doctors: 6 OB&GYN, 3 GP, 5 doctors (with Bachelor of Medicine and Bachelor of Surgery degree)
					Ongoing pregnancy	0/542 (0.0)	5/535 (0.9)	0.1 (0.0–1.6)	
					Incomplete TOP	14/542 (2.6)	15/535 (2.8)	0.9 (0.5–1.9)	
					Haemorrhage	0/542 (0.0)	0/535 (0.0)	No estimate	

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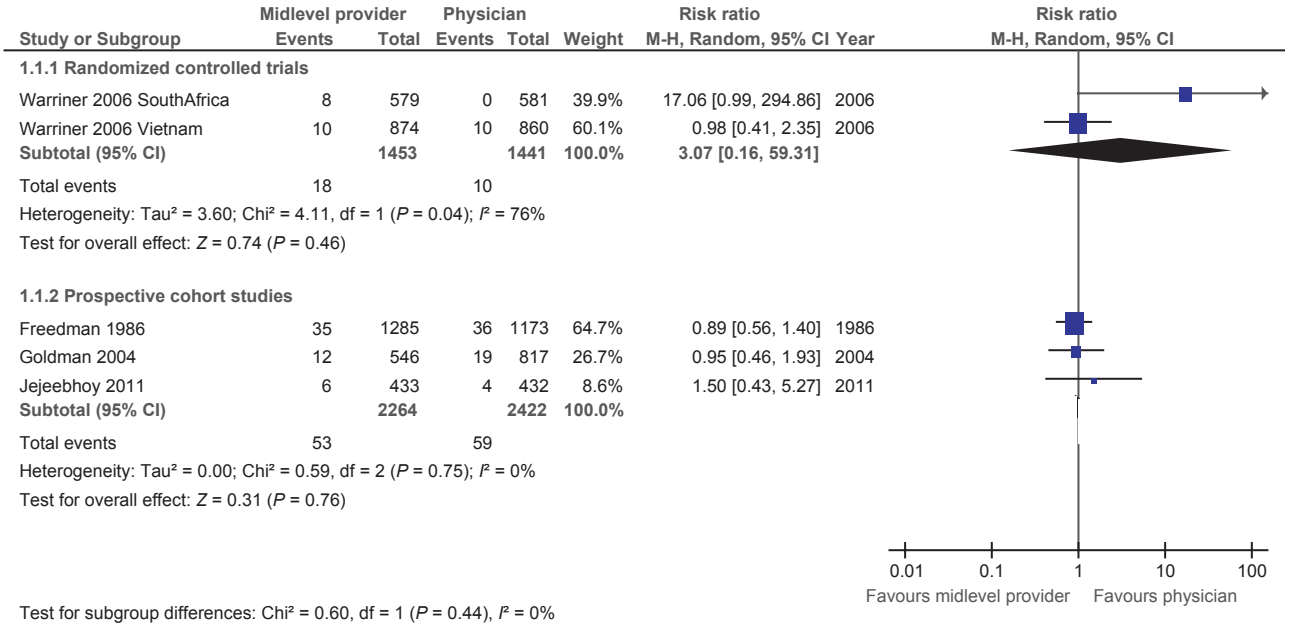

Figure 2. Forest plot of overall complications in surgical termination of pregnancy.

Prospective cohort studies

Overall complications, ongoing pregnancy, incomplete termination of pregnancy, haemorrhage, injury to the uterus, injury to the cervix and missed ectopic pregnancy showed no differences between provider groups in all studies (Table 1). Overall complications occurred in 112 (53 in the nurses and physician assistant group, 59 in the physician group) of 4686 women.[12–14] Only infection (18 of 1363 women) was less common among procedures performed by physician assistants than physicians (two versus 16).[14] In addition, one study compared the assessment of gestational age and completion of termination of pregnancy, both via bimanual examination by an experienced physician, who repeated the examination to verify the findings of the MLP, which did not differ between provider groups.[12]

Comparison 2: medical termination of pregnancy

RCT

Among 1077 women, none experienced a serious complication (haemorrhage requiring blood transfusion or condition necessitating hospitalisation).[10] None of the safety and efficacy outcomes [serious complication, ongoing pregnancy or incomplete abortion (retained products of conception possibly requiring aspiration)] showed a significant difference between provider types (Table 1). Of note, there were five ongoing pregnancies, all of which were in the physician group, and 29 incomplete abortions (14 in the MLP group [staff nurses and auxiliary nurse midwives] and 15 in the physician group). MLPs chose to discuss <2% of cases with a physician, and referred <1% for termination of pregnancy care elsewhere.

Discussion

Summary of main results

Two RCTs and three prospective cohort studies were included in this review which compared various formally trained provider groups with physicians providing surgical[11–14] and medical[10] termination of pregnancy.

Comparison 1: surgical termination of pregnancy

The RCT[11] and prospective cohort studies[12–14] showed that various MLP groups (nurses, midwives, doctor assistants, physician assistants) have effectively and safely provided surgical termination of pregnancy using manual or electric vacuum aspiration in clinic settings in South Africa, Vietnam, India and the USA. Overall complications in the RCT[11] resulted in RR = 3, favouring physicians, but the difference was not significant. The experience of physicians – 7 and 10 years in South Africa and Vietnam, respectively – compared with that of MLPs – 4 and 7 years, respectively, may have contributed to this finding, as a lack of experience is a known risk factor for complications.[15] The heterogeneity of the data is probably related to varying provider experience and the rarity of outcomes.

Complications were rare in all included studies; infection was the only complication that differed between provider groups, favouring the MLP group, in one study.[14] This

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result is confounded by different practices in antibiotic prophylaxis: MLP patients routinely received 1 week of antibiotics, whereas physicians' patients received either the antibiotic medication or only a prescription.

Comparison 2: medical termination of pregnancy

One RCT[10] did not identify any significant differences between efficacy, safety outcomes or women's satisfaction when comparing nurses and auxiliary nurse midwives with physicians using mifepristone and misoprostol.

Overall completeness and acceptability of the evidence

Studies have been conducted in various countries and settings: developing and developed countries, clinics and hospitals. This is a strength of the data, as it increases the generalisability, as does the inclusion of various groups of MLPs, including nurses, midwives, auxiliary nurse midwives and physician assistants.

Limitations of the evidence include the scarcity of RCTs, making the data imprecise. Data of prospective cohort studies are limited by imprecision, as well as by biases inherent to the study design. Studies on the surgical termination of pregnancy included women up to 15 weeks of gestation; however, women actually recruited had an average gestational age of 7 weeks (RCT) and <10 weeks (cohort studies), leaving few data for the later first trimester. Mortality has been shown to increase with increasing gestational age, particularly above 8 weeks.[16] Women undergoing surgical termination of pregnancy had access to care for complications and women undergoing medical termination of pregnancy resided within 90 minutes of the study site. The extrapolation of these data to care in the second trimester (medical or surgical) or to settings without access and referral for emergency care options may not be appropriate. No comparative study assessed active management of miscarriage.

Agreement or disagreement with other studies or reviews

The incidence of complications observed in the included studies is uncommon and consistent with other publications.[15–17] MLPs have been evaluated in cross-sectional studies and programme evaluations, usually without direct comparison with physicians. Although the evidence of these reports is subject to even more bias and of lower quality than the evidence included in this review, our findings are consistent with the conclusion that trained MLPs can safely provide surgical and medical termination of pregnancy. Providers used manual or electric vacuum aspiration (as opposed to sharp curettage) as is recommended in the literature.[18,19] Access to emergency care was available in all studies, and has been generally recommended for termination of pregnancy services.[15,17,19]

Conclusions

Implications for practice

Limited evidence suggests that MLPs can be trained to provide first-trimester surgical (using vacuum aspiration) and medical (mifepristone and misoprostol) termination of pregnancy services as safely and effectively as physicians. A learning curve probably affects complication risk, particularly in the provision of surgical services.

Implications for research

This review highlights the importance of further studies to address task sharing in termination of pregnancy care, such as the safety of providing surgical termination of pregnancy beyond 10 weeks of gestation, the use of other medical termination of pregnancy methods in the first or second trimesters, the safety and efficacy of post-termination of pregnancy care and management of miscarriage, implications for training for competency for different groups of providers and the impact of increasing access to safe termination of pregnancy services.

Disclosure of interests

R-MR, DB and NK have nothing to disclose.

Contribution to authorship

R-MR developed the protocol for this review and conducted all steps of the review, including the development of the search strategy, identification of the studies for inclusion, data extraction, analysis and interpretation, as well as writing the manuscript.

DB contributed to data analysis and interpretation, as well as to the manuscript, during her time at the Department of Reproductive Health and Research, World Health Organization.

NK also contributed to all aspects of this review. She was the second author who independently extracted the data, contributed to the analyses and their interpretation, as well as to the manuscript.

Details of ethics approval

Ethics review and approval were not necessary for the appropriate conduct of this systematic review.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search strategy.

Table S1. Grading of Recommendations Assessment, Development and Evaluation (GRADE) table for studies on surgical abortion for critical outcomes.

Table S2. Grading of Recommendations Assessment, Development and Evaluation (GRADE) table for studies on medical abortion for critical outcomes.

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OPEN ACCESS

Telemedicine medical abortion at home under 12 weeks' gestation: a prospective observational cohort study during the COVID-19 pandemic

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ABSTRACT

Background In response to the COVID-19 pandemic, legislation and guidance were introduced in Scotland permitting medical abortion at home by telemedicine for pregnancies at less than 12 weeks' gestation. Women had a telephone consultation with a clinician. Routine ultrasound was not performed. Medications and a low-sensitivity pregnancy test to confirm success of treatment were collected by or delivered to the woman, with telephone support provided as needed.

Methods A prospective cohort study of 663 women choosing medical abortion at home via the NHS Lothian telemedicine abortion service between 1 April and 9 July 2020. Interviewer-administered questionnaires were completed 4 and 14 days following treatment. Regional hospital databases were reviewed to verify abortion outcomes and complications within 6 weeks. Outcome measures included efficacy, complications and acceptability.

Results Almost all (642/663, 98.2%) the women were under 10 weeks' gestation. For 522/663 (78.7%) women, gestation was determined using last menstrual period alone. Some 650/663 (98%) women had a complete abortion, 5 (0.8%) an ongoing pregnancy and 4 (0.6%) an incomplete abortion. No one was treated inadvertently beyond 12 weeks' gestation, but one woman was never pregnant. One woman who had a pre-abortion ultrasound was later managed as a caesarean scar ectopic. There were two cases of haemorrhage and no severe infections. Some 123 (18.5%) women sought advice by telephone for a concern related to the abortion and 56 (8.4%) then attended a clinic for review. Most (628, 95%) women rated their care as very or somewhat acceptable.

Conclusions This model of telemedicine abortion without routine ultrasound is safe, and has high efficacy and high acceptability among women.

Key messages

- Telemedicine medical abortion at home in the first trimester without routine ultrasound is effective, with low complication rates and high acceptability.
- Telemedicine service models need flexibility and resources to accommodate those women requiring clinical review post-abortion including ultrasound assessment.
- If given the choice, most women would choose a telemedicine consultation again rather than an in-person visit.

INTRODUCTION

Until recently, medical abortion care in Britain typically involved an in-person clinical consultation and a routine ultrasound scan to assess gestational age.[1 2] Women had to take mifepristone in a clinical setting but for those less than 10 weeks' gestation, there was the option to self-administer the second part of the treatment, misoprostol, at home. Women over 10 weeks' gestation were admitted to a clinical facility for misoprostol.[3]

In March 2020, the COVID-19 outbreak in the UK resulted in legislation being introduced permitting home use of mifepristone.[4] Recommendations from the Royal College of Obstetricians and Gynaecologists for the provision of abortion care were introduced that supported telemedicine consultations (telephone or video call), gestational assessment based on the date of last menstrual period (LMP) and delivery of medical abortion drugs to women eligible for this care at home.[5] In Scotland, additional clinical guidelines were introduced that supported

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telemedicine provision of medical abortion at home up to 11 weeks and 6 days' gestation.[4]

NHS Lothian is the sole provider of abortion care in Edinburgh and the surrounding region. Just over 2600 women receive abortion care annually.[6] All abortion care including post-abortion contraception is provided at no cost to the patient, as is the norm in the National Health Service (NHS). As a result of the new legislation and clinical guidance,[4 5] the service moved wholly to provision of abortion care by telemedicine and without routine ultrasound on 1 April 2020.

Globally, telemedicine provision of medical abortion has largely been carried out in areas where abortion access is restricted, but existing evidence suggests that rates of complete abortion, emergency admissions to hospital and serious complication rates are similar to those after abortion care in a clinical setting and that acceptability for women is high.[7–11]

We initiated an evaluation of the NHS Lothian telemedicine medical abortion service, based at the Chalmers Sexual and Reproductive Health Centre in Edinburgh. The aims were to determine the number of women having medical abortion at home without routine ultrasound, the efficacy of the procedure when delivered by this model, safety based on serious complications after treatment, and women's acceptability of their care.

METHODS

The telemedicine model

Anyone aged 16 years or older who contacted the service to discuss an unwanted pregnancy was given an appointment for a telephone consultation with a clinician.[2] They were advised to visit the service website for more information on what to expect at the teleconsultation, including audiovisual resources.[12] Those aged less than 16 years were routinely offered an in-person appointment.

During the teleconsultation, women were assessed for the need for ultrasound (LMP uncertain or >12 weeks ago, pain, bleeding, or significant risk factors for ectopic pregnancy).[4 5] For eligible women (LMP <12 weeks ago, no contraindications to mifepristone and misoprostol) requesting medical abortion at home, informed consent was taken verbally, and arrangements made for collection of a medication pack from the service or for couriered delivery to the woman's home. In line with national guidance introduced in relation to COVID-19, anti-D prophylaxis was not provided or considered necessary for rhesus-negative women having medical abortion in the first trimester.[4 5] The contents of the medication pack included prophylactic antibiotics and are shown in online supplemental table 1. Post-abortion contraception was discussed during the consultation, and condoms and short-acting hormonal contraception were included in the medication pack if women wished.[13] Those who requested long-acting reversible contraception (LARC) were offered a clinic appointment 2 weeks later.

For women requiring an in-person consultation and/or ultrasound, this pack was provided at that visit. For women over 12 weeks' gestation or choosing surgical abortion, the existing arrangements for direct admission to the local hospital for this procedure were made.[14] An overview of the telemedicine care pathway can be seen in online supplemental figure 1.

Evaluation

We conducted a prospective observational study of women having medical abortion at home via telemedicine from its instigation on 1 April 2020 until 9 July 2020. We prospectively collected data on the numbers requiring a pre-abortion ultrasound, as well as routinely collected data on gestation, demographic characteristics, reproductive history and choice of post-abortion contraception. For the purposes of the evaluation only, women were contacted by telephone by a researcher for an interviewer-administered questionnaire on days 4 and 14 after misoprostol administration.

The day 4 questionnaire asked about acceptability of the care and preparedness for the procedure. The day 14 questionnaire recorded the result of the self-performed low-sensitivity urine pregnancy test (LSPT) to confirm the success of the procedure,[15] method of contraception provided and women's ratings on the importance of different parts of the telemedicine model for future service development. Responses were either binary (yes/no), rated on a five-point Likert scale (eg, very acceptable to very unacceptable) or by selection from a predefined list of possible options (online supplemental figure 2).

If research staff received a clinical query or elicited information about a possible complication, women were transferred to the abortion service clinical advice line for assessment and care as needed. All these calls for advice were recorded in patient electronic records.

The outcome of the pregnancy (complete abortion, incomplete abortion, ongoing pregnancy) and complications (haemorrhage defined as ≥500 mL blood loss, severe infection defined as requiring intravenous antibiotics) were verified at 6 weeks after abortion through a review of both the regional hospital electronic patient records (TRAK) and the sexual health service records (NaSH).

The primary outcome of the study was efficacy of medical abortion, with success of abortion defined according to the Medical Abortion Reporting of Efficacy (MARE) guidelines as successful expulsion of pregnancy without the need for surgical intervention.[16] Secondary outcomes were severe complications (haemorrhage and severe infection), adverse outcomes such as undiagnosed ectopic pregnancy, gestation beyond 12 weeks, unscheduled contact with the service, acceptability of the telemedicine service, and contraception uptake.

Statistics

A descriptive analysis has been presented: continuous data as mean and standard deviation (for example, age) and categorical data as numbers and percentages

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of total responders. In some instances due to small numbers categorical responses may have been grouped; however, unless otherwise indicated we have treated all responses in the categories they were collected in. All statistical analysis was performed using SAS Enterprise Guide v 7.15 (SAS Institute Inc., Cary, NC, USA) and Microsoft Excel 2016 by an independent statistician.

Approvals

The project received approval from the NHS Lothian Sexual and Reproductive Health Service Quality Improvement Team and was not deemed to require ethical approval following review by the local NHS Research Ethics Committee scientific officer.

Patient and public involvement

Patients and members of the public were not directly involved in the design of this study.

RESULTS

During the study period, 826 women had a teleconsultation. Thirty-five (4.3%) women chose to continue with the pregnancy, 31 (3.8%) had a miscarriage diagnosed so did not proceed to abortion and the outcome was not known in 2 (0.2%) cases. Of the remaining 758 women who proceeded to abortion, 663 (87%) had a medical abortion at home and were included in the study cohort. The remainder had either a medical or surgical abortion in a hospital setting or were referred to an external provider in England for abortion as they were over 20 weeks' gestation and so the abortion care could not be provided at the local hospital.

Characteristics of women

Table 1 summarises the demographic information and gestational age data. The mean (SD) age was 27.6 (6.6) years (range 16 to 50 years). In 522/663 (78.7%) cases the gestation was determined using LMP alone. In 141 (21.3%) cases a pre-abortion ultrasound was performed for uncertain gestation (n=95; 14.3%) or to confirm that pregnancy was intrauterine (n=33; 5.0%). Thirteen (2%) women had already had an ultrasound at a different service before attending. Capturing gestation in weeks, 56% of women had a gestation of 5 weeks to 6 weeks and 6 days.

Table 1 Demographic characteristics of the telemedicine cohort.

	Patients who had medical abortion at home	
Characteristic	**n**	**%**
Total	663	100
SIMD*		
Unclassified	2	0.3
1	120	18.1
2	198	29.9
3	101	15.2
4	111	16.7
5	131	19.8
Reproductive history		
Previous live birth	324	48.9
Previous medical abortion	222	33.5
Previous surgical abortion	39	5.9
Previous miscarriage	125	18.9
Previous ectopic pregnancy	12	1.8
Smoking status		
Never	367	55.4
Past	60	9
Current	193	29.1
Unknown	43	6.5
Gestation (weeks+days)†		
<3+6	1	0.2
4–4+6	72	10.9
5–5+6	188	28.4
6–6+6	182	27.5
7–7+6	112	16.9
8–8+6	58	8.7
9–9+6	29	4.4
10–10+6	15	2.3
11–11+6	6	0.9

*Scottish Index of Multiple Deprivation.[24]
†For 141 patients the gestational age was taken from an ultrasound result. For all the remaining patients the gestational age was taken from the last menstrual period (LMP).

Outcome of medical abortion

The outcomes of medical abortion are shown in table 2. A complete abortion took place in 650/663 (98%) cases. Eight of the nine failed abortions (ongoing or incomplete) were at gestations <10 weeks. No one was known to have been treated inadvertently beyond 12 weeks' gestation.

Complications and unscheduled care after abortion

Some 16/663 (2.4%) women made unscheduled attendances to the hospital. Two (0.3%) of these women were admitted with haemorrhage but neither required transfusion (both <10 weeks' gestation). A further 13 (2%) women attended hospital with pain and/or bleeding but required only observation (n=7) or intravenous fluids (n=3) or were sent home with oral antibiotics (n=3). One woman was admitted with an unrelated medical event. No one presented with severe infection requiring intravenous antibiotics.

Some 123/663 (18.5%) women telephoned the abortion service for clinical advice. In 67 (10.1%) cases only telephone advice was required. In 56 (8.4%) cases a clinic visit was subsequently scheduled because of a positive or invalid LSPT (n=34), symptoms of continuing pregnancy (n=18) or persistent pain (n=4). In total, a post-abortion

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Table 2 .Efficacy of medical abortion

Outcome	Cohort (n=663)* n (%)
Complete abortion	650 (98.0)
Ongoing pregnancy	5 (0.8)
Incomplete abortion	4 (0.6)

*The remaining four outcomes were: n=2 (0.3%) did not proceed to take the abortion medication and self-referred for antenatal care to continue the pregnancy. n=1 was presumed to have a caesarean scar ectopic pregnancy. She had an ultrasound at the hospital early pregnancy unit before referral for abortion that reported a small sac low within the uterus with a possible fetal pole. She re-presented 1 week after medical abortion with persisting pregnancy symptoms. A further ultrasound had unchanged findings and given her history of caesarean delivery, it was considered as a likely caesarean scar ectopic. She was managed by the hospital and treated uneventfully with methotrexate. n=1 reported no bleeding after medical abortion. She had an empty uterus on ultrasound 4 days following misoprostol and a negative serum human chorionic gonadotrophin (hCG), suggesting that she was probably never pregnant.

ultrasound was conducted in 66 (9.9%) cases (hospital admissions and clinic visits combined).

Contraception

The method of contraception provided to women is shown in table 3. The the most common method was the progestogen-only pill (desogestrel 75 µg) provided to 423 (63.8%) women. Fifty-eight (8.7%) women received long-acting reversible contraception (LARC).

Acceptability

Almost all (n=652, 98.3%) the women provided responses to at least one follow-up questionnaire. Complete questionnaires at both day 4 and day 14 post-abortion were available for 605 (91.3%) women. Forty-five (6.8%) women responded to the day 4 contact only and 2 (0.3%) only responded to the day 14 contact.

Table 3 Contraceptive method supplied (based on day 14 questionnaire response and clinic records)

Contraceptive method	Cohort (n=663) n	%
POP	423	63.8
COCP	49	7.4
Condoms	62	9.4
Injectable*	19	2.9
Implant*	17	2.6
IUD*	19	2.9
IUS*	20	3
No method	40	6
Patch	14	2.1

*These methods were initiated if women attended clinic for a pre-abortion ultrasound appointment (injectable and implant only) or at a rapid access clinic at a later date.
COCP, combined oral contraceptive pill; IUD, intrauterine device; IUS, intrauterine system; POP, progestogen-only pill.

Some 627 (94.6%) women stated at day 4 that they were 'very' (n=516, 77.8%) or 'somewhat prepared' (n=111, 16.7%) for their treatment following the telemedicine consultation.

Similarly, 628 (94.7%) women rated the abortion experience as 'somewhat' (n=43, 6.5%) or 'very' (n=585, 88.2%) acceptable at day 4. Asked on day 14, 588 (88.7%) stated that they would opt to have treatment at home again if they needed another abortion.

Regarding acceptability of the remote consultation (day 14), 574 (86.6%) women rated it as 'somewhat' (n=24, 3.6%) or 'very' (n=550, 83%) acceptable. Some 473 (71.3%) women stated that they would opt for a telephone consultation again if they required an abortion in the future.

Features of importance in an ideal abortion care service

On day 14, women were asked to rate the importance of the features listed in table 4 for a 'perfect abortion service'. The feature rated by most respondents as 'important' or 'very important' was 'being able to collect all my medications from a pharmacy' by 366/567 (64.6%) women. Ultrasound was rated 'unimportant or very unimportant' by 302/569 (53.1%) women.

DISCUSSION

Telemedicine medical abortion at home was used by almost nine out of ten women and, of these, only two out of ten women required a pre-abortion ultrasound. The study showed high rates of complete abortion, low rates of complications and low rates of unscheduled contact. These findings are similar to previous cohort studies from this service of women who took misoprostol at home having had routine ultrasound and mifepristone in clinic.[14 15 17] Women reported high levels of preparedness to use the medications in their own homes. Indeed, acceptability of care was high, and the majority of women expressed a preference for choosing this model of care again in the future.

This study provides support for continuing this model of care beyond the current pandemic. There was one instance of unnecessary treatment, where the woman had probably never been pregnant. The only ectopic pregnancy in the cohort had a pre-abortion ultrasound and was initially thought to have an intrauterine pregnancy. This highlights how routine ultrasound can provide false reassurance of intrauterine pregnancy.[18] Indeed, the treatment failure and persistence of pregnancy symptoms may have expedited diagnosis and treatment of this ectopic.

Not requiring pre-abortion ultrasound potentially expands the range of healthcare providers who can offer medical abortion,[19] as recommended by the World Health Organization (WHO).[20] There is also existing evidence to support the safety of medical abortion provision without ultrasound based on LMP alone.[21] When asked, more than half of the women in our study considered the use of routine

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Table 4 Aspects of a perfect abortion service from the day 14 questionnaire (ie, how important each aspect was considered by women)

	Unimportant		Neutral		Important	
Aspect	**n**	**%**	**n**	**%**	**n**	**%**
Having an ultrasound scan	302	53.1	116	20.4	151	26.5
Evening face-to-face clinic	133	23.8	206	36.2	230	40.4
Evening telephone consultation	61	10.8	208	36.7	298	52.6
Skype or video consultation	383	67.9	78	13.8	103	18.3
A mobile phone app to send or receive information in advance	92	17.5	101	18.0	367	65.5
Online booking	66	12.1	119	21.8	361	66.1
Medication posted to me	74	13.0	152	26.8	342	60.2
Medication that could be collected from a local pharmacy	58	10.2	143	25.2	366	64.6
Able to get the treatment from my general practitioner	112	19.8	160	28.2	294	51.8

Some women did not answer certain questions but responded to others and so the denominators and totals may vary slightly between variables.

ultrasound to be 'unimportant' and over half of the women also considered that general practitioners as abortion providers would be an important future development.

In our study, rates of telephone contact to the service for a concern related to the abortion were similar to our previous studies.[14 15] However, we did observe a higher proportion of women requiring a post-abortion clinic attendance (8.4%) compared with our former service model with routine pre-abortion ultrasound and clinic-administered mifepristone with misoprostol at home (2.7%).[14] The majority of the post-abortion clinic visits were to exclude continuing pregnancy following a positive or invalid LSPT. It is possible that the telephone contact from the researcher triggered more of these post-abortion visits since they actively questioned women about the pregnancy test result, rather than leaving them to call the service if they had a concern. It is also likely that without the knowledge of a pre-abortion ultrasound, staff have a lower threshold for arranging a clinic review post-abortion to minimise the chance of missing an ectopic or a pregnancy that may have been at a more advanced gestation. This need for post-abortion clinical support needs to be factored into provision of telemedicine abortion.

Most women received contraception, but this was mostly oral contraceptive pills, which are less effective than LARC methods[22] but can be initiated immediately if a woman has all her care by telemedicine. Fewer than one in ten women in this study received LARC in contrast to previous studies at our service where around one-third of women received LARC.[14] Although, strategies such as 'fast track' to post-abortion contraception clinics can facilitate access to LARC,[23] it is possible that the pandemic may have played a role in women's choice both to use contraception and also the method. Some women may have opted not to use LARC as it required a further visit to a clinic with risk of exposure to the virus, plus the convenience of receiving oral contraception in the treatment pack.

Our study also showed that there is support among women for several simple modifications to the service that could be developed in the future, including expanding the range of options for accessing medications such as postal delivery of medical abortion drugs or collection from a local pharmacy.

This study had an extremely high rate of follow-up for all outcomes. This may be in part because women were at home during the COVID-19 lockdown restrictions and so were easily contactable. Using the electronic patient record for the entire region, we were able to actively search for all serious complications within a 6-week timeframe, and verify abortion outcomes rather than relying on self-reporting at an earlier timepoint alone. Nevertheless, the study size, while considerable, is still too small to detect changes in rare events. While possible, it is extremely unlikely during this period when the study was conducted that many women will have travelled out of the region and suffered a complication. Of course, the telemedicine service was devised and evaluated during the COVID-19 pandemic and so is not yet embedded under 'normal' circumstances, where the proportion of women choosing or being invited for in-person care may be different. In addition, qualitative research is required to provide more nuanced information on women's views on the acceptability of the telemedicine medical abortion service.

CONCLUSIONS

This model of telemedicine medical abortion without routine ultrasound is safe, and has high efficacy and high acceptability among women. This study provides support for continuation of this model of care in this setting beyond the current pandemic.

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Contributors JRW and STC designed the study, analysed the data and drafted the manuscript. AJ and KM contributed to questionnaire design and collected the data. EE undertook statistical analysis. All authors reviewed the final manuscript prior to submission.

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PLOS ONE

RESEARCH ARTICLE

Effectiveness and safety of early medication abortion provided in pharmacies by auxiliary nurse-midwives: A non-inferiority study in Nepal

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Data Availability Statement: The authors are unable to make their data available in a public repository due to ethical restrictions, including the sensitive nature of the study topic (abortion) and particular privacy concerns for participants who are classified by the UCSF IRB as a vulnerable population (pregnant women, illiterate women, seeking a stigmatized service). De-identified data used to make the conclusions for this study will be made available upon written request to the first author (corinne.rocca@ucsf.edu) or Sarah Raifman

Abstract

Background

Expanding access to medication abortion through pharmacies is a promising avenue to reach women with safe and convenient care, yet no pharmacy provision interventions have been evaluated. This observational non-inferiority study investigated the effectiveness and safety of mifepristone-misoprostol medication abortion provided at pharmacies, compared to government-certified public health facilities, by trained auxiliary nurse-midwives in Nepal.

Methods

Auxiliary nurse-midwives were trained to provide medication abortion through twelve pharmacies and public facilities as part of a demonstration project in two districts. Eligible women were ≤63 days pregnant, aged 16–45, and had no medical contraindications. Between 2014–2015, participants (n = 605) obtained 200 mg mifepristone orally and 800 μg misoprostol sublingually or intravaginally 24 hours later, and followed-up 14–21 days later. The primary outcome was complete abortion without manual vacuum aspiration; the secondary outcome was complication requiring treatment. We assessed risk differences by facility type with multivariable logistic mixed-effects regression.

Results

Over 99% of enrolled women completed follow-up (n = 600). Complete abortions occurred in 588 (98·0%) cases, with ten incomplete abortions and two continuing pregnancies. 293/297 (98·7%) pharmacy participants and 295/303 (97·4%) public facility participants had complete abortions, with an adjusted risk difference falling within the pre-specified 5 percentage-point non-inferiority margin (1·5% [-0·8%, 3·8%]). No serious adverse events

(sarah.raifman@ucsf.edu) after obtaining the necessary ethical approvals.

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occurred. Five (1.7%) pharmacy and two (0.7%) public facility participants experienced a complication warranting treatment (aRD, 0.8% [-1.0%-2.7%]).

Conclusions

Early mifepristone-misoprostol abortion was as effective and safe when provided by trained auxiliary nurse-midwives at pharmacies as at government-certified health facilities. Findings support policy expanding provision through registered pharmacies by trained auxiliary nurse-midwives to improve access to safe care.

Introduction

Unsafe abortion contributes substantially to maternal mortality and morbidity worldwide, accounting for approximately 18% of maternal deaths [1, 2]. Unsafe abortion occurs predominantly in lower-income countries where abortion is illegal or highly restricted, and in remote areas where trained providers and equipment are scarce [3]. In Nepal, where abortion was legalized in 2002 [4], unsafe abortion still accounted for 7% of maternal deaths in 2009, with access to safe and legal care particularly constrained in rural regions [5].

Efforts to improve access to safe abortion have focused on expanding the provider base, as well as decentralizing medication abortion (MA) provision beyond traditional hospital and clinic settings. On the World Health Organization (WHO) Essential Medicines List for developing countries [6], mifepristone and misoprostol abortion is approximately 95% effective in pregnancies under nine weeks, with a gradual decline in efficacy with increasing gestation [7]. The safety and effectiveness of MAB when provided by non-physician clinicians, including nurses and auxiliary nurse midwives (ANMs), has been well-established [8–11], and 2015 WHO guidelines on appropriate health worker roles in abortion care recommend implementing nurse/ANM provision at scale [12]. Accordingly, nurses and ANMs now regularly provide abortion care in Nepal, including in primary-level public health facilities in many districts [13].

Expanding access to MAB through regulated pharmacies may also be a promising avenue to reach women with safe care, though no interventions have been evaluated [14]. In many countries including Nepal, pharmacies are a common first contact point for women seeking abortion and serve as important sources of information and referral [14, 15]. They are more accessible than clinics, particularly in rural areas and for women who have limited autonomy and mobility, and may offer increased privacy compared to public facilities [14, 16, 17]. MAB can be provided without laboratory tests or ultrasounds, and women can safely self-administer misoprostol, complete the abortion, and self-evaluate completion at home [18–20]. In Nepal and elsewhere, however, unskilled and untrained pharmacy workers often provide inaccurate information and dispense unsafe or ineffective methods [21–26], and formative research training pharmacy workers on MAB eligibility and dosing has only been moderately successful [15, 27]. As such the WHO does not currently recommend pharmacist provision [12]. However, other cadres of trained health care providers, including nurses and ANMs, working in pharmacy settings could potentially incorporate MAB provision with clinical protocols into their services, expanding access points for safe services.

Nepal is a leader in innovating access to abortion. Since abortion was decriminalized in Nepal in 2002 [4], access to legal services has expanded to all districts [28, 29]. Abortion is legal for any reason up to 12 weeks' gestation, and second-trimester procedures, allowed under

certain circumstances, became available in 2007. Mifepristone-misoprostol became legally available in 2009, and Nepal is one of the few lower-income countries with national MAB practice guidelines. Provision by nurses and ANMs, who have a tenth grade education and 18 and 24 months' pre-service formal training, respectively, is permitted. Declines in the severity of abortion complications following legalization have been attributed in part to nurse/ANM service provision as well as the availability of MAB [12, 30]. In a 2013 pharmacy study in two Nepali districts, over 10% of pharmacy workers were trained as nurses or ANMs, and 85% of pharmacies had private spaces for client consultation [31]. Leveraging nurses and ANMs–a trained clinical workforce with a record of safe MAB–to deliver services in pharmacy settings, where women already seek care, could be an important next step toward increasing access to safe abortion.

In this observational demonstration study, we tested the hypothesis that the effectiveness and safety of mifepristone medication abortion provided by trained ANMs through pharmacies would not be inferior to provision through public health facilities that are government-certified to provide MAB. Empirical data on the effectiveness and safety of MAB provision from pharmacies by trained providers do not yet exist but are essential to inform evidence-based policy in Nepal and elsewhere.

Materials and methods

Study design and participants

This study was an observational, non-inferiority study comparing outcomes of medication abortion provided by trained auxiliary nurse-midwives in two settings: pharmacies and government-certified public health facilities. Sites were located in both semi-urban and remote regions of the Chitwan and Jhapa districts in the lower Terai region, bordering India. Twelve sites participated: six privately-owned pharmacies and six public health facilities, including four primary health care centers and two health posts. Primary health care centers provide basic health care services, minor surgeries, and aspiration and medication abortion; they are typically staffed by a physician, a few nurses/ANMs, and non-clinical staff. Health posts provide basic health care services and are staffed by a nurse/ANM, a health worker, and non-clinical staff; some are approved to provide medication abortion. Participating pharmacies had to be registered with the Department of Drug Administration, Ministry of Health and Population; have locked storage for data; and have a private space for patient examination, a typical set-up in Nepal [31].

Clinical study procedures were conducted by six ANMs. Each was trained as a skilled birth attendant, had required government training and certification to provide MAB at a public facility, and worked in a pharmacy. MAB outcomes can vary substantially between providers based on experience and tendency to intervene [32]. Because we were evaluating the effect of location of administration, not provider experience or ability, we designed the study such that the same ANM provided services from one pharmacy and one public health facility [31]. Study ANMs were identified in consultation with the District Public Health offices overseeing study sites.

ANMs completed a three-day training on study procedures, ethics and voluntary informed consent, and provision of MAB through the pharmacy, including ensuring confidentiality, storage of clinical case reports, and referrals. At training completion, each participating pharmacy received certification from the Ministry of Health and Population to provide MAB for the experimental demonstration study period. One ANM was relocated during the study; a replacement was trained on-site by a study investigator. Six female research assistants with nursing training were selected and trained to conduct non-clinical data collection.

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Women presenting at study sites seeking medication abortion were eligible to participate if they were aged 16–45 and had an established pregnancy of ≤63 days based on pelvic exam performed at the site. Women were excluded if they had already attempted abortion with the same pregnancy, lived outside of Nepal, had any medical contraindications to mifepristone-misoprostol, or were unable to provide consent or complete study visits.

Data were collected October 2014-September 2015. A pilot phase among 57 participants was conducted October-December 2014 to assess feasibility and test instruments. Results of an interim analysis were shared with two University of California, San Francisco (UCSF) obstetrician-gynecologists to determine that complications or incomplete abortions at pharmacy sites were not higher than expected. As pre-specified in the protocol, because no changes to the protocol were required, pilot data were included in analyses.

Ethical approval was obtained from the UCSF Committee on Human Research and the Nepal Health Research Council. The study was endorsed by the Family Health Division, Ministry of Health and Population, Nepal. We followed published guidelines for reporting of non-inferiority trials [33].

Procedures

For women presenting at all study sites requesting medication abortion, ANMs completed clinical screening for MAB eligibility, as is standard patient care. ANMs recorded last menstrual period and MAB contraindications. They conducted a pelvic exam to assess gestational length and identify signs of ectopic or adnexal mass or infection. Women meeting MAB eligibility criteria (both those enrolling and not enrolling) received MAB counseling, services, and information on when and where to seek care for complications.

Clinical procedures at all sites followed the standard Nepali medication abortion protocol [34], which is consistent with international safe abortion guidelines [18]. Ultrasound and pregnancy confirmation via urine pregnancy test are not part of routine care, but providers could use them or refer women at their discretion. Participants took 200 mg mifepristone orally in front of the provider, followed by 800 μg misoprostol sublingually or intravaginally 24 hours later, usually at home (Medabon®, Sun Pharmaceutical Industries Ltd., Gujarat, India). Due to shortages of Medabon® in study districts, and to eliminate pressure on women to enroll to obtain the drug, the study purchased and provided mifepristone-misoprostol to all women presenting to study sites, regardless of participation. All participants and non-participants were charged 500 Rupees ($5) for MAB care, standard price at public facilities at the time.

Women meeting eligibility criteria provided verbal informed consent. After taking mifepristone, participants completed interviewer-administered baseline questionnaires assessing sociodemographics, pregnancy and contraceptive history, pregnancy intentions, and experiences seeking services.

In the Nepali protocol, patients are provided context-appropriate instructions for when to seek care for a complication or incomplete abortion; follow-up visits are not mandatory [34]. However, to capture study outcome data, participants were asked to return after 14–21 days. At follow-up, ANMs completed a clinical interview about symptoms experienced and any medical care received since enrollment. They conducted a pelvic exam, providing or referring patients for care as needed, including for aspiration abortion for incomplete abortion; additional doses of misoprostol were not provided. Additional follow-up visits were scheduled at the ANM's discretion until all medical issues were resolved and abortions were complete. Finally, research assistants administered a follow-up questionnaire to capture participant satisfaction. All study procedures were conducted privately and confidentially. Participants received a gift worth 150 Rupees ($1.50) after each interview and 150 Rupees for travel costs at

follow-up. Costs of aspiration abortions and treatment for medical care received were covered by the study.

Data were managed by the Center for Research on Environment Health & Population (CREHPA). Research assistants secured data collection instruments at the study sites. Instruments were transferred to the CREHPA offices monthly.

Outcomes

The primary outcome was successful complete abortion (versus incomplete abortion or continuing pregnancy), without aspiration abortion, within 30 days of mifepristone [9]. Incomplete abortion was defined as the products of conception remaining in the uterus with continued bleeding, enlarged uterus, and open cervix. Continuing pregnancy was when symptoms of pregnancy continued and aspiration abortion was necessary to terminate the pregnancy. Aspiration abortions reported by participants and those determined as necessary by study ANMs at the follow-up visits were included.

The secondary outcome was experience of complications requiring treatment, including any case in which participants sought treatment or ANMs provided or referred for care at a follow-up visit. Serious adverse events, including hemorrhage needing blood transfusion and conditions requiring hospitalization, were captured. Finally, we assessed side effects experienced and satisfaction with services and MAB itself. Data for all outcomes were recorded on follow-up clinical case reports and questionnaires.

Statistical analysis

This non-inferiority study was designed to assess relative differences in complete abortion among women at pharmacies versus certified public health facilities. We conducted sample size calculations using an expected 97% complete abortions, based on a *Lancet* study of mid-level provider MAB provision [9]. The non-inferiority limit defined -5% as the acceptable difference in successful abortion proportions, based on prior research and feasibility [9, 33]. A sample size of 586 was calculated to be sufficient to establish non-inferiority of pharmacy distribution, with two-sided alpha of 5% and 80% power; an enrollment ratio of 1:1; and increases in the sample of 10% for attrition, 10% to control for sociodemographic differences by arm, and 40% to account for clustering. We based the intraclass correlation coefficient (ICC) on prior research (0.001) [9, 35], increasing it to 0.005 to be conservative. Calculations were replicated varying the expected outcome by 1%, and results did not change substantially.

To assess differences in participant characteristics by arm, we fit a series of bivariable mixed effects models, including random effects for provider and site for clustering. We calculated the proportions of women experiencing complete abortion overall and by arm. To assess non-inferiority of pharmacy MAB as compared to public health facility MAB, we fit a logistic mixed effects model with random provider and site effects. Based on this model, we calculated the crude risk difference by arm and 95% confidence intervals (CI). If the CI fell above -5%, the predetermined non-inferiority margin, we could conclude that pharmacy provision is not inferior to public health facility provision. We repeated mixed effects analyses adjusting for covariables found to differ between arms (education, parity, prior contraceptive use), as well as age and gestational length. We examined complications similarly. We conducted sensitivity analyses, assuming that the five participants who were lost-to-follow-up required aspiration abortions and had complications. Analyses were conducted using Stata v14 (College Station, TX). Results were reported at $p \leq 0.05$.

Results

Participating ANMs were all female and a median of 37 years old (range 30–57). They had spent a median of 16 years (range 6–34) in medical practice and had five years' experience (range 3–5) providing medication abortion.

Overall, 660 women presented to study sites seeking MAB during the enrollment period (Fig 1), with 326 presenting at pharmacies and 334 at public health facilities. Of these, 50 did not meet eligibility criteria, with 47 >63 days gestation and three having medical contraindications (two chronic adrenal failure, one bleeding disorder). Two women at pharmacies and three at public health facilities were not enrolled for other reasons (concern of possible uterine infection, anemia, cholelithiasis, hypertension medication, and heart disease). Five of the 605 women enrolled into the study were lost to follow-up after treatment (<1%).

The 605 participants were on average 28 years old (Table 1). Almost all were married (99%), and 94% had children. A majority (61%) worked outside of the home, mostly in farming or livestock. About half had ever used an effective contraceptive method, and 62% wanted no more children. Participants presenting at pharmacies and public health facilities were similar by age, gestational length, prior abortion (33%), and knowledge of abortion legality (50%). However, pharmacy participants had more education (mean 8 vs. 7 years), lower parity (mean 1.7 vs. 2.1), were less likely to have used an effective contraceptive (40% vs. 57%), and were slightly less likely to desire no more children (55% vs. 67%, p = 0.06). Pharmacy participants experienced slightly shorter travel times to the facility than public facility participants (mean 28 vs. 34 minutes, p = 0.06).

The proportion of women having complete abortions overall was 98.0%, with 1.7% (n = 10) having an incomplete abortion and 0.3% (n = 2) having a continuing pregnancy (Table 2). By arm, the complete abortion proportions were 98.7% for pharmacy and 97.4% for public health facility, for a crude risk difference of 1.3% [-0.9%, 3.5%]. After adjusting for covariables, the risk difference was 1.5% [-0.8%, 3.8%], with the 95% CI well above the non-inferiority limit of -5%, indicating non-inferiority for abortion effectiveness. All participants with incomplete abortions and continuing pregnancies received manual vacuum aspiration from the study ANM or by referral.

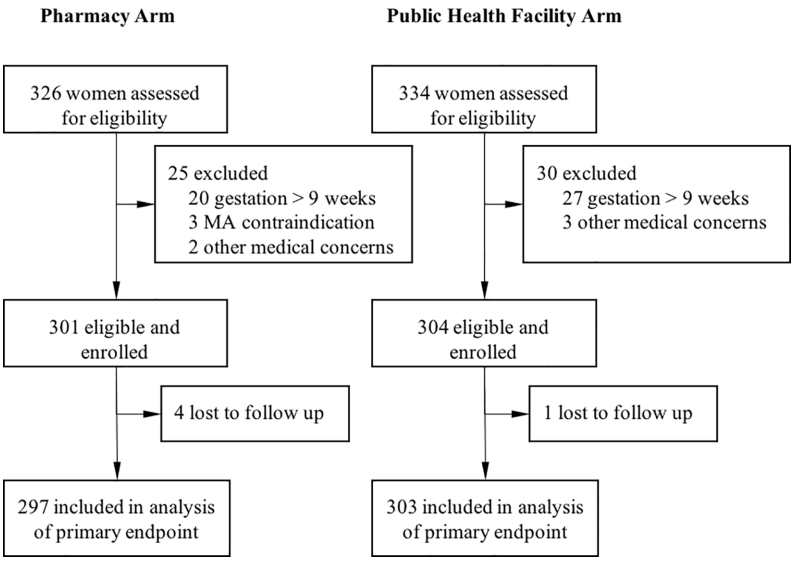

Fig 1. Study profile.

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Table 1. Participant characteristics, by facility type (n = 605).

	Pharmacy	Public Health Facility	p	Total
	(n = 301)	(n = 304)		(n = 605)
	Mean (SD)	Mean (SD)		Mean (SD)
Age (years) (range: 16–44)	27.2 (5.9)	28.0 (6.0)	0.24	27.6 (5.9)
Education (years) (range: 0–17) (n = 604)	7.7 (4.0)	6.8 (4.2)	0.02	7.2 (4.1)
Household assets* (proportion) (range: 0–1) (n = 604)	0.6 (0.2)	0.5 (0.2)	0.12	0.6 (0.2)
Parity (years) (range: 0–7)	1.7 (1.0)	2.1 (1.2)	0.02	1.9 (1.1)
Gestation (days) (range: 35–63)	44.9 (6.0)	44.8 (5.9)	0.57	44.9 (5.9)
Travel time to facility (minutes) (range: 2–240)	28.0 (26.2)	34.2 (36.6)	0.06	31.1 (32.0)
	n (%)	n (%)		n (%)
Married	297 (98.7)	303 (99.7)	0.14	600 (99.2)
Working outside home	192 (63.8)	175 (57.6)	0.24	367 (60.7)
Caste/Ethnicity				
Brahman/Chettri	139 (46.2)	139 (45.7)	0.74	278 (46.0)
Relatively Advantaged Janajatis	17 (5.7)	13 (4.3)		30 (5.0)
Disadvantaged Janajatis/Non-Dalit	119 (39.5)	111 (36.5)		230 (38.0)
Dalit/Untouchable	26 (8.6)	41 (13.5)		67 (11.1)
Parity				
0	23 (7.6)	15 (4.9)	<0.01	38 (6.3)
1	115 (38.2)	79 (26.0)		194 (32.1)
2	117 (38.9)	129 (42.4)		246 (40.7)
3+	46 (15.5)	81 (26.7)		127 (21.2)
Prior abortion	97 (32.2)	101 (33.2)	0.83	198 (32.7)
Future fertility preference				
No more children	167 (55.5)	205 (67.4)	0.06	372 (61.5)
Child > 2 years	116 (38.5)	83 (27.3)		199 (32.9)
Child within 2 years	6 (2.0)	5 (1.6)		11 (1.8)
Don't know	12 (4.0)	11 (3.6)		23 (3.8)
Ever use of effective contraception	121 (40.2)	172 (56.6)	0.01	293 (48.4)
Know abortion is legal	150 (49.8)	151 (49.7)	0.75	301 (49.8)

* Assessed with 8 items asking whether participants' households had amenities such as electricity, radio, landline phone, and bicycle.

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No serious adverse events occurred. Seven participants experienced a complication that warranted treatment based on provider assessment (Table 2). By arm, 1.7% (n = 5) of pharmacy participants and 0.7% (n = 2) of public health facility participants required treatment, mostly antibiotics for fever and potential infection. The risk difference was not statistically significant (aRD = 0.8% [-1.0%, 2.7%]). Participants reported expected side effects, most commonly abdominal cramping (92%), nausea (61%), and chills (42%), with no differences by arm.

Proportions of complete abortions and complications for individual ANMs ranged from 95.6%-99.3% (ICC = 0.001) and 0–3.5%, respectively. Results were consistent assuming the five participants lost-to-follow-up had negative outcomes: complete abortion aRD = 0.4% [-2.2%, 3.1%]; complication aRD = 1.7% [-0.8%, 4.2%].

Acceptability of services was high across sites, with no differences by study arm (Table 3). Satisfaction with MAB as a method was high (64% satisfied, 34% highly satisfied), as was

Table 2. Medication abortion outcomes (n = 600).

	Pharmacy (n = 297)	Public Health Facility (n = 303)	Risk Difference (95% CI)	Adjusted Risk Difference* (95% CI)
Complete abortion (%)	98.7	97.4	1.3 (-0.9, 3.5)	1.5 (-0.8, 3.8)
Serious adverse event (%)	0	0		
Complication (%)	1.7	0.7	0.9 (-1.0, 2.8)	0.8 (-1.0, 2.7)

* Adjusted models control for age, education, parity, prior contraceptive use, and gestation.

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satisfaction with services received (62% satisfied, 36% highly satisfied). Women experiencing an incomplete abortion, continuing pregnancy, or complication were less likely to report satisfaction with MAB (56.3% vs. 99.7%, $p<0.001$) or services received (78.6% vs. 99.7%, $p<0.001$). 95% of pharmacy participants and 98% of public health facility participants reported they would prefer to go to a pharmacy and public facility, respectively, if MAB services were needed again ($p<0.05$).

Discussion

In this observational non-inferiority study, the effectiveness and safety of early mifepristone-misoprostol medication abortion provided by auxiliary nurse-midwives at pharmacies was as effective and safe as compared to when provided by ANMs at government-certified health facilities. Our study showed ANM provision of MAB in both pharmacies (98.7%) and public facilities (97.4%) was as effective as has been demonstrated in other studies using the same regimen (91–99%) [7]. Our findings provide evidence that with minimal additional training, ANMs with previous experience providing MAB can administer services as effectively and

Table 3. Participant experiences with medication abortion, by facility type (n = 600).

	Pharmacy (n = 301)	Public Health Facility (n = 304)	p
Symptoms experienced:			
Abdominal cramping/pain	92.3	91.4	0.82
Nausea	62.0	60.4	0.68
Chills/shivering	46.1	37.3	0.12
Felt able to manage any symptoms	99.0	97.7	0.23
Satisfaction with MAB as a method			
Highly satisfied	35.0	33.7	0.87
Satisfied	64.0	64.0	
Not satisfied	1.0	2.3	
Satisfaction with services at facility			
Highly satisfied	38.4	35.4	0.82
Satisfied	60.9	63.6	
Not satisfied	0.7	1.0	
Preferred facility for future services if needed			
Pharmacy	94.6	1.7	<0.05*
Public Health Facility	4.7	97.7	
Don't know/no opinion	0.7	0.7	

* Assessed as preferring to come to the same facility type.

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safely at a pharmacy as a government-certified facility in a low-resource setting, with high satisfaction across settings.

While nurse and ANM provision expands the abortion provider base, the potential of this trained workforce to reach women is limited by the requirement that services be provided from government-certified public health facilities. Pharmacies are more accessible than clinics, particularly in rural and mountainous areas, and are often the first contact point for women seeking services [14]. The leveraging of pharmacies to expand access to other reproductive health technologies, including injectable and emergency contraceptives, has already been successful in Nepal [36]. Although interventions to train pharmacy workers in harm reduction strategies in Zambia and Nepal have achieved moderate improvement in knowledge and referral practices [15, 27], pharmacists and pharmacy workers, often provide unsafe abortion care [14, 21–26], and the WHO does not currently recommend they provide care. Allowing nurses and ANMs with MAB training to deliver services from pharmacy settings may be the next step in an incremental approach to increasing access to care. Safe pharmacy care from nurses/ANMs may not only mitigate the unsafe or ineffective care women might otherwise receive, but could also expand safe provision beyond hospitals and clinics to a location where women already seek care, thereby reducing unsafe abortion-related morbidity and mortality.

This study has limitations. Public health facility participants returning to the facility for care may have been more likely to receive intervention due to the presence of other clinicians, thereby biasing results in favor of pharmacies; however, incomplete abortions and complications were infrequent in both facility settings in this study. The 14–21 day follow-up period might not have detected delayed complications or ongoing pregnancies. However, study ANM remained in touch with participants until any issues detected were fully resolved, and it is reasonable to believe that most participants who experienced a delayed complication would return to the study facility for care. Our measures of satisfaction did not capture the acceptability of specific aspects of care provided. Finally, given feasibility constraints for a government-approved demonstration project, we were limited to including twelve recruitment sites and six ANMs. We had planned originally for pharmacy providers to rely on self-reported date of last menstrual period for assessment of gestation. Study ANMs, however, were uncomfortable omitting the pelvic exam because they were accustomed to conducting it. Our findings are thus not generalizable to pharmacies without clinical exam space, nor do they apply to unregulated pharmacies or those without ANMs with abortion training. Research should examine whether removing the pelvic exam from the baseline clinical assessment affects abortion effectiveness and safety.

This study is the first to our knowledge to evaluate with a rigorous design and control group the effectiveness of medication abortion provision by trained clinicians in pharmacy settings. Our design isolated the effects of facility environment from the qualifications of providers on medication abortion outcomes. We had high (>99%) follow-up, supporting the internal validity of results. Importantly, this research with ANMs was clinically and ethnically appropriate, conducted in a manner consistent with World Health Organization guidelines, the scientific literature on ANM provision of abortion care, and current clinical practice and law in Nepal. Specifically, the safety and effectiveness of MAB when provided by non-physician clinicians, including nurses and ANMs, has been firmly established in peer-reviewed research [8–11]. The WHO has published evidence-based guidelines delineating the appropriate roles of different cadres of health providers in providing abortion care, recommending the implementation of nurse and ANM provision of first-trimester MAB care at scale as a safe and effective strategy for increasing access to safe pregnancy termination [12]. ANM provision of first-trimester MAB care is legal in Nepal for nurses and ANMs trained as skilled birth attendants and

who have completed government training and certification. ANMs currently provide medication abortion care throughout Nepal [13, 29].

Conclusion

Despite improvements in access to safe abortion care in Nepal, women continue to face obstacles to safe abortion and to seek care from unskilled providers, with access to safe care particularly constrained in rural regions [5]. This study provides data supporting the expansion of medication abortion services to registered pharmacy settings when care is provided by an appropriately trained ANM. Future research should build on these findings by investigating ways to safely implement pharmacy ANM provision at scale and monitor quality of care provided.

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Making Abortion Safe

RCOG's global initiative to advocate for women's health

Royal College of Obstetricians & Gynaecologists

Best practice in abortion care

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Introduction to RCOG Best Practice Papers

The Royal College of Obstetricians and Gynaecologists (RCOG) Best Practice Papers are peer-reviewed, easy-to-use, adaptable documents that set out the essential elements for evidence-based clinical practice.

The best practices described are drawn from current evidence-based guidance produced by organisations such as the World Health Organization (WHO), the RCOG and the National Institute for Health and Care Excellence (NICE).

To be readable and useful to people providing healthcare on a daily basis, the papers have been deliberately kept short and succinct. Therefore, the primary evidence for recommendations and the strength of that evidence have been omitted but can be found in the original source documents. Very recently published evidence has been assessed to determine whether any recommendations from current guidelines should be amended.

The Best Practice Papers may also be used as a tool to assist policy makers in improving services.

While the Best Practice Papers may be used for reference in any country, local legal, regulatory, policy and service-delivery contexts may require adaptation of some recommendations; however, it is important to ensure that evidence-based practice is maintained.

For support on adapting the document while still maintaining good practice, please contact cfwgh@rcog.org.uk.

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This paper was updated as part of the RCOG's Making Abortion Safe programme – a three-year programme working to increase healthcare providers' capacity to address the barriers to safe abortion care and/or post-abortion care, globally. For more information, visit www.rcog.org.uk/en/global-network/centre-womens-global-health/our-work/making-abortion-safe.

Language note

Globally, most abortions are provided to women; however, trans men and non-binary people also experience pregnancy and abortion. Therefore, this paper refers to 'women' and 'pregnant people' to reflect a range of identities.

RCOG guidelines disclaimer

The RCOG produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians/gynaecologists and other relevant health professionals.

The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available. This means that RCOG guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management.

Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.

Background

An estimated 25 million unsafe abortions occur every year, making it one of the leading causes of maternal mortality and morbidity worldwide. Abortion-related deaths and morbidity are largely preventable by providing safe abortion care (performed in line with clinical best practice) and timely post-abortion care, as well as by access to contraception and comprehensive sexuality education (CSE). Denying, delaying or restricting access to safe abortion care may lead to violations of the right to life, the right to health and the right to privacy, and can in some cases amount to cruel, inhumane or degrading treatment.

Abortion need not be unsafe. Morbidity and mortality rates following abortion that is provided using best practice are lower than those that would be faced in an ongoing pregnancy and in childbirth. Surgical abortions provided according to evidence-based guidance are generally straightforward procedures and can be provided by a range of clinician groups in a variety of settings. In addition, with appropriate support, individuals can safely manage medical abortions at under 12 weeks of pregnancy themselves at home. As with many other medical procedures, adherence to best practice standards will ensure that the most effective and the safest services are delivered. This Best Practice Paper is designed to be used by health workers delivering abortion and post-abortion care.

The two methods of abortion are:

- **medical abortion:** the use of medications to end a pregnancy; the most commonly used medications are misoprostol alone or misoprostol in combination with mifepristone.
- **surgical abortion:** the use of transcervical procedures to end a pregnancy, including manual vacuum aspiration (MVA), electric vacuum aspiration (EVA) and dilatation and evacuation (D&E).

> All aspects of abortion care should be delivered in a respectful and sensitive manner that is person-centred and recognises women and pregnant people as the decision makers.

Information for individuals requesting an abortion

Women and pregnant people should be informed about their options so that they can make an informed choice about their preferred course of action. Their choice should be respected without any unnecessary delay, as the earlier in pregnancy an abortion is undertaken the safer it is likely to be.

> If performed in line with best practice, an abortion is safer than continuing a pregnancy and childbirth.

Whenever possible, offer individuals a choice of abortion method. Their choice will depend on their individual circumstances and how they feel about the different options.

The following information should be provided to those requesting an abortion, in a clear, understandable, non-judgemental and respectful way:

- Abortion is a safe procedure for which major complications are rare at all pregnancy durations.
- The choice of abortion methods available.
- What will happen during and after the abortion (see Table 1).
- What pain management options are available.
- Side effects, risks and complications of abortion methods (see Table 2).

- How to be sure the pregnancy has ended for those having a medical abortion at home.
- How to identify the need to seek urgent medical attention during or after the abortion.
- The range of potential emotions experienced after an abortion.
- Other available services, such as sexually transmitted infection (STI) screening, counselling for those who need it and support for those experiencing, for example, sexual coercion or domestic violence and abuse.
- What contraception options are available and how they can be accessed.

Those who are unsure about whether to continue the pregnancy or have an abortion should be offered counselling/decision-making support.

Table 1 What abortion methods entail; adapted from the WHO (2014) ***Clinical Practice Handbook for Safe Abortion*** and the NICE (2019) patient decision aids published with the ***Abortion Care*** guideline

Medical abortion	Surgical abortion
• Avoids surgery. • Mimics miscarriage. • May take place at home (depending on stage of pregnancy). • Takes time (hours to days) to complete and the timing may not be predictable. • The medications can cause nausea, vomiting, diarrhoea, chills and fever (1 in 10). • Will experience abdominal cramping and bleeding while passing the pregnancy (worse than during a period). • Abdominal cramping can last, on and off, for a week and bleeding for two to three weeks. • May see the pregnancy as it passes. • Serious complications are uncommon (see Table 2). • All contraceptive methods can be started at the time of the medical abortion, except intrauterine devices (IUDs), which can be inserted immediately after the pregnancy is expelled.	• Takes place in a healthcare facility. • Will experience some discomfort during procedures conducted with sedation and/or local anaesthetic. • Will experience no discomfort during procedures conducted under general anaesthetic. • The medications used to prepare the cervix cause cramps and bleeding and can cause nausea, vomiting, diarrhoea, chills and fever (1 in 10). • Will experience some pain and bleeding for one to two weeks afterwards. • Will not usually see the pregnancy, unless wishes to do so. • Requires a pelvic examination and insertion of surgical instruments into the uterus. • Serious complications are uncommon (see Table 2). • All contraceptive methods can be started at the time of the procedure, including the IUD.

Table 2 Complications and risks of abortion; adapted from the NICE (2019) ***Abortion Care*** guideline and the RCOG (2011) ***Care of Women Requesting Induced Abortion*** guideline

Complication/risk	Medical abortion	Surgical abortion
Continuing pregnancy	1–2 in 100	1 in 1000 Higher in pregnancies <7 weeks
Need for further intervention to complete the procedure	<14 weeks: 70 in 1000 >14 weeks: 13 in 100	<14 weeks: 35 in 1000 >14 weeks: 3 in 100
Infection*	Less than 1 in 100	Less than 1 in 100
Severe bleeding requiring transfusion	<20 weeks: less than 1 in 1000 >20 weeks: 4 in 1000	<20 weeks: less than 1 in 1000 >20 weeks: 4 in 1000
Cervical injury from dilation and manipulation**	–	1 in 100
Uterine perforation	–	1–4 in 1000
Uterine rupture	Less than 1 in 1000 for second-trimester medical abortions***	–

* Upper genital tract infection of varying degrees of severity is unlikely but may occur after abortion and is usually associated with pre-existing infection. Infection after surgical abortion is reduced with use of prophylactic antibiotics.
** Cervical injury is less likely if cervical preparation is undertaken in line with best practice.
*** The presence of a uterine scar (e.g. following a previous caesarean) is a risk factor.

Further treatment (e.g. blood transfusion, laparoscopy, laparotomy or hysterectomy) may be required, should any serious complications occur.

There are several myths about the consequences of abortion. Individuals who express concerns can be reassured that there are no proven associations between having an abortion and subsequent ectopic pregnancy, placenta praevia, infertility, breast cancer or mental health problems.

It is best practice to invite a discussion about contraception at the initial consultation. If a contraceptive method is chosen, that method should be provided, where possible, at the time of the abortion.

Young people
Adolescents deserve the same amount of respect as everyone else accessing abortion care. It's important to remember how vulnerable a young person might feel when requesting an abortion, especially if it's their first time seeking healthcare. If the law requires an adult to consent to their procedure, this should be clearly explained to the young person at the start of the consultation. While all adolescents should be encouraged to involve a trusted adult in their decision, if possible, do **not** insist on parents' authorisation unless it is a legal requirement.

Information for health workers assessing individuals prior to abortion

Communicate information in a clear, understandable way. Providers should not impose personal values or beliefs on clients but focus on their needs and show empathy and respect for their reproductive decisions.

Unless contraindicated, women and pregnant people should be offered a choice of abortion method.

Clinical history taking should identify any health conditions that might affect eligibility for a particular method of abortion and any extra considerations that might affect the location of care and/or pre-treatment planning, including individuals with serious medical conditions who need to be referred for specialist care.

Health workers should check that the person seeking an abortion is doing so voluntarily and is not being coerced into ending the pregnancy. They should also ask about sexual and domestic violence and abuse (physical and emotional) and be able to refer the person to appropriate support services. If the assessment is being conducted by telephone, video call or online, the provider should be confident that the person is able to speak privately without risk of being overheard.

Health workers should be aware of the anxiety that clients may have about perceived negative and judgemental attitudes from healthcare providers.

Health workers can help relieve anxiety, create a safe and respectful environment, and counteract abortion-related stigma by:

- using welcoming words when they first meet the patient (making eye contact and smiling in face-to face meetings)
- introducing themselves, explaining what the consultation will entail
- structuring the consultation so that there is time to build up a rapport before exploring feelings about the pregnancy
- giving clear, concise and accurate information and encouraging questions.
- trying not to make assumptions and by using value-neutral, unbiased language
- conveying how common abortion is.

> It is important that abortion eligibility by pregnancy duration is determined, that any contraindications to methods are identified and that post-abortion contraception is offered.

Determining pregnancy duration

The duration of the pregnancy will influence the method of abortion and whether the abortion can take place at home or should take place in a clinical facility. Pregnancy duration can be assessed from the first day of the last menstrual period (LMP). Most people can determine the duration of their pregnancy with reasonable accuracy by LMP alone.

Routine pre-abortion ultrasound scanning is unnecessary but, if available, should be used if there is clinically relevant uncertainty about the pregnancy duration or if there is a suspected ectopic pregnancy.

In circumstances where the pregnancy duration cannot be assessed by reliable LMP and where ultrasound scanning is not available, an abdominal examination can help determine pregnancy duration when it is over 12 weeks. A bimanual examination can be performed if the practitioner is still not sure of pregnancy duration after an abdominal examination and the information gained would change clinical management.

Contraindications and extra considerations

Medical abortion

There are few **contraindications** to medical abortion:

- known or suspected ectopic pregnancy
- previous allergic reaction to mifepristone or misoprostol
- severe uncontrolled asthma*
- chronic adrenal failure*
- inherited porphyria.*

* Mifepristone should not be used as there is a theoretical risk of exacerbation of the underlying condition, but use of misoprostol alone could be considered.

Extra consideration and additional care planning might be necessary for those:

- on **long-term steroid therapy** – theoretically, since mifepristone is a glucocorticoid receptor antagonist, it might inhibit the action of the steroid therapy and exacerbate the underlying condition; seek specialist input on whether dose adjustments to a corticosteroid regimen are required
- on **anticoagulant medication** – anticoagulants may need to be stopped before abortion medications are administered and then restarted after the abortion
- with a **bleeding disorder**, who may need care in a clinical setting rather than at home
- with **symptomatic anaemia**, where the haemoglobin concentration should be measured and who may need additional care in a hospital setting.
- with an **IUD in place** – the IUD should ideally be removed in advance of treatment; if the IUD cannot be retrieved, it is important to confirm that it is expelled during the procedure, by using imaging such as an abdominal X-ray after the abortion.

Surgical abortion

Surgical methods of abortion are contraindicated if the pregnancy cannot be removed through the cervix, for example due to an obstructing tumour.

In the very rare case that a medical abortion is also not suitable in these circumstances, hysterotomy or gravid hysterectomy may be undertaken.

Medical (or other) conditions and considerations can affect the choice of anaesthetic, indicate a need for the abortion to be undertaken in hospital, or require additional or specialised equipment. These include bleeding disorders and abnormal placentation, use of anticoagulant medication, and severe cardiopulmonary disease. A very high body mass index (BMI), distortion of the uterine cavity by fibroids or another anomaly, previous cervical surgery or type 3 female genital mutilation (FGM) can also make access to the cervix or pregnancy challenging. Procedure planning can include variations in patient positioning, use of longer instruments for evacuation, ultrasound guidance, and cervical preparation.

STI screening

It is best practice to undertake an STI risk assessment for everyone and conduct screening if appropriate, e.g. for chlamydia and gonorrhoea, which might be implicated in post-abortion infection, and for blood-borne viruses such as HIV and syphilis if such testing is available. This should be done without delaying the abortion.

Administer treatment doses of antibiotics to those with signs or symptoms of an STI. Partners of individuals with an STI also require treatment; ideally, a system for partner notification and follow-up or referral would be in place.

Prevention of post-abortion infection

Prophylactic antibiotics are not required for medical abortion but should be used for surgical abortion as they have been shown to reduce the risk of infection following the abortion. However, surgical abortion should not be delayed if antibiotics are not available.

The optimal regimen is not known but nitroimidazoles (e.g. metronidazole), tetracyclines (e.g. doxycycline) and penicillins have been shown to be effective.

The following regimen can be considered for surgical (or incomplete) abortion antibiotic prophylaxis:

- oral doxycycline 100mg twice a day for 3 to 7 days, starting within 2 hours of the procedure (there is evidence that a 3-day course is as effective as a 7-day course).

Blood tests

Pre-abortion assessment does not require routine blood tests. A determination of Rhesus blood status may be considered if the duration of pregnancy is over 12 weeks and anti-D is available. Measurement of haemoglobin concentration or other blood tests is not required unless there are good clinical indications for doing so, such as for those with symptomatic anaemia.

Contraception

Discussions about contraception should be sensitively initiated. Not all people will want to discuss contraception at the time of their abortion. Those who do should be offered information about all their contraceptive options, without any pressure to choose a particular method.

Advice can be given on the greater effectiveness and duration of long-acting reversible contraception (LARC) methods (implants and IUDs) and of their safety, but no pressure should be put on clients to accept these methods.

All contraceptive methods can be started at the time of a surgical abortion.

All contraceptive methods except for IUDs can be started at the time mifepristone and/or misoprostol is taken for medical abortion. An IUD can be inserted following expulsion of the pregnancy after a medical abortion.

Additional contraceptive precautions are not required if contraception is initiated immediately or within 5 days of an abortion.

If sterilisation is requested, this should ideally only be performed after some time has elapsed after abortion. Individuals who request that tubal occlusion be performed at the time of an abortion should be advised of the possible increased failure rate and risk of regret.

If a client's chosen method is not available, they should be provided with an interim, bridging method that they can start immediately and they should be referred to a service where the preferred method can be provided.

Telemedicine

Telemedicine (telephone, video call or online) can be used for consultations for any kind of abortion. Consultation by telemedicine also allows people to have a medical abortion (depending on stage of pregnancy) in their own home with remote support from the abortion provider. They do not need to see a healthcare provider in person or visit an abortion clinic, unless there is a reason to do so (e.g. unsure of date of LMP, ectopic pregnancy risk, complex medical conditions) or they prefer an in-person visit. This model of care for medical abortion at home has been shown to be safe, effective and acceptable to clients and it improves access to abortion care, enabling them to be treated earlier in their pregnancy. Where eligible, people should always be given the option to choose this model of care.

Information for health workers providing abortions

Medical abortion

Before 12 weeks of pregnancy

If mifepristone is available, it is best practice to use it in combination with misoprostol as it is more effective than misoprostol alone, shortens the time taken to complete the abortion (the induction-to-abortion interval), reduces side effects and decreases the rate of ongoing pregnancy. There is no lower limit of pregnancy duration at which medical abortion can be performed. Medical abortion in the first 12 weeks can be safely managed by most people at home, is as safe and effective as in-facility treatment, and can be more convenient and private for people.

The most effective regimen is mifepristone 200mg orally, followed 24–48 hours later by misoprostol 800 micrograms taken by the vaginal, buccal or sublingual route.

- If expulsion of the pregnancy has not occurred within 4 hours, a further 400 micrograms of misoprostol should be taken by the vaginal, buccal or sublingual route.
- If misoprostol is provided for use at home, additional doses should be provided in case they are required. This is especially important to consider for pregnancy durations of over 9 weeks as the effectiveness of a single dose of 800 micrograms of misoprostol starts to decline from then onwards.

If mifepristone is not available, use misoprostol 800 micrograms taken by the vaginal, buccal or sublingual route, followed by misoprostol 400 micrograms every 3 hours until the pregnancy has passed.

12–24 weeks of pregnancy

At 12 weeks or more, medical abortion is usually undertaken in a medical facility. However, there is no evidence indicating that out-of-facility medical abortion is unsafe.

If mifepristone is available, it should be used in combination with misoprostol as it shortens the induction-to-abortion interval, reduces side effects and decreases the rate of ongoing pregnancy.

The most effective regimen is mifepristone 200mg orally, followed 24–48 hours later by misoprostol 800 micrograms vaginally, buccally or sublingually, followed by misoprostol 400 micrograms vaginally, buccally or sublingually every 3 hours until abortion occurs.

Where mifepristone is not available, use misoprostol 800 micrograms followed by misoprostol 400 micrograms every 3 hours until abortion occurs.

The uterus is more sensitive to misoprostol as pregnancy advances, and therefore, in pregnancies over 24 weeks, lower doses of misoprostol should be used and increased intervals between misoprostol doses may be considered, especially for people with uterine scars.

Pain management for medical abortion

Analgesia (pain relief) should **always** be offered.

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended either prophylactically or at the time that cramping begins.
- Non-pharmacological pain management measures (e.g. hot water bottle/heat pad) may be helpful.
- Pain increases with pregnancy duration so narcotic analgesics may be required when other pain management measures are insufficient. Epidural anaesthesia can also be used, where available.

Surgical abortion

Before 14 weeks of pregnancy

Surgical abortion before 14 weeks can be performed using **vacuum aspiration** (electrical (EVA) or manual (MVA)).

Vacuum aspiration involves evacuation of the contents of the uterus through a plastic or metal cannula, attached to a vacuum source. EVA employs an electric vacuum pump. With MVA, the vacuum is created using a hand-held, hand-activated, plastic 60 ml aspirator (also called a syringe).

- MVA aspirators accommodate 4–12 mm cannulas.
- There is no lower limit of pregnancy duration for surgical abortion.
- It is best practice to inspect aspirated tissue at all durations of pregnancy, to confirm that the pregnancy has been fully removed.
- During vacuum aspiration, the uterus should be emptied using only a suction cannula (and forceps if required). The procedure should **not** be routinely completed by sharp curettage.

14–24 weeks of pregnancy

Surgical abortion between 14 and 24 weeks can be performed using dilatation and evacuation (D&E).

D&E requires preparation of the cervix using osmotic dilators or pharmacological agents, and evacuating the uterus using long forceps and vacuum aspiration with cannulas. It is the safest and most effective surgical technique after 14 weeks, as long as skilled, experienced providers are available.

Vacuum aspiration can be used up to 15–16 weeks of pregnancy with larger bore suction tubing and cannulas up to 16 mm in diameter.

> Dilatation and sharp curettage (D&C) is an obsolete method of surgical abortion and should not be used.

Cervical preparation before surgical abortion

Cervical preparation should be used for all patients as it reduces the risk of incomplete abortion and makes dilation easier. It may cause some bleeding and pain before the procedure. If osmotic dilators are used, consider inserting them the day before the abortion, especially if pregnancy duration is 19 weeks or greater.

Before 12 weeks of pregnancy:

- mifepristone 200mg orally, 24–48 hours before the procedure, or
- misoprostol 400 micrograms sublingually, 1–2 hours before the procedure, or
- misoprostol 400 micrograms vaginally or buccally, 2–3 hours before the procedure.

12–18^{+6} weeks of pregnancy:

- combination of mifepristone and misoprostol* (using above regimens), or
- osmotic dilators plus either mifepristone or misoprostol, or with both mifepristone and misoprostol (using above regimens in all cases).

19–24 weeks of pregnancy:

- osmotic dilators plus either mifepristone or misoprostol, or with both mifepristone and misoprostol (using above regimens in all cases).

Pain management for surgical abortion

Analgesia should **always** be offered.

- In most cases, analgesics, such as NSAIDS, local anaesthesia and/or conscious sedation, supplemented by verbal reassurance, are sufficient.
- General anaesthesia is not recommended for routine use in pain management for abortion procedures, as it has been associated with higher rates of complications, and with longer hospital stays, than local anaesthesia.
- Local anaesthesia, such as lidocaine given as a paracervical block, can be used to alleviate discomfort from mechanical cervical dilatation and uterine evacuation.
- Where conscious sedation is available, it should be offered with a cervical block.
- If general anaesthesia is used, consider intravenous propofol and a short-acting opioid (such as fentanyl) rather than inhalational anaesthesia.
- NSAIDS can be used to alleviate abdominal cramping caused by misoprostol given for cervical preparation.

Information for health workers providing care after abortions

People can experience a range of emotions after an abortion. Health workers should provide information on how to access emotional support after an abortion in case this is needed.

Health workers should ensure that individuals know what to expect following the procedure and where to get help if necessary. They should also ensure that everyone who wants a method of contraception is able to leave with their method of choice or know how and where to access it.

Information to provide after an abortion

Clients should receive instructions about signs and symptoms that might indicate a complication that requires urgent medical help, including if they:

- soak through two or more maxi-size sanitary towels per hour, for 2 hours in a row
- develop an unusual, unpleasant-smelling vaginal discharge
- develop a fever or flu-like symptoms after 24 hours
- develop worsening pain, including that which might indicate an undiagnosed ectopic pregnancy (for example, if lower abdominal pain is one-sided, under the ribs, or goes up to the shoulders).

* Sometimes more than one dose of misoprostol may be required to get adequate dilation.

Health workers should also provide information on signs and symptoms that might indicate an ongoing pregnancy for which clients should seek medical attention, including if they:

- have no bleeding or only spotting or smearing of blood on sanitary towel or underwear in the 24 hours after misoprostol for medical abortion
- still feel pregnant 1 week after the abortion.

Contraception

See above.

Anti-D

If available, anti-D should be offered to non-sensitised RhD-negative individuals from 12 weeks of pregnancy and provided within 72 hours of the abortion.

Follow-up

There is no need for routine follow-up nor for a routine post-abortion ultrasound. Rather, individuals should be given clear information on when to seek medical help, as outlined above.

For people having medical abortion at home

Confirming whether the pregnancy has ended can usually be determined by individuals from witnessing the pregnancy as it passes or from the amount and duration of bleeding experienced and the disappearance of pregnancy symptoms. If available, the success of the abortion can be confirmed with either a low-sensitivity urine pregnancy test (detection limit 1000IU hCG) from 2 weeks after treatment or with a high-sensitivity test (detection 50IU hCG or less) from 4 weeks after treatment.

Management of incomplete abortion

Post-abortion care can reduce the morbidity and mortality associated with complications of either miscarriage or incomplete abortion, including abortion that was performed unsafely. Options for management for incomplete abortion include surgical and medical methods of uterine evacuation.

For those who wish to avoid another pregnancy, a contraception discussion should be offered and the chosen method provided.

Assessment

Incomplete abortion should be suspected when a person of reproductive age presents with vaginal bleeding or abdominal pain after one or more missed menstrual periods. Ectopic pregnancy should be suspected if the uterus is small, the cervix is closed or there is an adnexal mass or tenderness.

Unsafe abortion

An abortion is unsafe when it is carried out either by a person lacking the necessary skills or in an environment that does not conform to minimal medical standards, or both.

In many settings it is important to distinguish between safe and unsafe abortion because the latter is much more likely to be associated with infection. Indications that an abortion has been attempted by unsafe methods include the presence of:

- vaginal laceration

- cervical injury
- uterine enlargement equivalent to a pregnancy of more than 12 weeks' duration
- products of conception visible at the cervix or in the vagina
- in patients with uterine injury, any of fever, significant lower abdominal pain, tenderness or abdominal distension
- the presence of a foreign body in the vagina or cervix.

Infection

It is vital to identify those who may have an infection and to manage this urgently. Infection is much more likely, and much more likely to be severe, if the abortion has been performed unsafely. Clinical features suggestive of infection include:

- temperature above 37.5°C
- localised or general abdominal tenderness, guarding or rebound
- unusual, unpleasant odour or pus visible in the cervical os
- uterine tenderness.

Features suggestive of sepsis and indicating the need for urgent intervention include:

- hypotension
- tachycardia
- increased respiratory rate.

Management

If there is no suspicion of infection and uterine size is less than 14 weeks

- Medical management with misoprostol 400 micrograms sublingually, buccally or vaginally or 600 micrograms orally:
  - for a missed abortion (retained non-viable fetus), mifepristone 200mg orally should be administered 24–48 hours before the misoprostol.

OR

- Uterine evacuation with vacuum aspiration and antibiotic prophylaxis (see above).

If there is no suspicion of infection and uterine size is 14 weeks or larger

- Medical management with misoprostol:
  - 14–24 weeks: misoprostol 400 micrograms administered sublingually, buccally or vaginally every 3 hours
  - the uterus is more sensitive to misoprostol as pregnancy advances, and therefore, in pregnancies over 24 weeks, lower doses of misoprostol should be used and increased intervals between misoprostol doses may be considered, especially for people with uterine scars
  - in order to align protocols, services may use the same dosing and intervals as recommended in regimens for induced abortion
  - for a missed abortion (retained non-viable fetus), mifepristone 200mg orally should be administered 24–48 hours before misoprostol.

OR

- Surgical management with antibiotic prophylaxis (see above):
  - vacuum aspiration for removal of retained tissue when the fetus has been expelled; blunt forceps may also be needed to remove a retained placenta
  - if the fetus is retained, vacuum aspiration is suitable before 14 weeks of pregnancy; from 14 weeks and up to 16 weeks of pregnancy, forceps removal of larger fetal parts may also be required; from 16 weeks of pregnancy, a dilatation and evacuation (D&E) may be performed
  - if removal of the pregnancy requires the use of forceps, either in combination with vacuum aspiration or for a D&E, this should only be carried out by a skilled provider; if not available, medical management is recommended.

If infection is present, the uterus should be evacuated urgently

- Start broad-spectrum antibiotics immediately – intravenously if infection is severe.
- Transfer to a unit with the facilities for undertaking surgical evacuation if it cannot be done in the facility to which the individual presents.
- If the patient is in septic shock, they should be transferred immediately to a specialist unit for surgical uterine evacuation – broad-spectrum antibiotics, such as a combination of ampicillin 0.5–1g every 6 hours, metronidazole 500mg every 8 hour and gentamicin 120mg daily (with appropriate monitoring), should be administered intravenously prior to transfer if available.
- If the skills necessary for urgent surgical uterine evacuation are not available, misoprostol can be administered using the dose regimens above.

Information to provide after an abortion

See above.

Contraception

See above.

Anti-D

See above.

Service delivery

The provision of a safe and effective abortion care service depends on everyone involved in the service ensuring that everything can be done to achieve best practice for safe abortion care. It is not enough for doctors, nurses and midwives to perform effectively if the facilities and tools that they need are not reliably available and if the service is not organised in a way that ensures safe and effective abortion care. **Best practices for service delivery** are listed below.

Access to services

1. Abortion services should be available to the fullest extent that the law allows. Healthcare providers should know what the law *does* allow in their country and be clear about the circumstances for which abortion is legal.
2. If a person requesting abortion fulfils the legal criteria, there should be no further restriction of access on grounds such as age, marital status or the number of previous abortions.

3. Abortion is safer the sooner it is done. Services should be able to meet the local demand for abortion so that people can have their abortion as early as possible and as close to home as possible.
4. As the equipment and space required for a safe abortion service are similar to those needed for routine women's healthcare and contraception services, efforts should be made to provide safe abortion services in a wide range of health facilities and in an integrated manner.
5. All healthcare providers should be trained to provide safe abortion care in line with their skills and licences. This can help spread the workload and improve the skills of *all* providers of women's healthcare, thereby enhancing access to and increasing the safety of abortion care.
6. Integrating abortion services within mainstream maternity and women's health services minimises the stigma associated with abortion care for both patients and providers.
7. Where abortion services are provided but there is no provision for emergency or specialist care, there must be robust and timely pathways for referral.

Information provision

1. There should be local arrangements in place for providing information to women and pregnant people and to healthcare providers on routes of access to safe abortion care.
2. Services should ensure that written, objective, evidence-guided information is available in a way that is understandable to all people considering abortion. Information should be available in a variety of languages and formats.
3. Women and pregnant people should have access to objective information and, if required, counselling and decision-making support about their pregnancy options. However, there should be no requirement for compulsory counselling or mandatory time for reflection before an abortion.

Initial assessment

1. There should be a pathway to appropriate medical care for people with known significant medical conditions (e.g. heart disease) that require specialist abortion care in a hospital.
2. People presenting for abortion who are found to have a non-viable pregnancy also require contraception and sexual healthcare.
3. People requesting abortion but who subsequently decide to continue the pregnancy should be referred for antenatal care (together with all their relevant information).
4. Services should identify people who may be particularly vulnerable (e.g. some adolescents, those in controlling, abusive relationships, people addicted to drugs/alcohol, people with moderate/severe mental health problems) and refer/signpost them on to appropriate support services.

Arrangements for the procedure

1. To minimise delay, service arrangements should be such that an abortion can be provided as soon as possible, ideally on the same day as the assessment.
2. The setting for abortion services (consultation rooms, procedure rooms and recovery rooms) should respect the need for clients' privacy and dignity.

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Appendix: Post-abortion contraception

Adapted from World Health Organization (2014) *Clinical Practice Handbook for Safe Abortion*

Method of post-abortion contraception	Medical eligibility criteria (MEC) category		
	First trimester	Second trimester	Immediate post-septic abortion
CHC	1	1	1
POP	1	1	1
Progestogen-only injectable	1	1	1
Progestogen-only implant	1	1	1
Cu-IUD	1	2	4
LNG-IUD	1	2	4
Condom	1	1	1
Spermicide	1	1	1
Diaphragm	1	1	1

CHC = combined hormonal contraception (pill, patch, ring, injectable).
POP = progestogen-only pill.
Progestogen-only injectable = depot medroxyprogesterone acetate or norethisterone enanthate.
Progestogen-only implant = levonorgestrel or etonogestrel.
Cu-IUD = copper-bearing IUD.
LNG-IUD = levonorgestrel-releasing IUD.
Condom = male latex condom, male polyurethane condom or female condom.
Diaphragm = diaphragm (with spermicide) or cervical cap.

MEC categories for contraceptive eligibility	
1	A condition for which there is no restriction for the use of the contraceptive method.
2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks.
3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method.
4	A condition which represents an unacceptable health risk if the contraceptive method is used.

Recommendations for contraceptive use among women at high risk of HIV infection

- Women at high risk of HIV infection are eligible to use all hormonal contraceptive methods without restriction (MEC category 1), including combined hormonal contraception, progestogen-only pills, and progestogen-only injectables and implants.
- Women at high risk of HIV infection are also eligible to use Cu-IUD and LNG-IUDs without restriction (MEC category 1).

Contraception for individuals on antiretroviral therapy for HIV

There are potential drug interactions between some antiretroviral drugs and hormonal contraception that may affect efficacy of some methods of hormonal contraception. Providers should advise clients on the risk so that they can make an informed choice of method.

Making Abortion Safe

RCOG's global initiative to advocate for women's health

Royal College of Obstetricians & Gynaecologists

Original Article

Patient and provider experiences using a site-to-site telehealth model for medication abortion

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Background: In the site-to-site telehealth for medication abortion model, patients visit a health center to meet with a remote clinician using telehealth technology. This model is safe, effective, and acceptable to patients and providers. The objective of this study was to document the experiences of patients and providers using telehealth for medication abortion in Planned Parenthood health centers across different geographical contexts in the United States.

Methods: We conducted in-depth interviews with Planned Parenthood medication abortion patients who either met with a clinician at the clinic via telehealth or in-person about their experiences receiving care. We also interviewed Planned Parenthood staff members about their experiences implementing telehealth for medication abortion at their health center.

Results: We interviewed 29 patients who received care at Planned Parenthood health centers in five states. Both telehealth and in-person patients described positive interactions with health center staff and clinicians. The vast majority of telehealth patients said that they felt comfortable speaking with the clinician over telehealth and had no trouble using the telehealth technology. We interviewed 12 providers, including clinicians and administrative staff, who worked in seven states. Providers largely thought that telehealth for medication abortion expanded access to medication abortion.

Conclusions: Across different locations, our findings indicate that patients found telehealth for medication abortion services to be highly acceptable and providers found that telehealth services may help improve medication abortion access. As the use of telehealth for medication abortion expands, future research should include additional measures of quality to ensure that services are acceptable across different identities and experiences, including age, race, gender, and income level.

Keywords: Telehealth; medication abortion; patient experiences; provider experiences

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Introduction

Abortion can be difficult to access in the United States for many reasons, including state and federal regulations that restrict how a pregnant person can access abortion care (1-3); decreasing numbers of abortion providers (4,5); the need to travel long distances to reach an abortion-providing facility (6-8); and costs associated with the procedure and/or travel to the facility (9,10). Over the past decade, abortion providers have implemented site-to-site telehealth for medication abortion (referred to here as "site-to-site TeleMAB") services to allow health centers that do not have a clinician onsite to provide medication abortion services remotely. Similar to in-person medication abortion care, site-to-site TeleMAB patients visit a health center where they meet with staff to receive pregnancy options counseling and diagnostic testing, such as an ultrasound. Instead of meeting with the clinician in-person, patients meet with the clinician via online videoconference platform on a clinic computer in a private room. Prior to the clinician-patient encounter, clinic staff set up the videoconference platform and ensure that the audio and video functions are working. If the patient is eligible for medication abortion, the clinician will answer questions and give the patient information about how to take the medication and when to seek follow-up care. The site-to-site TeleMAB model can mitigate some obstacles to accessing abortion care by increasing the availability of medication abortion in facilities that would otherwise not have services or have only limited availability (11,12), thereby enabling some patients to obtain care closer to home (12).

Site-to-site TeleMAB is safe, effective, and comparable to in-person care (11,13-17). However, quality abortion care must be more than just safe and effective; Price and Hawkins' social analysis framework for reproductive health services defines quality as the social experience of services and includes the extent to which a program "is responding to the perceived needs and demands of patients and potential patients" (18). They suggest that assumptions about quality do not always align between patients and providers, and therefore patient and provider interactions are an important—and often neglected—aspect of quality, which can provide critical insights into how to improve quality of care (18). Price and Hawkins' approach to evaluating reproductive health services provides an important basis for examining the acceptability of the site-to-site telehealth model for patients and providers. Ibis Reproductive Health (Ibis) has partnered with Planned Parenthood Federation of America (PPFA) to assess the acceptability of the site-to-site TeleMAB services for patients and providers and identify areas for improvement. In 2011, an evaluation of site-to-site TeleMAB services in Iowa demonstrated that both patients and providers found the service to be highly acceptable and most patients reported feeling positive or indifferent about meeting with the provider over videoconference (14). In addition, a 2013 study of provider experiences with a site-to-site TeleMAB service at Planned Parenthood health centers in Alaska found that the service allowed the clinic to increase the number of medication abortion appointments, which supported patients in receiving care sooner and at earlier gestational ages (13).

As the use of site-to-site TeleMAB services continues to expand, it is important to examine providers' and patients' experiences to ensure that these services meet the needs and expectations of both groups. This study sought to document the experiences of patients and providers using site-to-site TeleMAB with a focus on acceptability and perceptions of access. The findings presented below fill a gap in the literature by providing evidence about experiences using the site-to-site TeleMAB model across multiple locations in the United States. We present the following article in accordance with the Standards for Reporting Qualitative Research (SRQR) reporting checklist (available at https://mhealth.amegroups.com/article/view/10.21037/mhealth-22-12/rc).

Methods

Patient interviews

We conducted in-depth interviews with 29 abortion patients as part of a larger study that aimed to evaluate patient acceptability of medication abortion services received at Planned Parenthood affiliate health centers in five states: Alaska, New York, Maryland, Montana, and Nevada. Participants received medication abortion care by visiting a health center and meeting with the clinician either in person or via telehealth technology. When patients contacted Planned Parenthood, they received information about their abortion care options (i.e., medication or aspiration) and were offered appointment options based on the option they preferred.

Patients seeking abortion were eligible to participate in the study if they obtained a medication abortion (i.e., were ≤70 days' gestation and did not have other medical contraindications), were at least 18 years of age, were able to read and speak English, and were able to give informed consent. The gestational age limit for medication abortion

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was set by the Planned Parenthood health centers. As part of the larger medication abortion acceptability study among Planned Parenthood patients, eligible patients were invited to complete an online survey two weeks after the appointment where they received the medication abortion pills. We recruited interview participants from the pool of patients who completed the online survey; upon completing the survey, participants interested in interviewing were redirected to an anonymous online interview interest form where they could provide their contact information. We did not link participant survey responses to the interview interest form or subsequent interview responses to ensure confidentiality and to increase the candidness of the interviewee's responses. Patients who expressed interest in participating in the interview by completing the online interest form were contacted by phone and screened by study staff to determine eligibility.

We initiated recruitment for interviews on a rolling basis as site-to-site TeleMAB services were introduced across different health centers between August 2016 and January 2019. Patient interviews were conducted by telephone using a semi-structured interview guide adapted from a previously published study assessing patient acceptability of site-to-site TeleMAB services in Iowa (14). We aimed to assess acceptability of services by asking participants about various aspects of perceived quality of care (19), such as how they were treated in the clinic and if they felt comfortable in the exam room. We also asked site-to-site TeleMAB patients about their comfort level meeting with the doctor remotely, if they had all of their questions answered, the level of privacy, the sound quality of the videoconference, and things they liked and disliked about the experience. We also asked both site-to-site TeleMAB and standard in-person medication abortion (MAB) patients whether they would recommend site-to-site TeleMAB services or the standard in-clinic MAB services to a friend. Patient interviews lasted from 15 to 50 minutes. Patients received a $40 electronic Amazon gift card upon completing the interview.

Provider interviews

We also conducted in-depth phone interviews between June 2017 and July 2019 with 12 providers who were involved with both in-person and site-to-site TeleMAB services. Providers were eligible to participate if they were a doctor, advanced practice clinician, nurse, medical assistant, health center manager, counselor, or other administrative personnel on staff involved in the implementation or administration of site-to-site TeleMAB. We included a broad range of providers, both clinical and administrative staff, in order to capture a holistic and nuanced perspective of the impact and acceptability of site-to-site TeleMAB services. Study team members from PPFA screened for initial interest among eligible providers, and Ibis study team members conducted the interviews by telephone. Prior to the interview, participants were read the study consent form and informed that participation in the study was voluntary and confidential. The provider interview guide was adapted from a previously published study examining provider acceptability and perspectives of a site-to-site TeleMAB model in Alaska (13). In order to capture provider acceptability of the site-to-site TeleMAB services, we asked providers to share their opinions about the services, including benefits and challenges. We also asked providers to share their perspectives of the site-to-site TeleMAB services, including its impact on abortion access, who benefitted the most from the site-to-site TeleMAB services, and if there were patients who might be better served by an in-person visit. Provider participants did not receive compensation. Provider interviews lasted from 30 to 60 minutes.

All study participants, patients and providers, provided verbal informed consent to participate in the study and to be audio recorded. For those who did not want their interview recorded (n=1 patient), study staff took handwritten notes. Audio files were transcribed verbatim by a third-party transcription company and study staff performed quality assurance checks on all transcriptions. De-identified transcriptions were analyzed qualitatively with inductive coding using modified grounded theory methods (20). A modified grounded theory approach was applied to our analysis to assess the factors that impacted participants' perspectives of acceptability and impact on access (21,22). Analyses were facilitated by the use of Dedoose to identify themes related to acceptability of medication abortion and site-to-site TeleMAB by study staff. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by Allendale Investigational Review Board (No. IRB00005829).

Results

Patients

Participant characteristics

Twenty-nine medication abortion patients participated in an interview. Sixteen of these participants met with a

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Table 1 Participant characteristics-patients (N=29)

Participant characteristics	n	%
Age (median, range), years	25 [19–41]	
Education		
Some high school	1	3.4
High school or GED	5	17.2
Some college or Associate's degree	12	41.4
Bachelor's degree	9	31.0
Master's degree	2	6.9
Student		
Yes	9	37.5
No	15	62.5
Missing	5	20.8
Relationship status		
In a relationship	9	31.0
Married	6	20.7
Single	14	48.3
Race/ethnicity		
Asian American/Pacific Islander	3	10.3
Black	7	24.1
Hispanic	4	13.8
Multi-racial	2	6.9
White	13	44.8
Parous		
Yes	15	51.7
No	14	48.3
Past abortion		
Yes	7	24.1
No	22	75.7
Dependents at home		
Yes	14	48.3
No	15	51.7

GED, general education development.

remote provider via site-to-site TeleMAB. Thirteen of the 29 participants met with the provider in-person at the health center ("MAB" patients). Patients received care at Planned Parenthood health centers in five states, including Alaska, New York, Maryland, Montana, and Nevada. Patient demographics are summarized in *Table 1*. Patient participants ranged in age from 19 to 41 years old, with a median age of 25. Nearly 80% of participants reported having at least some college education, and roughly a third (38%) were students. About half of the participants (52%) were in a relationship or married and most participants identified as White (45%) or Black (24%). Seven participants reported having had a previous abortion.

Site-to-site TeleMAB and MAB patients' health center experiences

Both site-to-site TeleMAB and MAB patients were required to visit the health center in order to receive the medication abortion pills. When asked about their experiences in the clinic, the vast majority of participants reported that they had positive experiences with staff and were comfortable in the health center including one site-to-site TeleMAB patient who said, "*[The staff] were very nice, not judgmental. It was just—I felt like a regular patient coming in for something very regular and normal, and there's not—it didn't seem like a taboo situation*". Two participants described mixed feelings about their comfort level in the health center; one said they were "fairly" comfortable, but felt a little awkward because of the medical illustrations of reproductive anatomy on the wall. One participant's negative interactions with staff resulted in an uncomfortable health center experience.

Patient experiences with telehealth platform

Site-to-site TeleMAB patients were asked to describe their experience using telehealth to meet with the provider. Many participants reported feeling comfortable during the telehealth visit, including one person who said that they felt more comfortable than they would have in an in-person visit, "*I think I felt more comfortable speaking to her on the screen than I would be in person*". Several participants reported that they would have felt more comfortable during an in-person visit, and of those participants, some reported a preference for in-person care. However, the telehealth participants who reported a preference for in-person care reflected that they still felt comfortable during the site-to-site TeleMAB visit. In addition, all reported having had an opportunity to have their questions answered, though some didn't have specific questions to ask. One participant said, "*[the doctor] answered any questions I had. It's just as much as—I mean it's not the same as a doctor next to you, but it's just as much the same. I mean I thought it was very good. I look at it as good technology*".

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Site-to-site TeleMAB participants were also asked to describe what they thought about the privacy in talking with the doctor by videoconference, including whether they thought that the level of privacy was different from an in-person visit. Of the 13 participants who were asked about privacy, most thought that the privacy in a site-to-site TeleMAB visit was no different from how it would be during an in-person visit. Some described their appointment as private, including one participant who said, "*I wasn't worried about anybody over-hearing or—it felt comfortable with the confidentiality that Planned Parenthood provided in the first place, so that privacy wasn't an issue when it came to the telemedicine*". However, some participants said that they would have preferred a greater level of privacy, including two people who noted that a door was left ajar while they were waiting to meet with the doctor, and two others who reported that they would not have known if there was anyone listening in on the doctor's end. In addition, one person said the level of privacy felt different and they would have preferred to meet with the doctor in-person, and another said they were not sure if the visit would have been any different. An additional person said that they were not concerned with privacy.

The majority of site-to-site TeleMAB participants said that the sound quality was good, and one person said there was a slight delay in the audio. Many noted that they did not encounter any technical difficulties throughout their appointment, however, four participants mentioned that they experienced minor technical glitches, such as their internet connection briefly cutting out, or a wait for the teleconference system to load prior to meeting with the doctor. Only one person reported experiencing a connectivity issue that delayed their appointment by about two hours.

When asked to describe anything they liked about the site-to-site TeleMAB appointment, participants identified positive aspects of their visit, including liking their interaction with the provider via telehealth. Of these, one participant said, "*I was expecting it to be awkward, but it wasn't. And the nurse practitioner was kind and I thought that maybe it would be [rushed]—or my concerns would be [rushed] over, but they were not. She still listened and addressed my concerns just as if she was in the room with me*". Patients also reported that they liked that telehealth increased the availability of medication abortion and abortion care generally, including one person who said, "*Being able to be seen sooner than later, obviously, because I was really adamant about doing the pill abortion. So they did mention that they're starting this [telehealth] program to be able to see more patients a day, which I was extremely grateful for*", and another who said that they would otherwise not have been able to access care. Other positive aspects of the site-to-site TeleMAB visit described by patients included that it was a more personal experience than an in-person visit with a shorter wait time for meeting with the physician, and that the virtual waiting room gave them time to acclimate to the visit.

Some participants highlighted things they disliked, or perceived to be negative, about the site-to-site TeleMAB visit itself. Some participants who indicated a preference for in-person care also reported that they disliked the remote aspect of the visit or that the visit would have been improved by having an in-person encounter with the doctor. One participant expressed a negative experience discussing birth control options, and two participants, as mentioned above, shared concerns about privacy because of a door left ajar. Another person, also mentioned above, had technical issues that resulted in a longer-than-anticipated wait time. In contrast, four participants reported that there were no aspects of the site-to-site TeleMAB visit that they disliked.

Lastly, site-to-site TeleMAB participants were asked if they would recommend that a friend receive the medication abortion in the same way they did, via telehealth. Of these, the majority said that they would. Some participants said that they would recommend site-to-site TeleMAB if their friend was comfortable meeting with a doctor over videoconference. Of those who said they would recommend the service, some said they would make sure their friend understood that they would be meeting with the clinician remotely. In contrast, one participant said that they "*didn't really mind the web cam. I really don't care either way. So I don't even think I would bring that up to a friend, really. I don't think that was anything to change my mind about anything*".

We also described the site-to-site TeleMAB system to MAB participants and asked if they would recommend site-to-site TeleMAB to a friend; some said site-to-site TeleMAB sounded like it could be a good option, and others said they would recommend site-to-site TeleMAB based on their friend's preferences or situation. Of those MAB patients who said they would recommend an in-person visit over a site-to-site TeleMAB visit, some thought an in-person visit seemed more personal and comforting than a site-to-site TeleMAB visit, one stated a personal preference for in-person care based on their medical history, and one participant said that, if they were already in the health center, they would prefer to see the clinician in-person; however, this participant added that if they could avoid going into the health center at all, they would meet with the clinician over telehealth from their home.

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Providers

Participant characteristics

We interviewed 12 clinicians and/or administrative staff from Planned Parenthood affiliates, including eight health center managers/directors, two medical directors, one nurse, and one administrator. Of these, two held clinical positions, eight held administrative positions, and two split their time between clinical and administrative tasks. Providers worked in four of the same states as the patients, including Maryland, Montana, New York, Nevada, while others worked in Oregon, Idaho, and Washington.

Improving access to medication abortion via telehealth

Participants were asked whether they thought the introduction of site-to-site TeleMAB services had an impact on abortion access. The majority said that the service had increased access to abortion. One manager said that site-to-site TeleMAB increased the availability of medication abortion appointments: "*So I think that women have been able to have a medication abortion either closer to the timeline that they would prefer or closer to home, and I think that that's a really good thing*". In addition, when asked what they liked about the telehealth service, the majority of participants said that they liked that the telehealth service expanded access to abortion, especially in areas where there are few abortion providing facilities. One administrator said, "*[Telehealth]… improves access to our patients and provides an opportunity for patients to receive their healthcare in a more localized way… just seven years ago, there were many more abortion facilities and abortion providers but due to increased state regulation… we've gone in this state from having 13 abortion providers to now I believe the number is down to five or six*". One participant said that they thought the implementation of telehealth would impact access to abortion once word spread, but that many people were still unaware of the service.

Some participants also commented on whether the site-to-site TeleMAB service impacted how soon pregnant people were able to access abortion care. Of these, some thought that people were able to access care earlier in a pregnancy, including one participant who also added that site-to-site TeleMAB provided an additional care option for patients: "*I mean, some patients like to do the in-clinic procedure regardless of how far along they are. Having the option to do the telemed, they have the option of [experiencing the abortion] at home if they choose so*". Another participant said that they thought telehealth increased availability, but did not necessarily impact how early in pregnancy people were able to access care.

Some participants described whether they thought there was any particular population or type of patient who benefited the most from site-to-site TeleMAB. Of these, some said that patients whose pregnancy was at the upper gestational limit for medication abortion, prefer medication abortion over aspiration abortion, need to travel long distances to care, and those who may need to take time off of work for the procedure would benefit from telehealth. Another participant thought telehealth benefited all patients.

Additionally, some participants discussed whether certain types of patients might be better served by an in-person visit than a telehealth visit. Of those, five reported that the majority of patients would not necessarily be better served by an in-person visit unless they had a medical condition that would put them at risk for complications or if they were uncomfortable being on video. One participant said in-person visits may be better for those who prefer a face-to-face visit. Another participant, a clinician, said that they were able to provide the same level of emotional support over videoconference as in-person: "*I actually got to do a counseling session like that through telemedicine where a patient was just crying and it went really well… And so, I kind of felt really comfortable with that. I felt like I was able to do the same level of counseling that I do with people in person, and it was fine*". One participant, an administrator, said they were not sure if patients might be better served by an in-person visit with the clinician physically present in the room.

Provider experiences delivering telehealth care

Providers were asked to share their experiences using site-to-site TeleMAB, including things they liked and challenges they encountered. One director said they liked that the telehealth service enabled teamwork among the remote clinician and the health center staff. Another director said that the telehealth service was "great" but more marketing was needed to get the word out. In addition, a nurse practitioner said that they were looking forward to adapting telehealth services for other family planning services. Some participants said they encountered technical problems, such as issues with connectivity or equipment, system outages, and a lack of technical familiarity among staff. The vast majority of these participants, however, also noted these issues did not prevent the delivery of care. One person said they had not encountered any technical problems.

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Discussion

Our findings indicate that most site-to-site TeleMAB patients felt comfortable using the telehealth service, and that providers thought that site-to-site TeleMAB made medication abortion more accessible. Although the majority of the site-to-site TeleMAB patients reported feeling comfortable, some respondents reported a preference for meeting with the clinician in-person, rather than over videoconference. A few site-to-site TeleMAB patients discussed concerns around privacy during their conversation with the clinician, and some patients reported encountering technical difficulties. Two participants noted negative interactions with staff.

These findings align with previous evidence on patient acceptability of site-to-site TeleMAB services, and add new evidence of high acceptability for site-to-site TeleMAB across a range of different geographic settings. Consistent with previous findings, the majority of site-to-site TeleMAB and MAB patients reported positive interactions with clinic staff (13,14). Our results are also consistent with earlier findings on patient-provider interactions, as the majority of site-to-site TeleMAB patients felt comfortable with their conversation with the clinician, and, in some cases, were more comfortable meeting with the clinician via telehealth than in-person (14,23). In addition, the reasons why some site-to-site TeleMAB patients would have felt more comfortable with an in-person visit align with previous qualitative studies that have found that some people prefer in-person care (14,15). Reasons for privacy-related concerns, including not being able to tell if anyone else was in the room with the remote physician, have been documented in a previous study (14). Results from provider interviews add to existing evidence demonstrating that providers perceive that site-to-site TeleMAB services expand access to abortion care by increasing the availability medication abortion closer to where patients live, and that they are able to provide the same level of care regardless of whether they are in-person or on videoconference (13,14).

Providers in this study highlighted the ways in which the site-to-site TeleMAB model could address some of the disparities in abortion access in the United States. They reported that site-to-site TeleMAB benefited people who lived far away from the clinic, and that the services helped increase medication abortion availability in states where abortion care options are limited. Their experiences align with findings from a recent study that found that the introduction of site-to-site TeleMAB in Montana and Nevada led to an increase in the uptake of medication abortion in both states (11). Providers also reported that the site-to-site TeleMAB model may have helped patients get to the health center earlier, and that the populations who may benefit the most from the site-to-site TeleMAB services include those who prefer medication abortion over aspiration abortion and are close to the gestational age limit for medication abortion. Current evidence suggests that many abortion patients who express a preference for medication abortion encounter delays in accessing care and are beyond the gestational age limit for medication abortion, making them ineligible for the procedure (24). This underscores the importance of increasing overall availability of medication abortion, as well as reducing delays in access.

There are several limitations to this study. First, the qualitative findings from this study do not allow us to assess whether site-to-site TeleMAB services are meeting the needs of different groups equally. In addition, the vast majority of patients were not told ahead of their abortion appointment that it would be conducted via telehealth and, as a result, we were not able to assess whether knowledge of site-to-site TeleMAB services impacted patients' decision making when scheduling an appointment. Lastly, the small number of participants per state did not allow us to immediately identify any trends or differences in experiences across states. Despite these limitations, this study fills a gap in the literature by documenting the use of site-to-site TeleMAB across different geographical settings, and by providing additional data on site-to-site TeleMAB patient and provider experiences.

These findings also provide a strong foundation for further telehealth for medication abortion evaluations. Future studies of telehealth for medication abortion services should incorporate additional quality of care measures to gain deeper insight into how telehealth for medication abortion is meeting the care needs of patients. Researchers should also include measures such as accessibility of accurate and unbiased information about abortion care and telehealth in order to better understand care decision-making. In addition, future quality of care measures should also assess how patients from groups that are targeted by systems of oppression experience telehealth for medication abortion; for example, how provider use of gendered terminology and other cultural competencies can impact patient-provider interactions. Lastly, our study did not evaluate differences in feelings about privacy for site-to-site TeleMAB and MAB patients, however this information would be valuable for

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identifying ways to ensure patient confidence in the privacy and security of TeleMAB and MAB appointments, especially for those who are experiencing intimate partner violence, which is common among people seeking abortion (25).

All of the participating sites in this study provided site-to-site telehealth, such that patients still had to travel to a health center. During the onset of the COVID-19 pandemic, in-clinic requirements for medication abortion were lifted in some countries, including the United States, in order to mitigate the risks of contagion associated with in-person care. As a result, abortion providers were able to implement direct-to-patient medication abortion using telehealth. Studies in the United States found that the direct-to-patient models implemented during the pandemic were safe, effective (26,27), and acceptable to patients (27). These findings were also echoed in studies examining patient experiences using direct-to-patient models during the pandemic in 2020 in the United Kingdom (28-30) and France (31). Given the recent change in mifepristone's Risk Evaluation and Mitigation Strategy (REMS) (32) more US providers will be able to implement direct-to-patient telehealth for medication abortion provision services. Additional research on direct-to-patient telehealth models for medication abortion is needed to support broadening the use of telehealth to further increase access to medication abortion.

Although both the direct-to-patient and the site-to-site model offer opportunities to expand access to abortion care in the United States, more work is needed to dismantle the structural systems that prevent access to telehealth (33). Digital redlining, for example, has resulted in a lack of internet access for communities of color compared to wealthier white communities (34). Studies evaluating the use of telehealth during the COVID-19 pandemic also demonstrated that the use of telehealth was lower among communities of color, rural populations, and those using Medicare or Medicaid (35,36). These findings underscore the need to address inequitable policies and practices in order to maximize the potential of telehealth. Additionally, some patients may prefer the direct-to-patient model because they do not want to (as one participant in our current study suggested) or are not able to visit a health center to obtain abortion care.

The high quality of care provided in-person and via telehealth suggests that Planned Parenthood health centers should continue to offer and seek ways to improve and expand telehealth services. The high-level of acceptability for the site-to-site TeleMAB services demonstrated in this study and others, suggests that this service model should be offered as part of a range of safe and acceptable service models available to patients to ensure they receive care the way they prefer. More context is still needed to better understand how telehealth for medication abortion services is experienced by different groups. Further research should aim to broaden the aspects of perceived quality assessed in this study to ensure that telehealth for medication abortion services is acceptable and accessible to patients with a range of identities and experiences across age, race, gender, and income levels.

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Footnote

Reporting Checklist: The authors have completed the SRQR reporting checklist. Available at https://mhealth.amegroups.com/article/view/10.21037/mhealth-22-12/rc

Data Sharing Statement: Available at https://mhealth.amegroups.com/article/view/10.21037/mhealth-22-12/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://mhealth.amegroups.com/article/view/10.21037/mhealth-22-12/coif). After the completion of this study, JWS served as a consultant to an independent US-abortion provider. In this capacity she provided technical assistance with data analysis regarding the effects of implementation of a telemedicine for medication abortion care model on service delivery patterns. TAT, Principal Investigator of this study, reports that all payments from the anonymous grant that supported this research were made to the primary institution and used solely for research costs, including travel to meetings to present on work broadly related to telehealth for medication abortion but not specific to this manuscript. DG has received payment from Lawyering Project and Planned Parenthood Federation of America for his role as an expert witness in legal cases challenging laws that limit the use of telemedicine in abortion care. The other authors have no conflicts of interest to declare.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Allendale Investigational Review Board (No. IRB00005829). All study participants, patients and providers, provided verbal informed consent to participate in the study and to be audio recorded.

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Ectopic Pregnancy and Medical Abortion

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OBJECTIVE: **Medical abortion regimens have become more widely used to terminate early pregnancies. Medical abortion providers are concerned to diagnose and exclude women with ectopic pregnancy before initiating treatment, as with any early pregnancy termination. Yet, there is little information about whether the various pretreatment screening methods used are adequate. We reviewed published literature to determine the overall success of screening for ectopic pregnancy before medical abortion treatment.**

DATA SOURCES: **We searched MEDLINE for articles on medical abortion regimens published before July 2003.**

METHODS OF STUDY SELECTION: **We selected English language articles of studies of medical abortion with sample sizes greater than 100, which reported on ectopic pregnancy diagnosed after medical abortion treatment. Fifty-seven of 85 prospective studies and randomized trials (69%) met these inclusion criteria. We also included data from 2 unpublished studies because they were large and well-controlled and because they included serious adverse events known to us, which we did not deem fair to exclude from our analysis.**

TABULATION, INTEGRATION, AND RESULTS: **Each article was reviewed by one author. Data from selected studies were compiled, and the frequency of ectopic pregnancy diagnosed after medical abortion treatment was calculated. Ectopic pregnancy was diagnosed very infrequently following medical abortion procedures, occurring in only 10 of 44,789 (0.02%) women.**

CONCLUSION: **The very low frequency of ectopic pregnancies diagnosed after medical abortion treatment demonstrates that the various pretreatment screening methods that providers use to exclude patients with ectopic pregnancies are successful. Further, there is no evidence to suggest that medical abortion treatment leads to unusual complications for women with ectopic pregnancies. (Obstet Gynecol 2004;104:161–7. © 2004 by The American College of Obstetricians and Gynecologists.)**

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Excluding women with ectopic pregnancies before abortion induction is a concern for early abortion providers—surgical and medical—because women are treated before an ectopic pregnancy is easily detectable by ultrasonography and before it causes symptoms or ruptures. Ectopic pregnancy is the leading cause of pregnancy-related death in the first trimester,[1] with an overall incidence of 19.7 per 1,000 pregnancies (1.97%)[2] in the United States, 11.5 per 1,000 pregnancies (1.15%)[3] in the United Kingdom, and 16 per 1,000 pregnancies in France (1.6%).[4] Approximately 22–34% of ectopic pregnancies rupture,[5] usually by 10 weeks of gestation at the latest,[6] and a history of ectopic pregnancy is associated with infertility and repeat ectopic pregnancy.

Over the past decade, medical abortion regimens have become more widely used to terminate early pregnancies. These procedures are often completed at home in the United States, so providers do not have the opportunity to examine expelled tissue in the same way they do for products of conception removed during surgical procedures. Therefore, providers remain concerned about failing to detect an ectopic pregnancy in patients undergoing medical abortion treatment. Additionally, although methotrexate medical abortion regimens may terminate an ectopic pregnancy, mifepristone-based and misoprostol-alone regimens do not. However, there is little published literature on the frequency of ectopic pregnancies diagnosed after medical abortion treatment, and consequently, little information on the success of pretreatment screening protocols used by clinicians to exclude women with ectopic pregnancies from treatment.

Based on U.S. Food and Drug Administration (FDA) adverse-event reports related to the use of mifepristone (Mifeprex; Danco Laboratories, LLC, New York, NY), a 2003 review by Hausknecht[7] noted 5 reported cases of ectopic pregnancy after the use of mifepristone-misoprostol regimens for medical abortion between late 2000 and May 2002. Because approximately 80,000 women in the United States are estimated to have undergone treatment in that period, the estimated frequency of ectopic pregnancy diagnosed after mifepristone-misoprostol medical abortion is 0.006%. Among the 5 cases reported

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by Hausknecht, one patient died as a result of a tubal rupture after refusing hospitalization and treatment the day before her death. Two additional patients had ruptured ectopic pregnancies but were treated successfully with surgery, and the remaining 2 cases also were treated successfully before rupture. (For more detail on outcomes, refer to regulatory agency reports for Mifeprex between September 28, 2000, and September 28, 2001, and for Mifegyne [Exelgyn, Oxon, UK] between December 1, 1999, and May 31, 2001.)

Data based on regulatory reports, however, are generally presumed to underestimate the true incidence of an event, because reporting is voluntary and unsolicited. To analyze the success of pretreatment screening methods more systematically, we conducted a literature review of medical abortion studies.

SOURCES

We searched the MEDLINE database for articles published before July 2003, written in English, and with the following indexing terms: "medical abortion," "mifepristone," "misoprostol," "methotrexate," "abortion," and "pregnancy termination."

STUDY SELECTION

We used the following selection criteria for study inclusion: 1) sample size greater than 100 (although for randomized trials, the sample size for a particular study arm could be less than 100), 2) data on the frequency of ectopic pregnancy following the medical abortion procedure by treatment group, and 3) gestational age for enrollment less than 12 weeks, and 4) English language. Articles selected included reports of prospective, retrospective, and randomized studies. The population for all studies was women of reproductive age who received medical abortion treatment in the first trimester. The frequency of ectopic pregnancy diagnosed after medical abortion treatment was the outcome of interest for our review. Using this methodology, we retrieved 85 articles, 57 of which met the inclusion criteria for our review (69%).[8–64] We also included data from 2 studies being prepared for publication (unpublished data from a study in Canada, 2001; unpublished data from study in United States, 2002). The review encompassed regimens using mifepristone and gemeprost, mifepristone and oral misoprostol, mifepristone and vaginal misoprostol, methotrexate and vaginal misoprostol, and vaginal misoprostol only, including a total of 44,789 women undergoing medical abortion procedures, almost all of whom had early gestations (less than 9 weeks of amenorrhea). Five studies included women with gestations of up to 12 weeks of amenorrhea.[18,22,32,34,55]

Each article was reviewed by one author. Data from selected studies were compiled, and the frequency of ectopic pregnancy diagnosed after medical abortion treatment was calculated.

RESULTS

In the aggregated sample, diagnosis of an ectopic pregnancy after medical abortion treatment was rare, occurring in only 10 of 44,789 women (0.02%). Among women treated with mifepristone and gemeprost (Table 1), 4 women were diagnosed with ectopic pregnancy (0.04%, n = 10,348). Three cases required surgical intervention, and the treatment of one case was not detailed. Among those treated with mifepristone and oral misoprostol (Table 1), 2 women were diagnosed with ectopic pregnancies (0.01%, n = 13,377). In one case, tubal rupture occurred 2 days after administration of misoprostol; both patients recovered fully. Of 15,172 women who received mifepristone followed by vaginal misoprostol (Table 1), 3 (0.02%) women had an ectopic pregnancy after the procedure. Treatment for one case was not detailed. The other 2 women were successfully treated–one with surgical intervention, one with methotrexate.

Although intramuscular methotrexate is a standard treatment for ectopic pregnancy, one woman had an ectopic pregnancy after treatment with methotrexate and vaginal misoprostol (Table 1; 0.03%, n = 3,893). The woman required laparotomy and transfusion. In this case, an intrauterine gestational sac was reportedly visualized by ultrasonography at intake, and it is uncertain whether the ectopic pregnancy was misinterpreted as intrauterine or was part of an unrecognized heterotopic twin pregnancy.[16]

Finally, among the 1,999 women who underwent medical abortion procedures with vaginal misoprostol alone, there were no cases of ectopic pregnancies diagnosed after treatment reported in the literature. However, there is limited use of vaginal misoprostol-only regimens and a correspondingly small sample of such patients. This finding is not unexpected, based on the overall frequency of ectopic pregnancy diagnosed after medical abortion.

CONCLUSION

Results from previous clinical trials and this literature review demonstrate that medical abortion is a safe and effective method for terminating early pregnancies and may actually contribute to women's health through the early screening, detection, and treatment of ectopic preg-

Table 1. Ectopic Pregnancy and Medical Abortion

Article	Year	Regimen	n	GA (wk)*	Ectopic [% (n)]
Mifepristone and gemeprost					
Silvestre et al[50]	1990	600 mg MP; 1 mg GP	2,115	7	0.00 (0)
WHO Task Force[63]	1991	25 mg MP or 600 mg MP; 1 mg GP	385	7	0.00 (0)
WHO Task Force[62]	1993	200, 400 or 600 mg MP; 1 mg GP	1,151	4	0.00 (0)
UK Multicentre Study Group[55]	1997	600 mg MP; 1 mg GP, up to 5 doses	267	12	0.00 (0)
UK Multicentre Study Group[56]	1997	600 mg MP; 1 mg GP	1,018	9	0.10 (1)†
Bartley et al[14]	2000	200 mg MP; 0.5 mg GP	2,839	9	0.11 (3)‡
Bartley et al[13]	2001	200 mg MP; 0.5 mg GP	453	9	0.00 (0)
WHO Task Force[59]	2001	200 or 600 mg MP; 1 mg GP	896	8–9	0.00 (0)
WHO Task Force[60]	2001	50 or 200 mg MP; 0.5 or 1 mg GP	1,224	8	0.00 (0)
Subtotal			10,348		0.04 (4)
Mifepristone and oral misoprostol					
Aubeny[11]	1991	600 mg MP; 400 μg MS	1,208	7	0.00 (0)
McKinley et al[40]	1993	200 or 600 mg MP; 600 μg MS	220	9	0.00 (0)
Peyron et al[43]	1993	600 mg MP; 400 μg MS	505	7	0.00 (0)
Peyron et al[43]	1993	600 mg MP; 400 μg MS, 200 μg MS	390	7	0.26 (1)§
Sang et al[33]	1994	200 mg MP; 600 μg MS	149	7	0.00 (0)
Sang et al[33]	1994	50 mg MP, 25 mg MP; 600 μg MS	301	7	0.00 (0)
Aubeny et al[12]	1995	600 mg MP; 400 μg MS	1,108	7	0.09 (1)‖
el-Refaey et al[30]	1995	600 mg MP; 800 μg MS	130	9	0.00 (0)
Winikoff et al[58]	1997	600 mg MP; 400 μg MS	1,373	8	0.00 (0)
Spitz et al[51]	1998	600 mg MP; 400 μg MS	2,121	8	0.00 (0)
Jain et al[38]	1999	600 mg MP; 400 μg MS	100	8	0.00 (0)
Ngoc et al[41]	1999	600 mg MP; 400 μg MS	257	8	0.00 (0)
Aubeny and Chatellier[210]	2000	600 mg MP; 400 μg MS	119	7	0.00 (0)
ICMR Task Force[36]	2000	200 mg MP; 600 μg MS	440	4	0.00 (0)
WHO Task Force[61]	2000	200 or 600 mg MP; 400 μg MS	1,589	5	0.00 (0)
Elul et al[31]	2001	200 mg MP; 400 μg MS	315	8	0.00 (0)
Population Council study, Canada¶	2001	200 mg MP; 400 μg MS	319	8	0.00 (0)
Population Council study, Canada¶	2001	200 mg MP; 600 μg MS	319	8	0.00 (0)
Schaff et al[45]	2001	200 mg MP; 400 μg MS, 2 doses	548	9	0.00 (0)
Coyaji et al[25]	2002	600 mg MP; 400 μg MS	874	9	0.00 (0)
Population Council study, United States¶	2002	200 mg MP; 400 μg MS	353	7	0.00 (0)
Schaff et al[44]	2002	200 mg MP; 400 μg MS or 800 μg MS	489	9	0.00 (0)
Tang et al[52]	2002	200 mg MP; 800 μg MS	50	9	0.00 (0)
Tang et al[54]	2002	200 mg MP; 800 μg MS	100	9	0.00 (0)
Subtotal			13,377		0.01 (2)
Mifepristone and vaginal misoprostol					
el Refaey et al[30]	1995	600 mg MP; 800 μg MS	133	9	0.00 (0)
Penney et al[42]	1995	200 mg MP; 800 μg MS	360	9	0.00 (0)
Schaff et al[49]	1997	600 mg MP; 800 μg MS	168	8	0.00 (0)
Ashok et al[9]	1998	200 mg MP; 800 μg MS	2,000	9	0.00 (0)
Gouk et al[32]	1999	200 mg MP; 800 μg MS	313	9–12	0.00 (0)
Schaff et al[48]	1999	200 mg MP; 800 μg MS	933	8	0.21 (2)#
Aubeny and Chatellier[10]	2000	600 mg MP; 400 μg MS	118	7	0.00 (0)
Schaff et al[46]	2000	200 mg MP; 800 μg MS	2,295	8	0.00 (0)
Schaff et al[47]	2000	200 mg MP; 800 μg MS	1,137	9	0.00 (0)
Bartley et al[13]	2001	200 mg MP; 800 μg MS	457	9	0.22 (1)**
Bjorge et al[15]	2001	600 mg MP; 800 μg MS	226	9	0.00 (0)
Child et al[24]	2001	200 mg MP; 800 μg MS	533	9	0.00 (0)
Knudsen[39]	2001	600 mg MP; 400 μg MS	100	8	0.00 (0)
Population Council study, Canada¶	2001	200 mg MP; 800 μg MS	318	8	0.00 (0)
Schaff et al[45]	2001	200 mg MP; 800 μg MS	596	9	0.00 (0)
Ashok et al[8]	2002	200 mg MP; 800 μg MS	4,132	9	0.00 (0)
Schaff et al[44]	2002	200 mg MP; 800 μg MS	522	9	0.00 (0)
Tang et al[52]	2002	200 mg MP; 400 μg MS	100	5	0.00 (0)
Tang et al[53]	2002	200 mg MP; 800 μg MS	100	9	0.00 (0)
Creinin et al[26]	2003	200 mg MP; 800 μg MS	148	9	0.00 (0)
Hamoda et al[34]	2003	200 mg MP; 800 μg MS	483	7–13	0.00 (0)
Subtotal			15,172		0.02 (3)

(*continued*)

Table 1. Ectopic Pregnancy and Medical Abortion (*continued*)

Article	Year	Regimen	n	GA (wk)*	Ectopic [% (n)]
Methotrexate and vaginal misoprostol					
Hausknecht[35]	1995	50 mg IM MT; 800 μg MS	178	9	0.00 (0)
Creinin et al[29]	1996	50 mg IM MT; 800 μg MS	300	7	0.00 (0)
Carbonell et al[23]	1997	50 mg IM MT; 800 μg MS	287	9	0.00 (0)
Creinin et al[28]	1997	50 mg oral MT; 800 μg MS	300	7	0.00 (0)
Wiebe[57]	1997	50 mg IM MT; 750 or 500 μg MS	289	7	0.00 (0)
Carbonell et al[20]	1998	50 mg oral MT; 800 μg MS	300	9	0.00 (0)
Creinin et al[27]	1999	50 mg IM MT; 800 μg MS	240	7	0.00 (0)
Borgatta et al[16]	2001	50 mg IM MT; 800 μg MS	1,973	7	0.05 (1)††
Creinin et al[26]	2003	50 mg IM MT; 800 μg MS	26	9	0.00 (0)
Subtotal			3,893		0.03 (1)
Vaginal misoprostol only					
Bugalho et al[18]	1996	200 or 400 μg MS, up to 4 doses	134	5–11	0.00 (0)
Carbonell et al[21]	1997	800 μg MS (moistened with water), up to 3 doses	141	10	0.00 (0)
Wiebe[57]	1997	600 μg MS, 3 doses	241	7	0.00 (0)
Esteve et al[22]	1999	800 μg MS (moistened with water), up to 4 doses	720	9	0.00 (0)
Jain et al[38]	1999	800 μg MS; 800 μg MS	100	8	0.00 (0)
Bugalho et al[17]	2000	800 μg MS	103	6	0.00 (0)
Carbonell et al[19]	2001	1000 μg MS, up to 3 doses	300	7	0.00 (0)
Jain et al[37]	2001	800 μg MS, up to 3 doses	100	8	0.00 (0)
Zikopoulos et al[64]	2002	800 μg MS, up to 3 doses	160	8	0.00 (0)
Subtotal			1,999		0.00 (0)
Total			46,421		0.02 (10)

GA = gestational age; MP = mifepristone; GP = gemeprost; WHO = World Health Organization; UK = United Kingdom; MS = misoprostol; ICMR = Indian Council of Medical Research; IM = intramuscular; and MT = methotrexate.

* Gestational age based on first day of last menstrual period.

† Received full regimen; no comments on outcome.

‡ Required surgical intervention following regimen.

§ Received full regimen; given surgical intervention.

‖ Ruptured 2 days after misoprostol; treated with salpingectomy.

¶ Population Council, unpublished data.

Case 1: Had aspiration curettage; treated with methotrexate. Case 2: Adnexal mass treated with salpingectomy.

** Received full regimen; no details on treatment or treatment outcome.

†† One woman had undiagnosed ectopic pregnancy requiring laparotomy and transfusion; it is uncertain whether this was due to misdiagnosis or twin pregnancy.

nancy. Indeed, since ectopic pregnancy is a contraindication for medical abortion treatment (except for methotrexate regimens), if providers use adequate methods to screen patients before treatment, we would expect that ectopic pregnancy would be diagnosed after medical abortion treatment only very rarely. Further, because medical abortions are performed early in gestation, frequently before 7 weeks of gestation, providers are given an earlier-than-normal opportunity to screen and treat women for ectopic pregnancy.

In the studies reviewed here, the frequency of ectopic pregnancy diagnosed after medical abortion procedures was very low (0.02%), significantly lower than the incidence of ectopic pregnancy among all pregnancies (approximately 1–2%).[2–4] A review of data from the Planned Parenthood Federation of America confirms our finding that ectopic pregnancy is very rarely diagnosed after medical abortion treatment (0.01%, 7 of 58,950 cases treated with mifepristone and misoprostol between January 1, 2001 and June 30, 2003) (Mary Fjerstad, Planned Parenthood Federation of America, personal communication, January 13, 2004). This very low frequency suggests that, indeed, providers are successfully screening women for ectopic pregnancy before medical abortion treatment. These screened women thus avoid the risks inherent in later detection and treatment of ectopic pregnancy, including a higher risk of death, severe hemorrhage, and salpingectomy. In fact, of the 10 reported cases in this review, all were successfully treated. There was no evidence suggesting that medical abortion treatment led to unusual complications for women with ectopic pregnancies.

Despite the successful use of various screening approaches for ectopic pregnancy by early abortion providers (which may include use of some or all of these methods: bimanual examination, dating of the last menstrual period, β-hCG levels, and vaginal ultrasonography), even the most precise method, ultrasonography,

cannot be expected to detect all cases. The 2 primary reasons for failing to detect an ectopic pregnancy despite use of an ultrasound screen are that the pregnancy is so early it cannot be visualized and that clinicians can err in interpreting ultrasound images. Clinicians should therefore always be vigilant about the possibility of undiagnosed ectopic pregnancy and provide women with information about ectopic pregnancy and its symptoms to further increase the likelihood of early detection and successful treatment.

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Systematic Review

No-Test Medication Abortion

A Systematic Review

Marit Pearlman Shapiro, MD, MPH, Divya Dethier, MD, Melissa Kahili-Heede, MLIS, MEd, and Bliss Kaneshiro, MD, MPH

OBJECTIVE: To summarize the effectiveness and safety outcomes of medication abortion performed without prior pelvic examination or ultrasonogram ("no-test medication abortion").

DATA SOURCES: We searched the MEDLINE, Scopus, Web of Science, Cochrane (including ClinicalTrials.gov), CINAHL, Global Index Medicus, and CAB Direct databases to identify relevant studies published before April 2022 using a peer-reviewed search strategy including terms such as "medication abortion" and "ultrasonography." We contacted experts in the field for unpublished data and ongoing studies.

METHODS OF STUDY SELECTION: We reviewed 2,423 studies using Colandr. We included studies if they presented clinical outcomes of medication abortion performed with mifepristone and misoprostol and without prior pelvic examination or ultrasonogram. We excluded studies with duplicate data. We abstracted successful abortion rates overall, as well as rates by gestational age through 63 days, 70 days and past 84 days. We abstracted complication rates, including the need for surgical evacuation, additional medications, blood transfusion, and ectopic pregnancy.

TABULATION, INTEGRATION AND RESULTS: We included 21 studies with a total of 10,693 patients with outcome data reported. The overall efficacy of no-test medication abortion was 96.4%; 93.8% (95% CI 92.8–94.6%) through 63 days of gestation and 95.2% (95% CI 94.7–95.7%) through 70 days of gestation. The overall rate of surgical evacuation was 4.4% (95% CI 4.0–4.9), need for additional misoprostol 2.2% (95% CI 1.8–2.6), blood transfusion 0.5% (95% CI 0.3–0.6), and ectopic pregnancy 0.06% (95% CI 0.02–0.15).

CONCLUSION: Medication abortion performed without prior pelvic examination or ultrasonogram is a safe and effective option for pregnancy termination.

SYSTEMATIC REVIEW REGISTRATION: PROSPERO, CRD42021240739.

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Each author has confirmed compliance with the journal's requirements for authorship.

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The use of medication abortion is increasing. In 2018, half of all pregnancy terminations at less than 9 weeks of gestation were medication abortions.[1] This number is likely even higher today, because the coronavirus disease 2019 (COVID-19) pandemic triggered rapid shifts in abortion provision to minimize physical contact between patients and health care professionals and to reduce the time spent in medical facilities. Along with increasing use of telemedicine, health care professionals pivoted toward providing medication abortions without previously routine ultrasonograms or clinical examinations. Leading national professional organizations, including the American College of Obstetricians and Gynecolo-

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gists, Planned Parenthood Federation of America, and the National Abortion Federation, as well as the World Health Organization, published recommendations supporting this practice.[2–4] The practice of providing a medication abortion without a prior pelvic examination or ultrasonogram has been described as "low-test medication abortion" or "medication abortion with history-based screening." In this review, we describe this model as no-test medication abortion.

Abortion care globally is typically provided without a prior ultrasonogram.[5] The two benefits of an ultrasonogram are accurate estimation of gestational age and exclusion of ectopic pregnancy. Research has shown that, with appropriate counseling, a patient's certain last menstrual period can be accurately used for determining gestational age without the use of ultrasonography.[6,7] One study demonstrated that gestational age dating using patient reported estimates of last menstrual period resulted in 0.8% of patients being provided a medication abortion beyond 70 days of gestation, the U.S. Food and Drug Administration–approved limit on the use of mifepristone for medication abortion.[8] Improved accuracy and sensitivity of self-assessment of gestational duration can be achieved by broadening the screening questions, including date of conception and number of weeks pregnant.[9] Another potential concern is a missed diagnosis of ectopic pregnancy. Ectopic pregnancy rates in patients seeking abortions are lower than the general U.S. population. A study of 16,369 patients choosing medication abortion with pregnancies less than 49 days demonstrated an ectopic pregnancy rate of 1.3 per 1,000 pregnancies,[10] lower than the U.S. rate of ectopic pregnancy of 8.3 per 1,000 pregnancies.[11]

The shift to using telemedicine and no-test medication abortion during the initial lockdown for COVID-19 was critical to removing older practices that created barriers to safe early medication abortion. Experts in the field advocated for this approach for several years before the pandemic.[12] The no-test medication abortion approach eliminates significant barriers to abortion access, increases convenience for patients and health care professionals, and reduces cost. No-test medication abortion further promotes different models for patients to access the medications including mailing, pharmacy dispensing, and asynchronous visits. Before the COVID-19 pandemic, the published literature on no-test medication abortion was limited to a few small research studies and abortion provision outside the United States. In the context of changing practices due to COVID-19, increasing numbers of health care professionals worldwide have adopted these innovative practices and published their results. In this systematic review, we summarize the efficacy and safety outcomes of medication abortion performed without prior pelvic examination or ultrasonogram.

SOURCES

This systematic review follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, including registration in PROSPERO (registration number CRD42021240739). A health sciences librarian developed the literature search strategy (M.K.-H.). A second librarian outside of our institution peer-reviewed the search strategy. We searched the following electronic databases: PubMed, MEDLINE, EMBASE (Elsevier), Scopus, Web of Science, and CINAHL (EBSCOhost). The search employed a combination of keywords and controlled vocabularies related to abortion ("no test medical abortion," "medication abortion"), abortion medication ("mifepristone", "misoprostol"), and pretreatment methods ("ultrasound", "telemedicine") with no date or language restriction (see Box 1 for the PubMed search strategy and Appendix 1, available online at http://links.lww.com/AOG/C955, for complete search strategy). To identify any ongoing or recent clinical trials, we searched registries through Cochrane Central Register of Controlled Trials, which included ClinicalTrials.gov and the International Clinical Trials Registry Platform. We also searched grey literature databases, Google Scholar, Global Index Medicus, and CAB Direct. We scanned the reference lists of included studies or relevant reviews identified through the search to ensure literature saturation. Additionally, we contacted experts in medication abortion to identify studies currently undergoing peer review. Before publication, we again searched databases to include any relevant studies newly published since the initial search. No terms were added or deleted from the search strategy.

STUDY SELECTION

Only studies discussing the provision of medication abortion without prior pelvic examination or ultrasonogram were eligible for inclusion. We included randomized control trials, as well as prospective and retrospective comparative cohort studies. We excluded case studies, commentaries, letters and editorials, as well as any manuscripts where clinical outcomes were not reported. The included studies employed any abortifacient medication regimen, including mifepristone and misoprostol combined

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Box 1. Search Strategy (PubMed)

((("No test medication abortion" [tiab] OR "medical abortion" [tiab] OR "medication abortion" [tiab] OR "no touch abortion" [tiab] OR "telemedicine abortion" [tiab] OR "early medical abortion" [tiab] OR "self managed abortion" [tiab] OR telabortion [tiab] OR "online abortion" [tiab])) OR (("abortion, induced"[MeSH Terms] OR abort* [tiab] OR postabort* [tiab] OR preabort* [tiab]) AND ((mifepristone [tiab] OR "Mifepristone"[Mesh] OR misoprostol [tiab] OR "Misoprostol"[Mesh] OR methotrexate [tiab] OR "Methotrexate"[Mesh] OR abortifacient [tiab] OR "RU-486" [tiab] OR "abortion pill" [tiab])))) AND ("ultrasonography"[MeSH Terms] OR "Diagnostic Imaging"[Mesh] OR ultrasound* [tiab] OR ultrasonograph* [tiab] OR sonograph* [tiab] OR endosonogra* [tiab] OR "pelvic exam*" [tiab] OR "Gynecological Examination"[Mesh] OR telemedicine [tiab] OR "Telemedicine"[Mesh] OR telehealth [tiab])
See Appendix 1 (available online at http://links.lww.com/AOG/C955) for full search strategy.

regimens, as well as misoprostol alone regimens of any dosages.

Two authors (M.P.S. & D.D.) independently screened the results of the search based on titles and abstracts against the inclusion criteria using Colandr. We used EndNote reference management software to assess for duplication of articles. To determine whether multiple reports of the same study were published, we juxtaposed author names and indicated if all reports of the study were considered. We obtained full reports for all titles that appeared to meet the inclusion criteria or where there was uncertainty. The reviewers then screened the full text reports and determined whether they meet the inclusion criteria. Google Translate was used for articles in languages not spoken by the authors and two articles that were unable to be entered into the online translation service were translated by native speakers. If more information was needed, we contacted the study authors to resolve eligibility questions. The reviewers then independently and in duplicate extracted data from the reports. Study information included number of patients enrolled and with follow-up, regimen used, efficacy rates, and complication rates. Any disagreement was resolved through discussion with the full systematic review team.

Our primary outcome was *successful medication abortion*, defined as a complete abortion without the need for surgical management to complete the termination, as per MARE (Medical Abortion Reporting of Efficacy) guidelines.[13] *Failure* was defined as the need for further surgical intervention at either planned or unscheduled follow-up visits to complete the abortion. Adverse events are of primary interest for decision-making on the safety of no-test medication abortion. The following were abstracted, when reported: unscheduled emergency department or urgent care visits, hospital admissions, blood transfusions, additional unplanned medication treatments, additional unplanned surgical treatments, ectopic pregnancies including those requiring emergent surgical treatment, and death. If study results were not presented in these categories, we recalculated the data based on tables and text within the manuscript for no-test medication abortion. If no follow-up was documented, we excluded those patients from our summary statistics to ensure the most conservative estimations. We then combined outcomes across studies to produce summary statistics for efficacy and safety.

RESULTS

We identified 2,423 records in the literature search and reviewed 190 full-text articles for eligibility. We contacted 26 authors for additional information about their studies, as well as the primary investigators of seven ongoing studies identified in ClinicalTrials.gov and the Clinical Trial Register at the International Clinical Trial Registry Platform of the World Health Organization. Three unpublished studies were identified by experts in the field, though at the time of publication of this review two were subsequently accepted to peer reviewed journals. After full-text review and discussion with authors, 150 studies were excluded because an ultrasonogram or pelvic examination was obtained before provision of medication abortion. Twelve studies were excluded because of study design. Seven studies were excluded because we did not have adequate information and authors did not respond to queries. We included four studies that published aggregated results for patients who had no-test medication abortion with those who had an ultrasonogram after authors responded to our query and sent disaggregated data sets. The 21 studies in this review include medication abortions performed without prior pelvic examination or ultrasonogram (Tables 1 and 2). The results include no-test medication abortion performed in at least 24 countries. We followed PRISMA guidelines for reporting of study selection (Fig. 1).

We excluded six of the studies from the final summative analysis (Table 2). Three of the studies were published in the 1970s and 1980s and used medication regimens that are not current standard of care for medication abortion, including intramuscular carboprost and sulprostone.[14–16] Two of the studies included participants from the TelAbortion study

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Table 1. Summary and Description of Studies Included in the Systematic Review and Summary Statistics

Study Author, Year, Country	Study Design	Gestational Age (d)	Abortifacient Regimen	Method of Follow-up	No. of Participants	No. of Participants With Complete Outcome Data*	Brief Description	Possible Bias From Included Study
Wiebe, 2014,[26] Canada	Retrospective cohort	51 or less	Methotrexate 50 mg/m^2 and misoprostol 800 micrograms vaginally	Serum β-hCG level	11	5	Cohort of patients undergoing medication abortion by telemedicine in British Columbia, Canada	Selection bias
Aiken, 2017,[27] Ireland	Retrospective cohort	63 or less	Mifepristone 200 mg and misoprostol 1,200 micrograms (route not specified)	Self-report (through online evaluation form)	1,023	1,000	Cohort of patients seeking self-sourced medication abortion through Women on Web, an online telemedicine service	Reporting bias
Raymond, 2018,[28] Moldova, Mexico, United States	Prospective cohort	67 or less	Mifepristone 200 mg and misoprostol 400 micrograms sublingual or 800 micrograms buccal	Ultrasonogram, pelvic examination, serial serum or urine hCG testing	406	360	Case series of patients requesting medication abortion without a prior ultrasonogram at 5 study sites	Selection bias
Endler, 2019,[25] Poland	Retrospective cohort	63–100	Mifepristone 200 mg and misoprostol 800, 400, 400 micrograms sublingual	Self-report (through online evaluation form)	627	615 (419 had adverse-event data)	Cohort of patients seeking self-sourced medication abortion through Women on Web, an online telemedicine service	Reporting bias
Marval-Peck, 2019,† multiple countries	Retrospective cohort	35 or less	NR	Self-report	473	473	Cohort of patients at 5 wk of gestation or less seeking medication abortion through Women on Web, an online telemedicine service	Reporting bias
Chong, 2020,[29] 11 countries	Prospective cohort	56 or less	Mifepristone 200 mg and misoprostol 800 micrograms vaginal, sublingual, or buccal	Multilevel urine pregnancy tests	165	117	Cohort of patients seeking medication abortion through safe2choose.org, an online telemedicine service, and their ability to use MLPTs	Reporting bias

(*continued*)

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Table 1. Summary and Description of Studies Included in the Systematic Review and Summary Statistics (*continued*)

Study Author, Year, Country	Study Design	Gestational Age (d)	Abortifacient Regimen	Method of Follow-up	No. of Participants	No. of Participants With Complete Outcome Data*	Brief Description	Possible Bias From Included Study
Wiebe, 2020,[30] Canada	Retrospective cohort	70 or less	Mifepristone and misoprostol	Serum β-hCG level	149‡	138	Cohort of patients undergoing medication abortion by telemedicine in British Columbia, Canada	Selection bias
Godfrey, 2021,[31] United States	Retrospective cohort	70 or less	Mifepristone 200 mg and misoprostol 800 micrograms sublingual, buccal, or vaginal	Self-report	479‡	186	Cohort of patients requesting medication abortion from 3 family medicine physicians using Aid Access asynchronous online service	Attrition bias
Kapp, 2021a,[32] multiple countries	Retrospective cohort	91 or more	Mifepristone 200 mg or misoprostol 4–6 doses 400 micrograms sublingual or both	Self-report§	144	131	Cohort of patients requesting self-managed medication abortion at 13 or more wk of gestation from Women on Web, an online telemedicine service	Reporting bias
Reynold-Wright, 2021,[33] Scotland	Prospective cohort	83 or less	Mifepristone 200 mg and misoprostol 800 micrograms sublingual or vaginal or buccal	Urine pregnancy test	529†	529	Cohort of patients requesting medication abortion at home through the National Health Service Lothian telemedicine service	Selection bias
Kapp, 2021b,[34] Nepal	Retrospective cohort	91 or more	Mifepristone and misoprostol	Health care professional visualization of expelled fetus	301	301	Cohort of patients undergoing inpatient medication abortion in 8 hospitals in Nepal	Selection bias
Kapp, 2021c,[35] Cambodia	Prospective cohort	63 or less	Mifepristone and misoprostol	Self-report (mobile phone contact)	1,050‡	910	Cohort of patients purchasing abortion medication independently at a pharmacy or received from a clinic in Cambodia	Reporting bias
Moseson, 2021,[36] Argentina and Nigeria	Prospective cohort	154 or less	Mifepristone or misoprostol sublingual or both	Self-report	851‡	851	Cohort of callers from safe abortion accompaniment groups requesting information on self-managed abortion	Reporting bias

(*continued*)

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Table 1. Summary and Description of Studies Included in the Systematic Review and Summary Statistics (*continued*)

Study Author, Year, Country	Study Design	Gestational Age (d)	Abortifacient Regimen	Method of Follow-up	No. of Participants	No. of Participants With Complete Outcome Data*	Brief Description	Possible Bias From Included Study
Aiken, 2022,[37] United States	Retrospective cohort	70 or less‖	Mifepristone 200 mg and misoprostol 800 micrograms sublingual	Self-report (through online evaluation form)	3,186	2,797	Cohort of patients seeking self-managed medication abortion through Aid Access, an online telemedicine service	Reporting bias
Upadhyay, 2022,[19] United States	Retrospective cohort	77 or less	Mifepristone 200 mg and misoprostol up to 1,600 micrograms	Self-report, ultrasonogram, pelvic examination, serial serum or urine hCG testing	3,779	2,397	Cohort of patients obtaining medication abortion without screening ultrasonography at 14 independent, Planned Parenthood, academic-affiliated, and online-only clinics throughout the United States	Attrition bias

hCG, human chorionic gonadotropin; NR, not reported.
* Defined as completed abortion or ongoing pregnancy confirmed at least by patient report.
† Marval-Peck L, Izaguirre S, Yanow S, Jelinska K, Comendant R, Foster AM [abstract]. Self-administration of very early medication abortion provided through a global online telemedicine service. Contraception 2019: 319. doi: 10.1016/j.contraception.2019.07.051
‡ Additional unpublished data provided by authors.
§ Patients reported information to Women on Web; however, 30 confirmed by ultrasonography, 21 observed expelled fetus, 18 had resolution of pregnancy symptoms, eight had a negative pregnancy test result, and four had resumption of normal menses.
‖ Includes 395 patients at more than 10 weeks of gestation but does not give an upper limit.

and University of Hawai'i patients who were potentially included in a third manuscript.[17–19] Although this excludes some participants from the Kerestes et al and Anger et al studies not represented in the larger Upadhyay et al study, we excluded these two studies from the summary statistics to avoid duplicate data and ensure the most conservative estimates. Lastly, clinical outcome data were not available for the majority of the participants in the U.K. national cohort study published by Aiken et al.[20] Although this study included more than 18,000 participants, we excluded these data from the summary statistics.

We determined the remaining 15 studies to be sufficiently homogeneous in terms of design and comparator to create summary statistics for the primary and secondary outcomes. All of the studies reported the number of abortions completed without the need for surgical evacuation for any reason. Studies reported complete abortion through a variety of methods, including patient self-report, physician or nurse report including direct visualization of products of conception, reduction in quantitative serum β-hCG levels, negative urine pregnancy test several weeks after ingesting abortifacient medications or absence of a gestational sac on follow-up ultrasound evaluation.

Several of the studies note that patients may have obtained an ultrasonogram at a different clinic than the one providing the abortifacient medications. We confirmed by direct contact with authors that, for all of these studies, clinicians did not have access to the ultrasonogram reports or images in making management decisions before dispending medications.

The overall efficacy rate of no-test medication abortion is 96.4% (95% CI 96.0–96.7%) in the 10,693 patients included in this systematic review (Table 3). For patients with pregnancies at less than 70 days of gestation (n=8,166), the efficacy rate was 95.2% (95% CI 94.7–95.7%). For patients with pregnancies at more than 84 days of gestation (n=432), the efficacy rate was 83.8% (95% CI 80.0–87.2%).

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Table 2. Summary and Description of Studies Included in the Systematic Review Not Included in Summary Statistics

Study Author, Year, Country	Study Design	Gestational Age (d)	Abortifacient Regimen	No. of Participants Without Ultrasonogram	Reason for Exclusion
Fylling, 1977,[14] Norway	Prospective cohort	37–60	Carboprost 0.6 mg IM	60	Did not use mifepristone or misoprostol
Purandare, 1982,[15] global	Prospective cohort	56 or less	Gemeprost 1 mg	358	Did not use mifepristone or misoprostol
Csapo, 1982,[16] Finland and United States	Prospective cohort	45 or less	Sulproston 500 micrograms IM	200	Did not use mifepristone or misoprostol
Aiken, 2021a[20] United Kingdom	Retrospective cohort	69 or less	Mifepristone and misoprostol	18,435	Follow-up data not available for majority of participants; patient-reported outcome data available for 2,453 of 52,142 total abortions performed in the study, including those with ultrasonograms
Kerestes, 2021,[17] United States	Retrospective cohort	77 or less	Mifepristone 200 mg and misoprostol up to 1,600 micrograms	108	Participants overlap with Upadhyay, 2022[19]
Anger, 2021,[18] United States	Prospective cohort	69 or less	Mifepristone 200 mg and misoprostol 800 or 1,600 micrograms	287	Participants overlap with Upadhyay, 2022[19]

IM, intramuscular.

Adverse outcomes after no-test medication abortion are reported in Tables 4–7. The rate of surgical evacuation at less than 70 days of gestation was 3.8% (95% CI 3.3–4.3); for all participants it was 4.4% (95% CI 4.0–4.9). Of 7,987 patients for whom outcome data were available, only five ectopic pregnancies were

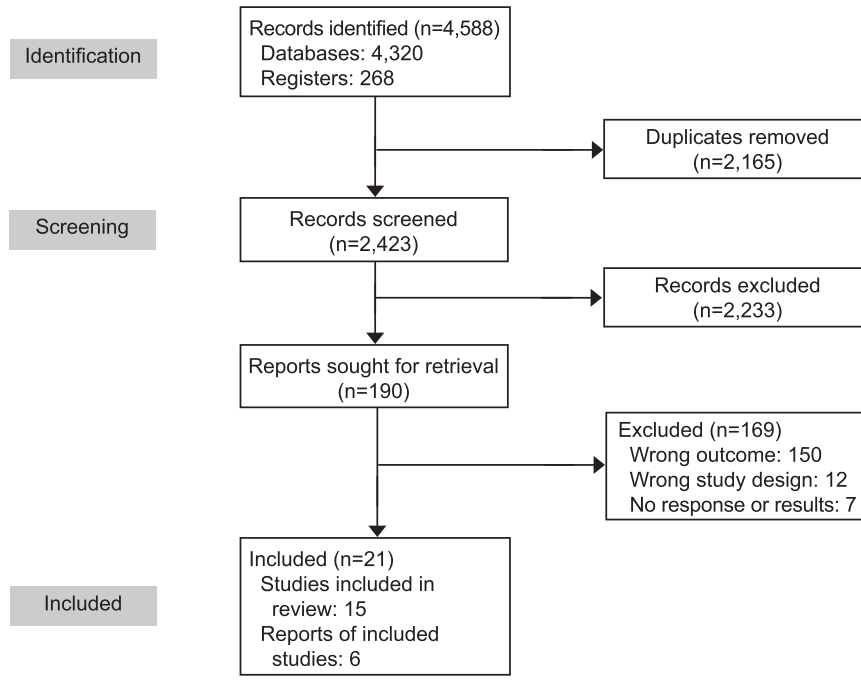

Fig. 1. No-test medication abortion flowchart.
Pearlman Shapiro. No-Test Medication Abortion. Obstet Gynecol 2023.

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Table 3. Efficacy Rates for Medication Abortion Without Prior Pelvic Examination or Ultrasonogram*

Gestational Age (d)	No. in Analysis	No. Successful†	% (95% CI)
Through 63	3,043	2,854	93.8 (92.8–94.6)
Through 70	8,166	7,774	95.2 (94.7–95.7)
More than 84	432	362	83.8 (80.0–87.2)
Overall‡	10,693	10,306	96.4 (96.0–96.7)

* Based on patients with known outcomes. Patients without follow-up are not included.
† Expelled pregnancy without need for surgical intervention per MARE (Medical Abortion Reporting of Efficacy) guidelines.[13] The MARE guidelines standardize definitions of medication abortion outcomes, facilitating comparison among studies and data synthesis.
‡ Includes studies not included in the above gestational age categories; therefore, will not add up completely.

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identified, for a total ectopic pregnancy rate of 0.06% (95% CI 0.02–0.15). For patients with pregnancies at less than 70 days of gestation (n=4,210), the rate of ectopic pregnancy was 0.02% (95% CI 0.0–0.13). There were no deaths reported. Blood transfusion was uncommon, with rates ranging from 0% to 0.7%.

DISCUSSION

This systematic review of 21 studies, which includes 10,693 patients, shows that no-test medication abortion is effective and safe. The cumulative efficacy rate of no-test medication abortion is 96.4% (95% CI 96.0–96.7%) confirmed completed abortions with only

Table 4. Complication Rates After Medication Abortion Without Prior Pelvic Examination or Ultrasonogram Through 70 Days of Gestation

Study Author, Year, Country	Total No. of Patients	Surgical Evacuation	Additional Misoprostol	Ectopic Pregnancy
Wiebe, 2014,[26] Canada	5	1 (20)	0	0
Aiken, 2017,[27] Ireland	1,000	45 (4.5)	NR	NR
Raymond, 2018,[28] Moldova, Mexico, United States	360	7 (1.9)‡	10 (2.8)	0
Marval-Peck, 2019,§ multiple countries	473	NR	33 (7.0)	NR
Chong, 2020,[29] 11 countries	117	NR	NR	NR
Wiebe, 2020,[30] Canada	138	5 (3.6)	7 (5.1)	0
Godfrey, 2021,[31] United States	186	3 (1.6)	1 (0.5)	NR
Kapp, 2021c,[35] Cambodia	910	71 (7.8)	13 (1.4)	1 (0.1)
Aiken, 2022,[37] United States	2,797	72 (2.6)	NR	0

Study Author, Year, Country	Blood Transfusion	Sought Unscheduled Medical Care*	Hospitalization	Antibiotics	Deaths	Chose to Continue Pregnancy†
Wiebe, 2014,[26] Canada	0	1 (20)	0	0	0	NR
Aiken, 2017,[27] Ireland	7 (0.7)	87 (8.7)	NR	26 (2.6)	0	NR
Raymond, 2018,[28] Moldova, Mexico, United States	0	3 (0.8)	2 (0.6)	NR	0	1 (0.2)
Marval-Peck, 2019,§ multiple countries	NR	51 (10.8)	NR	NR	NR	NR
Chong, 2020,[29] 11 countries	NR	2 (1.7)	NR	NR	NR	NR
Wiebe, 2020,[30] Canada	NR	NR	NR	NR	0	NR
Godfrey, 2021,[31] United States	1 (0.5)	3 (1.6)	0	4 (2.2)	0	NR
Kapp, 2021c,[35] Cambodia	NR	18 (2.0)‖	11 (1.2)	4 (0.4)	0	NR
Aiken, 2022,[37] United States	18 (0.6)	NR	NR	15 (0.5)	0	NR

NR, not reported.
Data are n (%) unless otherwise specified.
* Includes unscheduled visits to clinics, urgent care facilities, and emergency departments.
† Medication abortion initially unsuccessful and patient chose to continue pregnancy rather than take additional medications or undergo a procedure.
‡ Three procedures were performed for reasons other than ongoing pregnancy.
§ Marval-Peck L, Izaguirre S, Yanow S, Jelinska K, Comendant R, Foster AM [abstract]. Self-administration of very early medication abortion provided through a global online telemedicine service. Contraception 2019: 319. doi: 10.1016/j.contraception.2019.07.051
‖ Eighteen patients sought care at a private clinic, and 11 women were hospitalized.

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Table 5. Complication Rates After Medication Abortion Without Prior Pelvic Examination or Ultrasonogram, Including Patients at More than 70 Days of Gestation

Study Author, Year, Country	Total No. of Patients	Surgical Evacuation	Additional Misoprostol	Ectopic Pregnancy
Endler, 2019,[25] Poland	419‡	65 (10.5)	12 (2.9)	NR
Kapp, 2021a,[32] global	131	23 (17.6)	NR	NR
Reynold-Wright, 2021,[33] Scotland	529	4 (0.8)	7 (1.3)	0
Kapp, 2021b,[34] Nepal	301	49 (16.3)§	NR	NR
Moseson, 2021,[36] Argentina and Nigeria	851	11 (1.3)	NR	0
Upadhyay, 2022,[19] United States	2,397	88 (3.7)	37 (1.5)	4 (0.2)

Study Author, Year, Country	Blood Transfusion	Sought Unscheduled Medical Care*	Hospitalization	Antibiotics	Deaths	Chose to Continue Pregnancy†
Endler, 2019,[25] Poland	2 (0.3)	230/385 (59.7)	NR	41 (9.8)	NR	5 (1.2)
Kapp, 2021a,[32] global	NR	53 (40)	NR	NR	0	13 (10)
Reynold-Wright, 2021,[33] Scotland	0	3 (0.6)	10 (1.9)	NR	0	NR
Kapp, 2021b,[34] Nepal	0	NA‖	NA‖	0	0	NR
Moseson, 2021,[36] Argentina and Nigeria	4 (0.5)	156 (18.3)	NR	NR	0	NR
Upadhyay, 2022,[19] United States	8 (0.3)	NR	6 (0.2)	NR	0	9 (0.34)

NR, not reported; NA, not applicable.
Data are n (%) unless otherwise specified.
* Includes unscheduled visits to clinics, urgent care facilities, and emergency departments.
† Medication abortion initially unsuccessful and patient chose to continue pregnancy rather than take additional medications or undergo a procedure.
‡ Adverse-event data available for only 419 of the total 615 patients with outcome data available.
§ Forty-nine participants with retained products of conception were treated with either a surgical procedure or additional medications.
‖ Abortions were performed in the hospital.

4.4% (95% CI 4.0–4.9) of patients requiring surgical evacuation. These rates are comparable with rates of medication abortion efficacy with pretreatment ultrasonogram. Complication rates were low, the rate of ectopic pregnancy was 0.06% (95% CI 0.02–0.15) and no deaths were reported. The complication rates we

Table 6. Complication Rates for Medication Abortion Without Prior Pelvic Examination or Ultrasonogram

	Ectopic Pregnancy			Unplanned Surgical Evacuation
Gestational Age (d)	No. in Analysis	No. of Ectopic Pregnancies	% (95% CI)	No. in Analysis
Through 63	1,454	1	0.07 (0.0–0.38)	3,043
Through 70	4,210	1	0.02 (0.0–0.13)	5,396
More than 70	NR	NR	NR	827
Overall†	7,987	5	0.06 (0.02–0.15)	10,024

	Unplanned Surgical Evacuation		Transfusion		
Gestational Age (d)	No. of Unplanned Surgical Evacuations	% (95% CI)	No. in Analysis	No. of Transfusions	% (95% CI)
Through 63	167	5.5 (4.7–6.4)	1,370	7	0.5 (0.2–1.1)
Through 70	204	3.8 (3.3–4.3)	4,348	26	0.6 (0.4–0.9)
More than 70	96	11.6 (9.5–14.0)	NR	NR	NR
Overall†	444	4.4 (4.0–4.9)	8,845	40	0.5 (0.3–0.6)

NR, not reported.
Based on patients with known outcomes. Patients without follow-up are not included.
† Includes studies not included in above gestational age categories; therefore, will not add up completely.

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Table 7. Additional Complication Rates for Medication Abortion Without Prior Pelvic Examination or Ultrasonogram

Gestational Age (d)	Additional Misoprostol	Sought Unscheduled Medical Care*	Hospitalization
Through 70	64/2,072 (3.1, 2.4–3.9)	165/3,051 (5.4, 4.6–6.3)	13/1,461 (0.9, 0.5–1.5)
Overall	120/5,417 (2.2, 1.8–2.6)	685/4,869 (14.1, 13.1–15.1)	29/4,387 (0.7, 0.4–1.0)

Gestational Age (d)	Antibiotics	Deaths	Chose to Continue Pregnancy†
Through 70	49/4,898 (1.0, 0.7–1.3)	0/5,396 (0, 0.07)‡	1/360 (0.2, 0.1–1.5)
Overall	90/5,618 (1.6, 1.2–2.0)	0/9,605 (0, 0.04)‡	28/3,307 (0.9, 0.6–1.2)

Data are n/N (%, 95% CI) unless otherwise specified.
* Includes unscheduled visits to clinics, urgent care facilities, and emergency departments.
† Medication abortion initially unsuccessful and patient chose to continue pregnancy rather than take additional medications or undergo a procedure.
‡ One-sided 97.5% CI.

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observed are lower than similar complications during delivery in the United States.[21] Further, complication rates are far lower than the rates of complications seen with unsafe methods of abortion.[22] This systematic review further supports the abortion care guidelines from national and international organizations that ultrasonogram should not be a requirement for abortion provision.

No-test medication abortion is becoming increasingly common, as evidenced by the large increase in the number of studies on the subject published within the past few years. Eleven of the studies included in our analysis were published in 2021 or 2022. With legal restrictions on abortion, more patients will find themselves without access to abortion with considerable, unfeasible travel distances and expenses to the nearest abortion clinic. With the COVID-19 pandemic, telemedicine abortion care is already dramatically increasing, and no-test protocols will be crucial for the provision of abortion care to these patients. No-test protocols can be used to provide safe abortion care without a pretreatment ultrasonogram and, thus, with no in-person requirement for the vast majority of patients. There is ample evidence regarding the safety and acceptability of remote or telemedicine follow-up for medication abortion.[23]

One strength of our study is the size and makeup of patients included with documented efficacy and safety outcomes. Methodologically, we sought to include as many studies as possible. We did not impose a language limitation on study inclusion. We extensively corresponded with authors to clarify any questions about studies with the potential for inclusion and to inquire about de-aggregated data for studies in which patients who underwent no-test medication abortion were combined with patients with pretreatment ultrasonograms, and we included grey literature. More than 10,000 patients were included from countries across the world and in a variety of health care systems. Some patients from countries such as the United Kingdom sought care through the National Health Service, whereas others from the United States were from university hospitals or smaller abortion clinics. Some patients in Cambodia received care from pharmacies. Many sought care through online platforms outside traditional health care systems. The diversity of patients and variety of methods of abortion provision in these studies suggests our conclusions are generalizable to most populations.

Each individual study has the potential for bias, as described in Table 1. As in all pooled estimates, there is potential selection bias, particularly as not all of the included studies reported rates of all adverse events. Studies with a paucity of outcome data possibly have attrition bias, though this reflects evidence-based routine clinical practice of patients determining whether a medication abortion is successful rather than a true loss to follow-up. Many of the outcomes included in this review are self-reported by patients, introducing reporting bias, though research has shown that patients are very reliable at assessing the efficacy of medication abortions.[24]

In our analysis, efficacy and safety rates remained high despite using the most conservative estimates in our analysis. We only included patients in our analysis that had documented complete follow-up data. We deliberately made this decision to get the highest rate of known complications, and the lowest rate of complete medication abortion. Our rates likely underestimate the efficacy and safety of medication abortion as many patients who have a successful medication abortion forgo further follow-up as they understand they are no longer pregnant and do not require

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further medical care. Many studies included were from countries with national health care systems or in places with shared medical record systems. However, patients lost to follow-up may have experienced complications that were not captured within the medical records used for these studies. The success rate of 96.4% is potentially an underestimate of completion, and this analysis may even overestimate complication rates, further supporting the safety and efficacy of no-test medication abortion.

Although the studies lack uniformity in methods of reporting completed abortion, this reflects the current medical practice and expands the generalizability of our outcomes. Patients often do not return to the clinic or are lost to follow-up after medication abortions. Further, with increasing legal restrictions on abortion, we anticipate increasing numbers of abortions outside the formal health care setting. Self-assessment of the outcome of medication abortion completed at home has been shown to be noninferior to routine clinic follow-up.[24]

There are several limitations to our analysis. We excluded Aiken's 2021 study with the largest cohort of more than 18,000 patients from the British Pregnancy Advisory Service given the minimal number of confirmed patient outcomes available.[20] The study relied on data from a public, universal health system and offers a compelling case for not requiring follow-up for medication abortion. However, for this systematic review we included only cases in which the outcome data were available to avoid any underestimation of adverse events. Another limitation is that some patients may have had ultrasonograms or physical examinations performed by health care professionals other than those they were seeing for abortion care and that patients used this to inform their stated gestational age. However, in these cases, we confirmed with the study authors that the health care professional providing the abortion did not have access to the ultrasonogram report or use it to inform their management.

Another important limitation is the inability to determine whether the treatments patients received were necessary or appropriate for potential adverse events. Rates of surgical intervention after medication abortion are variable depending on clinical setting and regional differences in practice. Most of the studies, particularly those using self-report for follow-up, were unable to determine whether a surgical procedure was performed for an ongoing pregnancy or for adverse events relating to the abortion itself, such as retained products of conception, or if further complications resulted from the surgical management rather than the abortifacient medications themselves. Additionally, there are notable practice differences in medicine between countries that may have contributed to higher rates of interventions. For example, Endler's 2019 study suggests that the high rates of surgical evacuation found in Poland reflected either clinical practice or perhaps, "financial incentives to performing surgical procedures, rather than clinical indications."[25]

Directions for future research include finding ways to remove the last in-person requirement of blood typing for patients at more than 70 days of gestation and exploring the safety and efficacy of asynchronous medication abortion provision. Based on the available data presented in this review, health care professionals can feel confident in the safety and efficacy of no-test medication abortion. This large body of evidence should empower physicians to incorporate no-test medication abortion into their practices. Policies that mandate an in-person visit for abortion care stand in direct opposition to evidenced-based medicine. This review affirms our responsibility as physicians to advocate for the availability of this service to ensure access to basic reproductive health care for our patients.

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REPRODUCTIVE HEALTH matters

FEATURE

Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City

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Abstract: *Extensive evidence exists regarding the efficacy and acceptability of medical abortion through 63 days since last menstrual period (LMP). In Mexico City's Secretariat of Health (SSDF) outpatient facilities, mifepristone-misoprostol medical abortion is the first-line approach for abortion care in this pregnancy range. Recent research demonstrates continued high rates of complete abortion through 70 days LMP. To expand access to legal abortion services in Mexico City (where abortion is legal through 12 weeks LMP), this study sought to assess the efficacy and acceptability of the standard outpatient approach through 70 days in two SSDF points of service. One thousand and one women seeking pregnancy termination were enrolled and given 200 mg mifepristone followed by 800 μg misoprostol 24–48 hours later. Women were asked to return to the clinic one week later for evaluation. The great majority of women (93.3%; 95% CI: 91.6–94.8) had complete abortions. Women with pregnancies ≤8 weeks LMP had significantly higher success rates than women in the 9th or 10th weeks (94.9% vs. 90.5%; p = 0.01). The difference in success rates between the 9th and 10th weeks was not significant (90.0% vs. 91.2%; p = 0.71). The majority of women found the side effects (82.9%) and the use of misoprostol (84.4%) to be very acceptable or acceptable. This study provides additional evidence supporting an extended outpatient medical abortion regimen through 10 weeks LMP.* © 2015 Reproductive Health Matters

Keywords: medical abortion, mifepristone, misoprostol, Mexico

Medical abortion using mifepristone and misoprostol is a safe and effective method of pregnancy termination that has been used by millions of women worldwide over the past 25 years. Extensive evidence regarding both efficacy and acceptability supports the outpatient use of medical abortion through 63 days since the last menstrual period (LMP).[1–6] In this pregnancy range, among the World Health Organization's (WHO) recommended regimens is 200 mg mifepristone followed by 800 μg buccal misoprostol;[7] this protocol is routinely used for legal abortion in the outpatient facilities of the Secretariat of Health of Mexico City (SSDF),[6,8] where approximately 71% of women who obtain services have a medical abortion.[9]

In Mexico, abortion is legal in the first trimester of pregnancy, and the first mifepristone product was registered there in 2011. At around the same time, a study of medical abortion through 63 days LMP was conducted among 1,000 women who sought services in several SSDF outpatient facilities, confirming the high efficacy and acceptability of the mifepristone–misoprostol regimen.[6] The findings facilitated the SSDF in establishing medical abortion with mifepristone and misoprostol as its first-line approach for abortion care. Due to the

high demand for medical abortion and the advantages to service delivery it offers over aspiration (including reduced cost and in-clinic time), the Secretariat strives to offer outpatient medical abortion services to as many women seeking first trimester pregnancy termination as possible. A previous study of the characteristics of the women who have sought legal abortions in SSDF facilities found that they are diverse in age, marital status, and parity, and that a high percentage are Catholic.[10]

A 2012 study in the United States using 200 mg mifepristone + 800 µg buccal misoprostol demonstrated that the same regimen can be used in women at 64–70 days LMP as in women at 57–63 days LMP, with comparable efficacy (92.8% and 93.5%, respectively) and satisfaction (88.3% vs. 87.4% satisfied or very satisfied).[11] In addition, the US National Abortion Federation guidelines now include outpatient mifepristone-misoprostol medical abortion through 70 days LMP.[12] As a next step in the process of extending the clinical protocol for legal abortion in SSDF facilities, this study sought to assess the efficacy and acceptability of medical abortion through 70 days (the 10th week) provided as part of routine clinical services.

Methodology

This was an open-label clinical study (both clinicians and participants knew the treatment being provided). Women seeking pregnancy termination were enrolled at two study sites: the outpatient service at the Hospital Materno Infantil Inguarán and the reproductive health clinic of a primary care clinic, Centro de Salud Beatriz Velasco de Alemán. Women were invited to join the study if they were eligible for medical abortion and had pregnancies up to 70 days LMP. Women interested in participating had to agree to undergo a surgical intervention (vacuum aspiration) if necessary, be willing to provide contact information for purposes of follow-up, have easy access to both a telephone and emergency transportation, and comply with the study protocol. All participants gave written informed consent. Ethical approval was granted by the Ethics, Biosecurity and Research Commission of the Secretariat of Health of Mexico City.

All participants were given the same regimen of 200 mg mifepristone (Zacafemyl, Intelligence Pharmaceutical Network) to swallow in the clinic followed by 800 µg misoprostol (4 × 200 µg; either Cytotec [Pfizer] or Cyrux [Llama Serral]) to take at home 24–48 hours later. Women were instructed to retain the misoprostol buccally (two pills inside each cheek) for 30 minutes before swallowing any remains. Analgesics were prescribed according to the standard of care at each facility, and participants were told to call the clinic with any questions or concerns. Each participating clinic was provided a mobile phone to facilitate communication with study participants.

Participants were asked to return to the clinic seven days after taking the mifepristone to assess abortion status. Women with ongoing pregnancies were recommended vacuum aspiration. Women with non-viable pregnancies, including persistent gestational sac, retained products of conception or bleeding were given the choice between an additional dose of 800 µg buccal misoprostol, expectant management, or vacuum aspiration. Those choosing either of the first two options were asked to return one week later for further follow-up. At that time women with a persistent non-viable pregnancy or substantial debris were offered vacuum aspiration. Prior to exiting the study, all women were asked a series of questions by a member of the on-site study team regarding their experiences with medical abortion.

The primary outcome of the study was method efficacy, defined as complete abortion without vacuum aspiration at any point. Additional outcomes included extent of bleeding, extent of pain and other side effects, rate of abortions needing further treatment, and acceptability. Based on the success rates in studies by Winikoff in 2008 (≤ 63 days LMP: 96.2%)[2] and in 2012 (57–63 days LMP: 93.5%; 64–70 days LMP: 92.8%),[11] a sample size of 456 women was deemed sufficient to show overall success of 95% +/− 2%. The sample size was increased to 1,000 to account for high rates of expected loss to follow-up and homogeneity between sites. Data were analysed using SPSS version 19 (IBM, Armonk, NY, USA) and STATA version 11 (StataCorp, College Station, TX, USA).

Findings

Between January and March 2012, 1,001 women were enrolled in the study. Of these, forty-one women were lost to follow-up and no follow-up data could be collected; therefore, they are only included in the analysis of participant characteristics and are excluded from further analyses. One woman with a pregnancy 73 days LMP was

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Table 1. Participant characteristics (N=1,001)

Age in years: median (range)	24 (13–45)
Gravidity: median (range)	2 (1–8)
Reported previous abortion: n (%)	181 (18.1%)
Reported previous medical abortion: n (%)	124/181 (68.5%)
Duration of pregnancy LMP, in days: median (range)	52 (25–73)
Days since last menstrual period (LMP): n (%)	
≤56 days	654 (65.3%)
57–63 days	196 (19.6%)
64–70 days[a]	151 (15.1%)

a One woman was 73 days' LMP.

mistakenly enrolled in the study; her data are included in the analyses. Participant characteristics are presented in Table 1. Around two-thirds (65.3%) of women in the study were ≤56 days LMP, one-fifth (19.6%) were 57–63 days LMP, and 15.1% were 64–70 days LMP.

All but one study participant reported taking mifepristone and misoprostol as instructed; one woman said she took the misoprostol five days after the mifepristone. The great majority of women (93.3%; 95% CI: 91.6–94.8) had complete medical abortions without vacuum aspiration (Table 2). The reasons for the 64 vacuum aspirations included ongoing pregnancy (n = 15), bleeding problem (n = 17), persistent sac (n = 14), incomplete at study end (n = 15), clinically indicated intervention (n = 2) and psychological/emotional reasons (n = 1). Rate of complete abortion varied by study site: 98.5% vs. 92.0%.

Women at ≤8 weeks LMP (≤56 days) had significantly higher complete abortion rates than women in the 9th week (94.9% vs. 90%, p = 0.02), but statistical significance did not hold when comparing women ≤8 weeks LMP to those in the 10th week (94.9% vs. 91.2%, p = 0.12). The difference in complete abortion rates between the 9th and 10th weeks did not differ significantly (90.0% vs. 91.2%; p = 0.85). Twenty women (2.1%) attended another (non-study) medical facility for abortion-related care during the study after having received the two medications; these women were more likely to undergo surgical intervention than women who only received care at the study clinics (70.0% vs. 5.3%; p < 0.001). Seventy participants (7.0%) called the clinic with questions or concerns about the abortion process; women 10 weeks LMP were no more likely to call than women 9 weeks LMP (8.6% vs. 11.2%; p = 0.48; data not shown).

The most common side effects experienced during the abortion process included fever/chills (46.0%), diarrhoea (44.6%), nausea (27.0%), and vomiting (23.0%) (Table 3). Severity of side effects is presented in Figure 1. Slightly over half of the women (56.2%) reported that the pain they

Table 2. Medical abortion outcomes: n (%) (N=960)

	≤56 days (n=622)	57–63 days (n=190)	64–70 days[a] (n=148)	All women (n=960)[b]
Complete abortion	590 (94.9)	171 (90.0)	135 (91.2)	896 (93.3)
Surgical intervention	32 (5.1)	19 (10.0)	13 (8.8)	64 (6.7)
Ongoing pregnancy	4 (0.6)	6 (3.2)	5 (3.4)	15 (1.6)
Bleeding problem	7 (1.1)	8 (4.2)	2 (1.4)	17 (1.8)
Persistent sac	11 (1.8)	3 (1.6)	0 (0.0)	14 (1.5)
Incomplete at study end	10 (1.6)	2 (1.1)	3 (2.0)	15 (1.6)
Clinically indicated[c]	0 (0.0)	0 (0.0)	2 (1.4)	2 (0.2)
Psychological/emotional reason	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.1)
Returned for second scheduled follow-up visit	26 (4.2)	11 (5.8)	11 (7.4)	48 (5.0)

a One woman was 73 days LMP.
b Excludes 41 women lost to follow-up.
c Other medical reason for intervention, such as suspicion of infection.

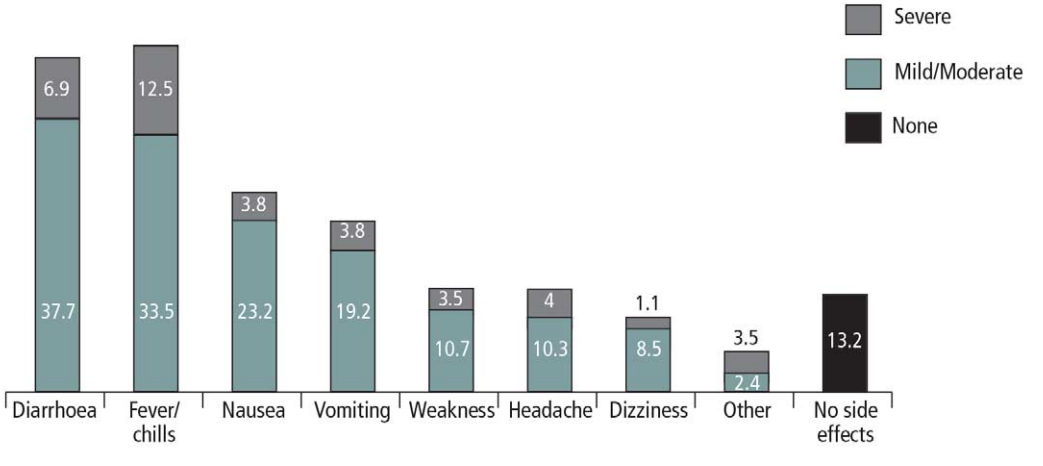
Table 3. Side effects women experienced n (%)

	≤56 days (n=622)	57–63 days (n=190)	64–70 days[a] (n=148)	All women (n=960)
Side effect				
Fever/chills	270 (43.4)	91 (47.9)	81 (54.7)	442 (46.0)
Diarrhoea	277 (44.5)	73 (38.4)	78 (52.7)	428 (44.6)
Nausea	166 (26.7)	54 (28.4)	39 (26.4)	259 (27.0)
Vomiting	131 (21.1)	51 (26.8)	39 (26.4)	221 (23.0)
Headache	84 (13.5)	26 (13.7)	27 (18.2)	137 (14.3)
Weakness	81 (13.0)	25 (13.2)	31 (20.9)	137 (14.3)
Dizziness	62 (10.0)	20 (10.5)	11 (7.4)	93 (9.7)
Mean pain level (using scale of 1–7)	**5.26**	**5.55**	**5.59**	**5.37**
Pain during treatment	**(n=603)**	**(n=182)**	**(n=144)**	**(n =929)**
Less than expected	167 (27.7)	40 (22.2)	27 (18.8)	234 (25.2)
As expected	182 (30.2)	55 (30.2)	51 (35.4)	288 (31.0)
More than expected	254 (42.1)	87 (47.8)	66 (45.8)	407 (43.8)
Bleeding during treatment	**(n=609)**	**(n=183)**	**(n=144)**	**(n=936)**
Less than expected	195 (32.0)	45 (24.6)	32 (22.2)	272 (29.1)
As expected	275 (45.2)	84 (45.9)	67 (46.5)	426 (45.5)
More than expected	139 (22.8)	54 (29.5)	45 (31.3)	238 (25.4)

a One woman was 73 days LMP.

experienced was less than or as expected, and three-fourths (74.6%) found the bleeding to be less than or as expected. Approximately the same proportion of women in the 10th week as in the 9th week reported having more pain than expected (45.8% vs. 47.8%, p = 0.74). Reported mean pain level (on a scale from 1–7) did not differ between women in the 9th and

Figure 1. Side effects and severity



10th weeks (5.59 vs. 5.55. p = 0.79) but was statistically significantly higher when women 9 and 10 weeks LMP were compared to those ≤56 days LMP (5.57 vs. 5.26; p = 0.003; data not shown).

Three-fourths of the women (76.6%) found the medical abortion process to be not at all difficult or only slightly difficult, while 9.5% thought it was very difficult (Table 4). The majority of women (86.9%) found the side effects to be very acceptable or acceptable; only 2.4% thought they were unacceptable or very unacceptable. Most participants (84.4%) also found the mode of misoprostol administration to be very acceptable or acceptable, with only 1.2% finding the mode of administration unacceptable or very unacceptable. If another abortion is needed in the future, 77.8% of the women would again choose medical abortion; only 2.9% would choose vacuum aspiration and 19.3% had no preference. Best aspects of medical abortion as reported by participants included ease or convenience (26.0%), efficacy (24.4%), the quality of care received (11.7%), and privacy (8.5%). For 16.3%, there was no best aspect. Cramps/pain were the most commonly reported worst feature (28.8%). Over half (52.7%) of the women said that there was no worst aspect (data not shown).

Discussion

This study demonstrated that outpatient medical abortion protocols can be extended through 70 days LMP with rates of efficacy and acceptability within the range seen in other studies with similar protocols.[11,13,14] The overall ongoing pregnancy rate of 1.6% in this study that included women through 70 days LMP was slightly higher than the 0.5% typically seen in studies among women ≤63 days.[2,6] However, a higher rate of ongoing pregnancies in the 9th week (3.2%) and 10th week (3.4%) was expected and concurs with the Winikoff et al. 2012 study, which reported ongoing pregnancy rates of 3.1% and 3.0%, respectively.[11] Compared to women with earlier pregnancies, the chance of an ongoing pregnancy following use of the medical abortion regimen among women in the 9th and 10th weeks increases from less than 1 woman per 100 to less than 4 women per 100. While the slightly higher rate of ongoing pregnancy might discourage some women from selecting this method of abortion,

Table 4. Acceptability of medical abortion as an outpatient abortion method: n (%)

	≤56 days (n=622)	57–63 days (n=190)	64–70 days[a] (n=148)	All women (n=960)
Experience with medical abortion	**(n=616)**	**(n=189)**	**(n=147)**	**(n=952)**
Not at all/slightly difficult	479 (77.8)	140 (74.1)	110 (74.8)	729 (76.6)
Moderately difficult	86 (14.0)	24 (12.7)	23 (15.6)	133 (14.0)
Very difficult	51 (8.3)	25 (13.2)	14 (9.5)	90 (9.5)
Acceptability of side effects	**(n=594)**	**(n=181)**	**(n=141)**	**(n=916)**
Very acceptable/acceptable	521 (87.7)	152 (84.0)	123 (87.2)	796 (86.9)
Neutral	56 (9.4)	28 (15.5)	14 (9.9)	98 (10.7)
Unacceptable/very unacceptable	17 (2.9)	1 (0.6)	4 (2.8)	22 (2.4)
Acceptability of misoprostol administration	**(n=592)**	**(n=180)**	**(n=144)**	**(n=916)**
Very acceptable/acceptable	523 (88.3)	160 (88.9)	127 (88.2)	810 (88.4)
Neutral	60 (10.1)	19 (10.6)	16 (11.1)	95 (10.4)
Unacceptable/very unacceptable	9 (1.5)	1 (0.6)	1 (0.7)	11 (1.2)
Preferred method for future abortion if needed	**(n=622)**	**(n=190)**	**(n=148)**	**(n=960)**
Vacuum aspiration	17 (2.7)	7 (3.7)	4 (2.7)	28 (2.9)
Medical abortion	491 (78.9)	143 (75.3)	113 (76.4)	747 (77.8)
No preference	114 (18.3)	40 (21.1)	31 (20.9)	185 (19.3)

a One woman was 73 days LMP.

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other women do not consider the drop in success to be a limiting factor. Outpatient medical abortion with this regimen for women 9 weeks LMP is recommended by the World Health Organization[7] and commonly used. That there is no incremental difference in the ongoing pregnancy rate when used by women 10 weeks LMP supports the expansion of outpatient medical abortion services to include this additional week of pregnancy. Each woman should be able to make an informed choice to select whichever method she thinks is best for her.

The overall success rate in this study is lower than in previous studies in Mexico City,[6] but it does not appear to be due to the inclusion of women with pregnancies of 64–70 days LMP since success dropped sharply in the 9th week. This may be due to chance, or in part to provider management, specifically non-study clinicians at other facilities. Clinical providers who do not offer medical abortion services will typically follow standard management of non-complicated incomplete abortion; in Mexico, these women are often hospitalized and treated with dilatation and curettage even if not clinically indicated. Among study clinicians, we cannot rule out the possibility of behavioural bias, as providers were not blinded to pregnancy duration. Heterogeneity among providers, that is, the differences in the way individual providers clinically manage a case, might also have contributed to site differences in success rate.

Women with pregnancies in the 9th and 10th weeks reported significantly higher mean pain scores than other study participants. However, the scores are so similar that they may not be clinically meaningful, that is, they may not call for different strategies in pain management. More importantly, the mean pain score of women in the 10th week was almost identical to that of women in the 9th week, further supporting the routine offering of outpatient medical abortion to women with pregnancies 64–70 days.

This study provides additional evidence to the published literature that supports extending outpatient medical abortion through 70 days (10th week) of pregnancy. In fact, based on these study results and the experience obtained through participating in this study, the SSDF has expanded outpatient care through 70 days as a part of routine care. Offering outpatient medical abortion as a treatment option for this population would further expand access to women, and if participation in this study is any indication, women 64–70 days LMP could represent as much as 15% of medical abortion users. In turn, this would be time- and resource-saving for providers and the health care system. It is possible that this medical abortion regimen could be an option for women beyond 70 days LMP as well, as it is unlikely that the rate of success would sharply plummet at 71 days LMP. Further research is necessary to explore efficacy later in the first trimester. In addition, as the pregnancy develops and becomes more recognizable upon expulsion at 11 and 12 weeks, it would be important to assess simultaneously the acceptability of outpatient medical abortion for women, as well as providers' comfort with providing it, to determine the feasibility of this service delivery option.

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Résumé

De nombreuses données existent sur l'efficacité et l'acceptabilité de l'avortement médicamenteux jusqu'à 63 jours depuis la date des dernières règles (DDR). Dans les centres ambulatoires du Secrétariat de la santé de Mexico (SSDF), l'avortement médicamenteux sous mifépristone et misoprostol est la méthode de première intention pour l'interruption de grossesses de cet âge gestationnel. Des recherches récentes montrent des taux élevés d'avortement complet jusqu'à 70 jours après la DDR. Pour élargir l'accès à des services d'avortement légal à Mexico (où l'avortement est autorisé jusqu'à 12 semaines après la DDR), cette étude a tenté d'évaluer l'efficacité et l'acceptabilité de la méthode ambulatoire standard jusqu'à 70 jours dans deux centres du SSDF. Mille et une femmes souhaitant avorter ont été recrutées et ont reçu 200 mg de mifépristone suivis de 800 µg de misoprostol 24–48 heures plus tard. Elles ont été invitées à revenir au centre une semaine après pour évaluation. Chez la grande majorité des patientes (93,3% ; IC 95% : 91,6–94,8), l'avortement était complet. Les femmes enceintes ≤8 semaines après la DDR avait des taux de réussite sensiblement plus élevés que les femmes à 9 ou 10 semaines (94,9% contre

Resumen

Existe extensa evidencia respecto a la eficacia y aceptabilidad del aborto con medicamentos hasta los 63 días desde la fecha de la última menstruación (FUM). En las unidades de salud ambulatorias de la Secretaría de Salud del Distrito Federal de México (SSDF), el aborto con medicamentos inducido con mifepristona-misoprostol es el enfoque de primera línea en los servicios de aborto para esta etapa de la edad gestacional. Recientes investigaciones demuestran continuas altas tasas de aborto completo hasta concluidos los 70 días desde la FUM. Con el fin de ampliar el acceso a los servicios de interrupción legal del embarazo en el Distrito Federal (donde el aborto es legal hasta las 12 semanas desde la FUM), este estudio buscó evaluar la eficacia y aceptabilidad del enfoque ambulatorio estándar hasta los 70 días en dos puntos de entrega de servicios de la SSDF. Mil y una mujeres que buscaban interrumpir su embarazo fueron inscritas y administradas una dosis de 200 mg de mifepristona seguida de 800 µg de misoprostol, 24 a 48 horas después. Se les pidió a las mujeres que regresaran a la clínica una semana después para la evaluación. La gran mayoría de las mujeres

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P Sanhueza Smith et al. Reproductive Health Matters 2015;Supplement(44):75–82

90,5% ; p = 0,01). La différence dans les taux de réussite entre la 9e et la 10e semaine était non significative (90,0% contre 91,2% ; p = 0,71). La majorité des femmes ont jugé les effets secondaires (82,9%) et l'utilisation du misoprostol (84,4%) très acceptables ou acceptables. Cette étude fournit des données supplémentaires soutenant un régime étendu d'avortement médicamenteux en ambulatoire jusqu'à 10 semaines après la DDR.

(93.3%; 95% IC: 91.6–94.8) tuvo un aborto completo. Las mujeres con embarazos ≤8 semanas desde la FUM tuvieron tasas de eficacia significantemente más altas que las mujeres en la novena o décima semanas (94.9% vs. 90.5%; p = 0.01). La diferencia en las tasas de eficacia entre la novena y décima semanas no fue significante (90.0% vs. 91.2%; p = 0.71). La mayoría de las mujeres encontraron que los efectos secundarios (82.9%) y el uso de misoprostol (84.4%) eran muy aceptables o aceptables. Este estudio ofrece evidencia adicional que respalda un régimen de aborto con medicamentos extendido hasta concluidas las 10 semanas desde la FUM para usuarias ambulatorias.

The Safety and Efficacy of a "No Touch" Abortion Program Implemented in the Greater Toronto Area During the COVID-19 Pandemic



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ABSTRACT

Objectives: To evaluate the safety and efficacy of first-trimester "No Touch" medication abortion programs at 2 clinics in Toronto, Ontario during their early implementation in response to the COVID-19 pandemic.

Methods: This retrospective study included all patients who underwent virtual consultation for mifepristone-misoprostol medication abortion between April 2020–August 2022 at 2 reproductive health clinics. In response to the pandemic, "No Touch" abortion protocols have been developed that align with the Canadian Protocol for the Provision of Medical Abortion via Telemedicine. Records were reviewed for demographic information, clinical course, investigations required, confirmation of complete abortion and adverse events. The primary outcome was complete medication abortion, defined as expulsion of the pregnancy without requiring uterine aspiration.

Results: A total of 277 patients had abortions initiated in the "No Touch" or "Low Touch" care pathways and had sufficient follow-up to determine outcomes. Of these patients, 92.8% (95% CI 89.7%–95.8%) had a complete medication abortion (n = 257) and 76.1% (n = 159) remained "No Touch" throughout their care. Investigations were performed for 102 participants before or after their abortion, classifying them as "Low Touch". Nineteen patients (6.9%) underwent uterine aspiration. The rate of adverse events was low, with 1 case of a missed ectopic pregnancy and 1 patient requiring hospitalization for endometritis.

Conclusions: "No Touch" provision of mifepristone-misoprostol medication abortion care was safe and effective with outcomes comparable to previous studies. These results provide evidence for the efficacy and safety of a "No Touch" approach in the Canadian context, which has the potential to reduce barriers to accessing abortion care.

Keywords: abortion; mifepristone; telemedicine; termination of pregnancy; COVID-19; pandemic

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RÉSUMÉ

Objectif : Évaluer l'innocuité et l'efficacité des programmes d'avortement médicamenteux sans contact au premier trimestre dans deux cliniques de Toronto, en Ontario, au début de leur mise en œuvre en réponse à la pandémie de COVID-19.

Méthode : Cette étude rétrospective porte sur toutes les patientes ayant obtenu une consultation virtuelle pour un avortement médicamenteux par mifépristone-misoprostol entre avril 2020 et août 2022 dans 2 cliniques de santé reproductive. En réponse à la pandémie, des protocoles d'avortement sans contact ont été mis au point en s'alignant sur le Protocole canadien de prestation de l'avortement médical par télémédecine. Les dossiers ont été examinés pour extraire les données sur les caractéristiques démographiques, l'évolution clinique, les examens réalisés, la confirmation de l'avortement complet et les événements indésirables. Le critère de jugement principal était l'avortement médicamenteux complet, défini comme l'expulsion de la grossesse sans nécessiter d'aspiration utérine.

Résultats : Au total, 277 patientes ont subi un avortement dans le cadre d'un protocole à faible ou sans contact et ont fait l'objet d'un suivi suffisant pour déterminer les résultats. De ce nombre, 92,8 % (IC à 95 % : 89,7–95,8 %) ont obtenu un avortement

médicamenteux complet (n = 257), et la totalité de la prise en charge s'est déroulée selon le protocole sans contact pour 76,1 % des patientes (n = 159). Des examens ont été réalisés auprès de 102 participantes avant ou après l'avortement, ce qui les classe dans la catégorie à faible contact. En tout, 19 patientes (6,9 %) ont subi une aspiration utérine. Le taux d'événements indésirables s'est avéré faible (1 grossesse extra-utérine non diagnostiquée et 1 hospitalisation pour une endométrite).

Conclusion : La prestation de l'avortement médicamenteux sans contact par mifépristone-misoprostol était sécuritaire et efficace, les résultats étant comparables à ceux d'études antérieures. Ces résultats démontrent l'efficacité et l'innocuité de l'approche sans contact dans le contexte canadien, laquelle pourrait réduire les obstacles à l'accès aux soins d'avortement.

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INTRODUCTION

The COVID-19 pandemic posed several risks to the reproductive health of people globally.[1,2] In Canada, abortion remained an essential and time-sensitive service during this period of social disruption.[3] Traditionally, medication abortion care in Canada has required in-person clinical assessment, ultrasound dating of the pregnancy and in-clinic follow-up. However, evolving clinical practice guidelines during the pandemic have eliminated the requirement for in-person care and routine testing in some cases.[4]

There is increasing evidence that medication abortion delivered through a "No Touch" approach, where patients who meet clinical criteria have only remote contact with the health system, is safe and acceptable to patients.[5,6] This "No Touch" format of care delivery, also described as "virtual" or "telemedicine" throughout the existing literature, has been shown to be non-inferior to standard in-person care.[7] Within Canada, telemedicine has been used successfully to provide abortion care in British Columbia since 2012.[6] In the context of the COVID-19 pandemic, studies on "No Touch" abortion care have been conducted in other high-income countries,[8-10] demonstrating high patient satisfaction and low complication rates that are comparable to standard in-person care. No similar research has occurred in Ontario, Canada with our unique publicly funded health care system and geographic barriers to abortion care.

The goal of this study was to assess the safety and efficacy of virtual first-trimester "No Touch" abortions provided at 2 clinics in Toronto, Ontario. Both clinics offer comprehensive reproductive health services, including medication and procedural abortion. In response to the COVID-19 pandemic, these clinics developed "No Touch" abortion protocols that align with the Canadian Protocol for the Provision of Medical Abortion via Telemedicine.[4] As described, the COVID crisis has placed additional barriers to accessing safe abortion care and "No Touch" medication abortion could alleviate some of those barriers. Beyond the pandemic, this approach to abortion care has the potential to improve access, require fewer resources, and increase patients' satisfaction with their care.

METHODS

This was a retrospective study of all patients who underwent consultation for a "No Touch" abortion between 1 April 2020 and 31 August 2022, at the Bay Centre for Birth Control (BCBC) or Choice in Health Clinic (CIHC). BCBC, an academic clinic affiliated with Women's College Hospital, serves 1300 patients and provides 500 medication abortions annually. CIHC is a community-based clinic that serves approximately 2230 patients and provides 670 medication abortions per year. Both clinics have been offering mifepristone-misoprostol medication abortions since 2017. Prior to April 2020, both clinics required that patients have an ultrasound-confirmed intra-uterine pregnancy of less than 70 days and attend the clinic for abortion consultation. In response to the COVID-19 pandemic, BCBC and CIHC adopted "No Touch" abortion protocols for abortions up to 10 weeks gestational age.[4] Only patients seen virtually for consideration of "No Touch" abortion were evaluated in our study. This study was approved by the research ethics boards at the University of Toronto (REB #41859) and Women's College Hospital (REB #2021-0071-B).

"No Touch" Abortion Protocol

Similar protocols for "No Touch" abortion were adopted by both clinic sites. The purpose of the initial virtual consultation is to assess eligibility for a "No Touch" abortion. A physician or nurse practitioner assesses the patient for contra-indications to mifepristone/misoprostol medication abortion and determines if ultrasound or laboratory investigations are required before proceeding (Table 1). For those who are eligible, the following medications are prescribed: mifepristone 200 mg orally, 2 doses of 800 mcg misoprostol (taken buccally or vaginally), analgesics and anti-emetics. The first dose of misoprostol (800 mcg) is to be taken buccally or vaginally 24–48 hours after mifepristone. Patients with an estimated gestational age >63 days are counselled to take the second dose of misoprostol 4 hours after the first dose. In accordance

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Table 1. Eligibility for first-trimester "No Touch" medication abortion

Ultrasound required if:	Laboratory investigations required if:	Contra-indications to mifepristone/ misoprostol medication abortion
• LMP uncertain • LMP >70 days ago • Signs or symptoms of ectopic pregnancy • Risk factors for ectopic pregnancy • Presence of an intra-uterine device	• Hemoglobinopathy or severe anemia suspected • Rhesus (Rh) status not previously documented and patient would want Rh immune globulins • Patient has risk factors for STIs (*optional*)	• Confirmed or suspected ectopic pregnancy • Chronic adrenal failure • Inherited porphyria • Uncontrolled asthma • Long-term use of corticosteroid therapy • Hemorrhagic disorder or anticoagulation therapy • Severe anemia

LMP: last menstrual period; STI: sexually transmitted infection.

with national guidance at the time, Rho(D) immuno-prophylaxis (for Rh-negative patients) was not routinely required at less than 8 weeks gestational age. For those between 8 and 10 weeks gestational age, the evidence for Rho(D) immune globulin prophylaxis is discussed with the patient. After this discussion, patients opting not to receive Rho(D) immuno-prophylaxis sign an additional consent form stating that they understand the possible risk to future pregnancies if Rh sensitization occurs. The physician or nurse practitioner then conducts a virtual follow-up visit via phone at 7 days and 4 weeks post-medication abortion. The patient is instructed to complete a home urine pregnancy test (UPT) at the 4-week visit. Both clinic sites had electronic messaging systems to facilitate clinician-patient communication between scheduled visits. A more detailed description of the clinical protocol can be found in online Appendix.

Data Collection and Analysis

We collected the following data from the patients' records: patient age, estimated gestational age, postal code (first 3 digits), gravidity, parity, complete abortion, repeat misoprostol, uterine aspiration (for ongoing pregnancy, incomplete abortion, or persistent bleeding), attendance at follow-up visits and how abortion was deemed complete. Safety outcomes included the number of emergency department visits, hospitalizations, hemorrhage requiring blood transfusion, and infections (defined as any treatment with antibiotics for uterine pain or tenderness). These were determined through patients' reports at the time of scheduled or subsequent clinical follow-up up to 6 weeks after administration of the medication abortion. Continuous data were recorded as median ± SE, and categorical data were recorded using counts and percentages.

Definitions

For the purposes of categorizing the clinical care pathways of the patients in this study, we applied the following definitions: A complete "No Touch" abortion was defined as expulsion of the pregnancy without the need for investigations or in-person care.[11] A "Low Touch" abortion was defined as requiring investigations at any point before, during or after expulsion of the pregnancy. Doing a home UPT did not qualify the care as "Low Touch" because there was no contact with the health care system. Investigations may have been required to confirm eligibility for a medication abortion, to investigate a potential complication and/or to confirm completion of the abortion. Some patients may also have chosen to receive investigations as reassurance, therefore categorizing their care as "Low Touch". Lastly, a "Full Touch" abortion was defined as requiring in-person clinical assessment related to the abortion at any point during the medication abortion process. This included clinic visits, emergency department visits, family physician visits, hospitalization and/or procedural management. A complete abortion was ascertained through a reassuring clinical history, negative UPT, negative quantitative beta-human chorionic gonadotropin, resumption of normal menses or procedural abortion. Patients who attended only the 7-day and not the 4-week follow-up appointment but provided clinical history consistent with passing the products of conception, were included in our evaluation as complete medication abortions.

RESULTS

Between 1 April 2020 and 21 August 2022, 327 patients had a virtual consultation for medication abortion through BCBC or CIHC. After initial consultation, 29 patients did not proceed, leaving 298 patients aged 14–48 years who continued with virtual, first-trimester medication abortion care. Demographic and pregnancy characteristics are reported in Table 2.

Of the 298 patients who proceeded with medication abortion, 209 (70.1%) were eligible for a "No Touch" approach (Figure). These were patients who met the

Table 2. Patient demographic characteristics (n = 298)

Characteristic	Number (%) of patients
Age, median ± SE (range)	30 ± 0.4 (14–48)
≤19	7 (2.3%)
20–24	57 (19.1%)
25–29	82 (27.5%)
30–34	72 (24.2%)
35–39	54 (18.1%)
40–44	23 (7.7%)
≥45	3 (1.0%)
Home postal code	
GTA	242 (81.2%)
Non-GTA	51 (17.1%)
Missing	5 (1.7%)
Gestational age at consultation, days, median ± SE (range)	43 ± 1.0 (24–69)
≤35	49 (16.4%)
36–42	96 (32.2%)
43–49	76 (25.5%)
50–56	52 (17.4%)
57–63	19 (6.4%)
64–70	6 (2.0%)
Gravidity, median (range)	2 (1–15)
Parity, median (range)	0 (0–6)
Previous SVD	114 (38.3%)
Previous cesarean delivery	31 (10.4%)
Previous surgical abortion	93 (31.2%)
Previous medication abortion	61 (20.5%)
Previous spontaneous abortion	63 (21.1%)
Previous ectopic pregnancy	7 (2.3%)

GTA: Greater Toronto Area (Etobicoke, North York, Scarborough, York, East York, Brampton, and Mississauga); SVD: spontaneous vaginal delivery.

eligibility criteria (Table 1) and so were prescribed mifepristone and misoprostol without requiring any investigations beforehand. The patients who had investigations were classified as initiating their care in the "Low Touch" pathway (N = 89, 29.9%). All patients who were not initially eligible for "No Touch" abortion were able to proceed with medication abortion once their investigations were complete. The most common reasons why patients were asked to do investigations were pain or vaginal bleeding (possible symptoms of ectopic pregnancy), history of anemia and uncertain last menstrual period. The most commonly performed investigation prior to medication abortion was an ultrasound, but other investigations included hemoglobin level, Rhesus status or testing for sexually transmitted infections. Figure displays the patient care pathways based on any interventions or investigations that were required before their abortion was complete.

A total of 277 patients had sufficient follow-up to determine the outcome of their abortion. Overall, 257 patients (92.8%, 95% CI 89.7%—95.8%) had a complete medication abortion. In Table 3, the medication abortion completion rate is reported by gestational age and whether the patient initiated their care in the "No Touch" or "Low Touch" pathway.

The rate of adverse events was low with only 1 case of an ectopic pregnancy and 1 patient requiring hospitalization for intravenous antibiotics. The patient with the ectopic pregnancy called the clinic about her pain and was advised to present to the emergency department. She delayed presentation until a few days later and was found to have a ruptured ectopic pregnancy requiring emergent laparoscopy. The patient who required hospitalization presented to the emergency department with fever 2 weeks after her abortion. She was admitted for 3 days for endometritis and was managed with intravenous antibiotics. There were no patients who required blood transfusion. A total of 13 patients (4.7%) presented to the emergency department during the process of their abortion. The reasons for and outcomes of these visits are displayed in Table 4.

Sixteen patients (5.8%) underwent a procedural abortion for incomplete medication abortion and 3 patients (1.1%) underwent a procedural abortion for an ongoing viable pregnancy. Nine patients (3.2%) required additional doses of misoprostol to complete their abortion.

DISCUSSION

This is the first evaluation of a "No Touch" medication abortion protocol in Ontario, Canada. The overall efficacy rate was high, with 92.8% (95% CI 89.7%—95.8%) of the patients who initiated their care in the "No Touch" or "Low Touch" care pathways having a complete medication abortion. Of these patients, 159 (76.1%) had complete "No Touch" medication abortions without any investigations or in-person care. Although our rates of complete medication abortion were lower than the 95.2% (CI 94.7%—95.7%) rate reported in a recent meta-analysis looking at telemedicine-based abortion outcomes globally, the confidence intervals overlap.[12]

Rates of adverse events were low in this study. Thirteen patients (4.7%) presented to the emergency department, however, only 2 (0.7%) experienced serious adverse

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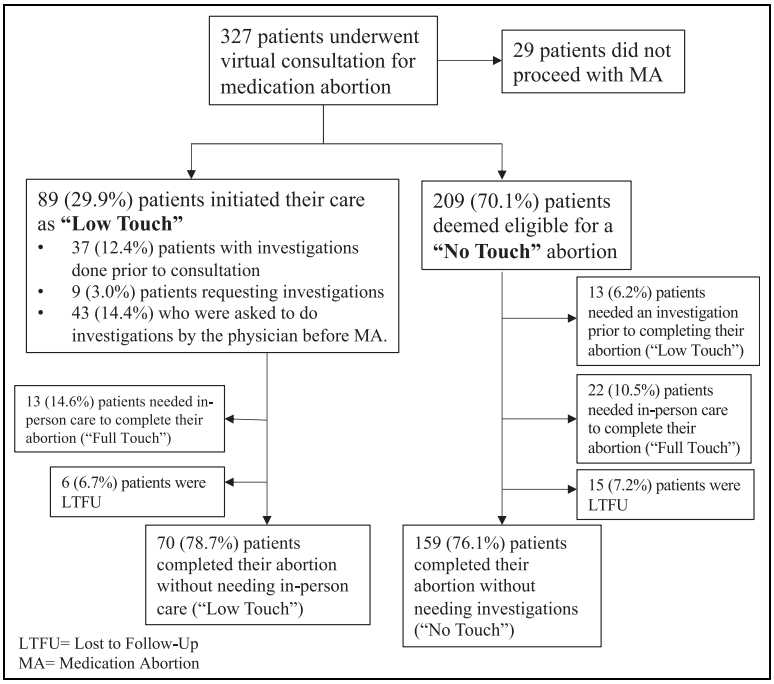
Figure. Care pathways of patients undergoing first-trimester virtual medication abortion (MA).



LTFU: loss to follow-up.

events. One patient (0.4%) required laparoscopy for an ectopic pregnancy. In a large meta-analysis, the reported rate of ectopic pregnancy was 0.06%.[12] Another patient required admission to hospital for management of endometritis with intravenous antibiotics. In a United States-based study of telemedicine abortion outcomes, 0.5% of patients had an infection requiring intravenous antibiotics.[13] Adverse events in this study were documented based on patient reports and thus may have been underreported, particularly in the minority of patients who were lost to follow-up. We similarly relied on patient report of passing the pregnancy for those who attended the 7-day follow-up, but not the 4-week follow-up visit for categorization of complete abortion. This may have contributed to overestimation of the complete medication abortion rate. However, evidence suggests that patients can reliably assess the efficacy of medication abortion.[14]

Intervention rates for incomplete or failed abortion were overall low. Nineteen patients (6.9%) had a procedural abortion and 9 patients (3.2%) required additional doses of misoprostol. In the systematic review by Shapiro et al.[12] rates of procedural abortion and need for additional misoprostol were similar at 4.4% and 2.2%, respectively. There are several factors that may have contributed to our procedural intervention rates, in addition to usual indications such as patient preference or failed repeat misoprostol doses. First, uterine aspiration was relatively accessible same-day in the out-of-hospital clinic involved

Table 3. Complete medication abortion (MA) rate by gestational age (GA) and care pathway

GA (days)	Patients with follow-up (n)	Complete MA, n (%)	Complete MA among those initiated as "No Touch", n (%)	Complete MA among those initiated as "Low Touch", n (%)
All GA	277	257 (92.8%)	182 (93.8%)	75 (90.4%)
≤ 49	207	192 (92.8%)	146 (93.6%)	46 (90.2%)
50+	70	65 (92.9%)	36 (94.8%)	29 (90.6%)

Complete MA is defined as expulsion of the pregnancy without need for procedural abortion.

Table 4. Emergency department visits and outcomes

Emergency department visit reason	Cases (n)	Rate (%)
Patients initiating care as "No Touch" (n = 194)	8	4.1%
Bleeding, requiring D&C	1	0.5%
Bleeding, requiring misoprostol	3	1.5%
Bleeding, requiring reassurance	1	0.5%
Pain, requiring analgesia	2	1.0%
Pain, requiring laparoscopy for ruptured ectopic	1	0.5%
Patients initiating care as "Low Touch" (n = 83)	5	6.0%
Bleeding, requiring D&C	3	3.6%
Bleeding, requiring misoprostol	1	1.2%
Fever, requiring admission for endometritis	1	1.2%
Total serious adverse events	2[a]	0.7%
Total emergency department visits	13	4.7%

[a]The patient who presented with pain and required laparoscopy for a ruptured ectopic was included as a serious adverse event. The patient who presented with fever and required admission for endometritis was also included as a serious adverse event.

in our study. Additionally, mifepristone has only been available in Canada since 2017, and all physicians participating in this pilot were new to a "No Touch" approach. Therefore, physicians may have been more likely to intervene (convert to "Full Touch") or order investigations (convert to "Low Touch") to avoid a possible complication. We observed that the rate of procedural intervention trended downward after our first year of providing "No Touch" medication abortions, possibly indicating increased provider comfort levels with this protocol. In 2020, the procedural abortion rate after starting as a "No Touch" or "Low Touch" medication abortion was 7.7%. The procedural abortion rate was 4.2% and 5.7% in 2021 and 2022 respectively.

COVID-19 acted as the impetus for the pilot of this care protocol in many settings and served as justification for easing regulatory barriers to telemedicine-based care.[15] Globally, this approach has enabled physicians to provide care across states and districts, improving access to timely abortion care, and enhanced care in rural areas.[16,17] Findings from previous Canadian literature have suggested "Low" or "No Touch" medication abortion as a mechanism to improve geographic equity.[18] Indeed, 51 patients (17.1%) in our study were from regions outside the Greater Toronto Area and otherwise would have needed to travel many hours to present to these same clinics in person. "No Touch" care also plays a crucial role in improving the personal safety of those seeking abortion care. It enables those seeking abortion to do so from their homes or other secure locations, with potential for reduced risks to physical and emotional safety, and reduced risks of COVID-19 transmission associated with their abortion.[19] However, "No Touch" abortion alone does not remove all barriers to accessing care, where insurance status, access to phone or Wi-Fi, and supportive pharmacies to dispense the medications[20] are only some of the ongoing challenges.

This study has some limitations. First, this is exploratory data from a new care pathway, which was delivered during a period of tremendous strain related to the pandemic. It is unclear whether practice patterns, outcomes or patient preferences will change in more "normal" times. Similarly, a significant limitation of this study is its small sample size. A larger study including multiple clinics across a wider geographic area would more accurately determine the medication abortion completion rate and rate of adverse events. Importantly, this study did not include patients' perspectives on this mode of care delivery, which we plan to assess in future studies. Projects that have explored patient experiences found that a "No Touch" approach is highly acceptable among patients for a variety of reasons, including improved privacy, convenience, accessibility, home comforts and reduced stigma.[8,21-23] Some studies even demonstrated preference and perceived benefits of "No Touch" over in-person abortion care.[8,21,23]

Ample data has proven the safety of a "No Touch" approach to abortion care when offered in the context of a strict eligibility assessment. Despite this, many patients globally face challenges in accessing abortion including stigma, policy, cost, safety, and travel. This mode of delivery has the potential to reduce these barriers, particularly in legally restrictive, rural, and resource-constrained settings.

CONCLUSION

"No Touch" provision of mifepristone-misoprostol medication abortion care in this cohort was safe and effective with outcomes comparable to previous studies. These results provide evidence for the efficacy and safety of a "No Touch" approach in the Canadian context, which has the potential to reduce barriers to accessing abortion care. Future directions of this study will include a 2-phase qualitative evaluation of patients' perspectives on and experiences of "No Touch" abortion, including consideration for its role beyond the COVID-19 pandemic.

GBP-PET00810

ETHICS

This study was approved by the research ethics boards at the University of Toronto (REB #41859) and Women's College Hospital (REB #2021-0071-B).

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jogc.2024.102429.

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EARLY PREGNANCY TERMINATION WITH MIFEPRISTONE AND MISOPROSTOL IN THE UNITED STATES

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ABSTRACT

Background Mifepristone and a prostaglandin have been used successfully to terminate pregnancy in Europe and China. We report the results of a large U.S. study of mifepristone and misoprostol in women with pregnancies of up to nine weeks' duration.

Methods We administered 600 mg of mifepristone and then 400 μg of misoprostol two days later to 2121 women seeking termination of their pregnancies at 17 centers. The women were observed for four hours after the administration of misoprostol and returned on day 15 for final assessment.

Results Two thousand fifteen women completed the final assessment. Among them, pregnancy was terminated in 762 of the 827 women pregnant for ≤49 days (92 percent), 563 of the 678 women pregnant for 50 to 56 days (83 percent), and 395 of the 510 women pregnant for 57 to 63 days (77 percent) ($P<0.001$). Termination occurred within 4 hours after the administration of misoprostol in 49 percent of the women and within 24 hours in 75 percent. Failures, defined as cases requiring surgical intervention for medical reasons or because the patient requested it, the abortion was incomplete, or the pregnancy was ongoing, increased with increasing duration of pregnancy. The largest increase was in failures representing ongoing pregnancy, which increased from 1 percent in the ≤49-days group to 9 percent in the 57-to-63-days group ($P<0.001$). Abdominal pain, nausea, vomiting, diarrhea, and vaginal bleeding also increased with advancing gestational age. Two percent of the women in the ≤49-days group, as compared with 4 percent in each of the other two groups, were hospitalized, underwent surgical intervention, and received intravenous fluids ($P=0.008$).

Conclusions This mifepristone–misoprostol regimen is effective in terminating pregnancies, especially in women with pregnancies of 49 days' duration or less. (N Engl J Med 1998;338:1241-7.)

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THE antiprogestin mifepristone (RU 486) causes abortion by competitively blocking progesterone receptors.[1-3] For maximal effectiveness, a prostaglandin should be given 48 hours after mifepristone.[1,3,4] The rates of termination of pregnancies 49 days old or less are similar, ranging from 96 to 99 percent, whether mifepristone is used with gemeprost or misoprostol, both prostaglandin E_1 compounds.[1,3,5-7] Gemeprost is expensive, requires refrigeration, and is not widely available, but misoprostol is inexpensive, stable at room temperature, and obtainable in many countries, including the United States.

Many American women do not have access to abortion,[8] and in developing countries up to 200,000 women die annually of complications after illegal abortions.[9] The availability of medical abortion in the United States and elsewhere could lead to greater access to safer abortion services. We conducted a multicenter trial of mifepristone and misoprostol to determine whether this combination could be used to terminate pregnancies of up to 63 days' duration.

METHODS

Participating Centers

From September 1994 to September 1995, we enrolled 2121 women, each with a documented pregnancy of 63 days' duration or less, requesting termination of pregnancy. Women with liver, respiratory, renal, adrenal, or cardiovascular disease, thromboembolism, hypertension, anemia, insulin-dependent diabetes mellitus, coagulopathy, or known allergy to prostaglandins were excluded, as were women less than 18 years of age or those more than 35 years of age who smoked more than 10 cigarettes per day and had another cardiovascular risk factor. Women were also excluded if they had in situ intrauterine devices, were breast-feed-

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The principal investigators and centers participating in the study are listed in the Appendix.

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ing, were receiving anticoagulation or long-term glucocorticoid therapy, had adnexal masses, had ectopic pregnancies, or had signs or symptoms suggesting they might abort spontaneously. All the women agreed to undergo surgical termination of pregnancy if the medical method failed. Among the 2121 women, 915 were enrolled at eight Planned Parenthood clinics, 538 at four university-hospital clinics, and 668 at five free-standing abortion clinics. The protocol was approved by the human investigational review board at each participating institution, and all the women gave informed consent.

Study Design

Pregnancy was measured from the first day of the last menstrual period according to menstrual history, pelvic examination, and vaginal ultrasonography. On the basis of the investigator's final assessment of these three measures, the women were assigned to the following arbitrarily defined gestational-age groups: the ≤49-days group (859 women); the 50-to-56-days group (722); and the 57-to-63-days group (540).

Three clinic visits were scheduled. At visit 1 (day 1), the women were assessed clinically and took 600 mg of mifepristone orally. At visit 2 (day 3), they took 400 μg of misoprostol orally unless a complete abortion had already occurred. After taking misoprostol, the women were monitored for four hours for adverse events, such as nausea, vomiting, diarrhea, and abdominal pain. These events were rated by the women and recorded as mild (felt but easily tolerated), moderate (uncomfortable enough to interfere with usual activity), or severe (incapacitating, preventing usual activity). Vaginal bleeding was recorded on a diary card and rated by each woman on days 1 through 15 of the study as spotting (less than normal menstrual bleeding), normal (similar to normal menstrual bleeding), or heavy (more than normal menstrual flow). During this period, the women were also monitored for expulsion of the conceptus. At visit 3 (day 15), the treatment outcome was assessed.

Efficacy was defined as the termination of pregnancy with complete expulsion of the conceptus without the need for a surgical procedure. The need for a surgical procedure (either vacuum aspiration or dilation and curettage) constituted a failure, and such a procedure was performed at any time if the investigator believed there was a threat to a woman's health (medically indicated), at a woman's request, or at the end of the study for an ongoing pregnancy or incomplete abortion. Follow-up was extended beyond visit 3 if there was uncertainty about the completeness of the abortion or if bleeding persisted.

A total of 106 women were excluded from the efficacy analysis because they did not return for visit 3. Evidence suggesting a successful outcome was available for 92 of these women, and evidence of failure for 1. The remaining 13 women were lost to follow up; 5 had continuing pregnancies when last seen at visit 2. The analyses of efficacy therefore included 2015 women.

Statistical Analysis

Statistical analysis was performed with the use of Statistical Analysis System software (SAS Institute, Cary, N.C.). One-way analysis of variance and Kruskal–Wallis tests were used to compare mean values in the gestational-age groups, and Pearson's chi-square tests were used to compare the distributions of categorical variables. Fisher's exact test was used to compare rates in the gestational-age groups. Stepwise logistic-regression analysis was used to evaluate the relation between success or failure and various base-line patient characteristics; the significance level required for a variable to stay in the model was 0.10. All statistical tests were two-tailed.

RESULTS

There were 859 women in the ≤49-days group, 722 in the 50-to-56-days group, and 540 in the 57-to-63-days group. The three groups were similar with respect to age (mean, 27 years; range, 18 to 45), gravidity, parity, number of spontaneous or previous elective abortions, and ethnic or racial distribution (white, 71 percent; black, 15 percent; Hispanic, 9 percent; Asian, 5 percent). Seventy-three percent of the women had had previous pregnancies, 51 percent elective abortions, and 15 percent spontaneous abortions.

Efficacy

Among the 2015 women who returned for the third visit, the rates of pregnancy termination were 92 percent in the ≤49-days group, 83 percent in the 50-to-56-days group, and 77 percent in the 57-to-63-days group ($P<0.001$) (Table 1). Of the 59 women who did not receive misoprostol, 56 had termination of their pregnancies after mifepristone alone. In the remaining three women, it subsequently became apparent that their pregnancies had not been terminated after mifepristone and they should have been given misoprostol; they later underwent surgical termination. The rate of termination after mifepristone alone also decreased significantly with increasing gestational age, from 5 percent to 0.8 percent (Table 1).

The rates of incomplete abortion were 8 percent in the 50-to-56-days group and 7 percent in the 57-to-63-days group, as compared with 5 percent in the ≤49-days group (Table 1). The failures for all other reasons were significantly higher in both the 50-to-56- and 57-to-63-days groups than in the ≤49-days group. The largest increase was in failures representing ongoing pregnancy, which rose from 1 percent in the ≤49-days group to 9 percent in the 57-to-63-days group. Ninety percent of the surgical terminations performed for medical reasons were for vaginal bleeding. A patient's request was the reason least often cited for surgical termination.

Although the study design called for analysis according to the three discrete gestational-age groups, there was in fact a steady decline in the frequency of termination of pregnancy with increasing duration of gestation (Fig. 1). Logistic-regression analysis indicated that the rates decreased with increasing gestational age, from more than 95 percent before day 40 to less than 90 percent after day 47 and to less than 80 percent after day 59. The only other factor that was related to outcome was the number of previous elective abortions (Fig. 1); the termination rates were higher for women with no previous abortions than for those with previous abortions. The differences in rates were less than 2 percent up to day 35, 2 to 3 percent from days 36 to 42, 3 to 4 percent from days 43 to 48, 4 to 6 percent from days 49 to 55, and 6 to 10 percent from days 56 to 63. The outcomes were unrelated to other base-line characteristics, including age, race, body weight, gravidity, and previous spontaneous abortions.

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TABLE 1. RESULTS OF MIFEPRISTONE AND MISOPROSTOL IN WOMEN SEEKING TERMINATION OF PREGNANCY.

OUTCOME	PREGNANT ≤49 DAYS (N=827)	PREGNANT 50 TO 56 DAYS (N=678)	PREGNANT 57 TO 63 DAYS (N=510)
	number (percent [95% confidence interval])		
Success	762 (92 [90–94])	563 (83 [80–86])*	395 (77 [74–81])*†
After mifepristone alone	40 (5)	12 (2)‡	4 (0.8)*
Failure (need for surgical intervention)			
Medical indication for intervention	13 (2)	26 (4)‡	21 (4)‡
Patient's request for intervention	5 (0.6)	13 (2)	
Incomplete abortion	39 (5)	51 (8)‡	12 (2)‡
Ongoing pregnancy	8 (1)	25 (4)*	36 (7)
			46 (9)*§
Total	65 (8)	115 (17)*	115 (23)*†

*P<0.001 for the comparison with the ≤49-days group.

†P=0.02 for the comparison with the 50-to-56-days group.

‡0.001≤P<0.03 for the comparison with the ≤49-days group.

§P<0.001 for the comparison with the 50-to-56-days group.

Complete expulsion of the conceptus occurred before the administration of misoprostol in 76 women (4 percent). This group included the 56 women who received only mifepristone and an additional 20 women who received misoprostol because their expulsion status was considered uncertain at the beginning of visit 2. It was subsequently determined that these 20 women had had complete expulsions before they took misoprostol. During the four hours of observation after the administration of misoprostol, 49 percent of the women expelled the conceptus, and during the fifth hour an additional 11 percent expelled the conceptus. By 24 hours after misoprostol administration, 75 percent of the women had expelled the conceptus (Fig. 2).

Vaginal Bleeding

Vaginal bleeding is a natural consequence of the abortion process, and it occurred in all the women whose pregnancies were terminated medically. The median duration of bleeding or spotting was 13 days in the ≤49-days group and 15 days in the other two groups (P<0.001). The proportions of women who reported heavy bleeding did not differ significantly in the three groups, were highest on day 3, and then decreased steadily. By day 15, 77 percent of all reported bleeding was considered spotting (Fig. 3). Nine percent of the women reported some type of bleeding after 30 days, and 1 percent after 60 days.

Excessive bleeding necessitated blood transfusions in four women and accounted for 25 of 27 hospitalizations (including emergency-room visits), 56 of 59 surgical interventions, and 22 of 49 administrations of intravenous fluid. Hospitalizations, surgical interventions, and intravenous-fluid administration were reported for 2 percent of the women in the ≤49-days group and for 4 percent of those in each of the other groups (P=0.008). Bleeding was managed by the administration of uterotonic agents, such as oxytocin, methylergonovine, or vasopressin, in 41 women (5 percent) in the ≤49-days group, 50 (7 percent) in the 50-to-56-days group, and 55 (10 percent) in the 57-to-63-days group (P<0.001).



Figure 1. Logistic-Regression Analysis of the Predicted Probability of Successful Pregnancy Termination, According to the Duration of Pregnancy for All the Women and for the Women Who Had and Those Who Had Not Had Previous Elective Abortions.

Other Adverse Events

Almost all the women (99 percent) reported at least one adverse event during the study period (Ta-

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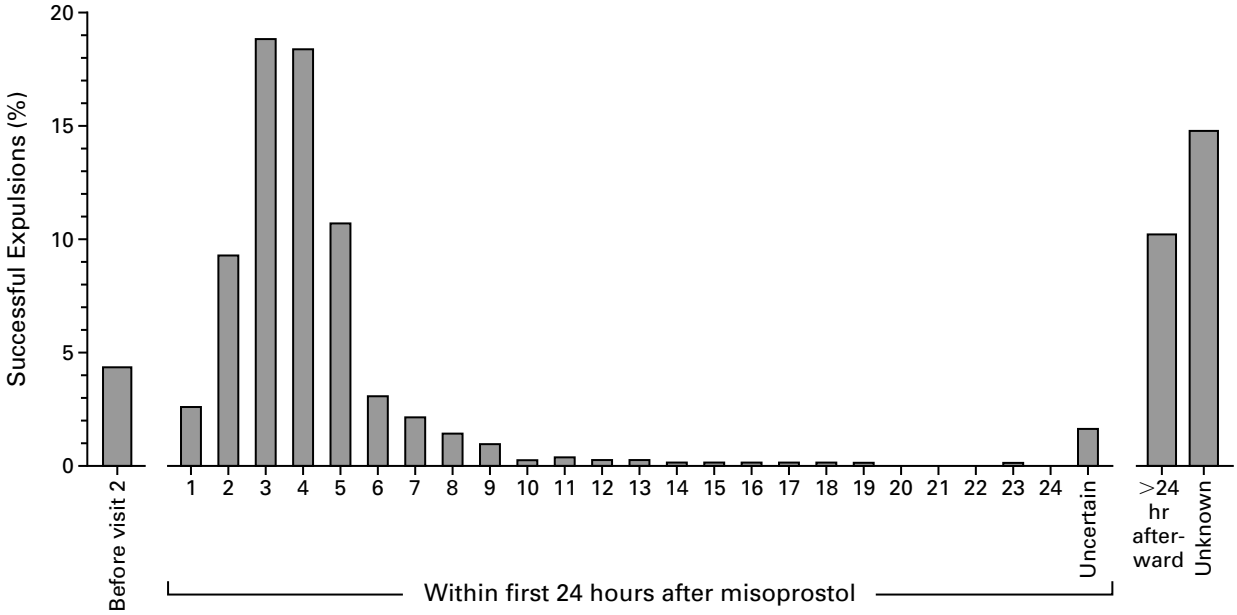

Figure 2. Times of Expulsion of the Conceptuses in 1720 Women with Successful Termination of Their Pregnancies.
The women received mifepristone at visit 1 and misoprostol two days later (visit 2). "Uncertain" indicates that expulsion occurred within the first 24 hours after misoprostol was given, but the exact time was not known. "Unknown" indicates that expulsion occurred more than 24 hours after misoprostol was given, but the exact time was not known.

ble 2). Nearly all had abdominal pain; its overall incidence did not differ among the three groups. However, 53 percent of the women in the 50-to-56-days group and 54 percent in the 57-to-63-days group had abdominal pain reported as severe, as compared with 43 percent in the ≤49-days group ($P<0.001$). Sixty-eight percent of the women received at least one medication for abdominal pain (usually acetaminophen), and 29 percent also received opiates (usually acetaminophen with hydrocodone or codeine). The women in the 50-to-56- and 57-to-63-days groups received significantly more analgesia and opiates than the women in the ≤49-days group ($P<0.001$). Abdominal pain resulted in one hospitalization and was the reason for two medically indicated surgical interventions.

As compared with the ≤49-days group, the 50-to-56- and 57-to-63-days groups had significantly more nausea and vomiting, and diarrhea was more frequent in the 57-to-63-days group. The overall percentages of events reported as severe were 3 percent for diarrhea, 10 percent for vomiting, and 20 percent for nausea. Medications for these adverse events were taken by 1 percent, 4 percent, and 19 percent of the women, respectively, with no differences among the gestational-age groups. Severe vomiting resulted in one hospitalization and was the reason for one medically indicated surgical intervention.

In the four-hour observation period after the administration of misoprostol, the number of adverse events and the percentage classified as severe were similar to those reported during the entire study period. During these four hours, nausea ($P<0.001$) and vomiting ($P<0.001$) were significantly more frequent in the 50-to-56- and 57-to-63-days groups than in the ≤49-days group, and abdominal pain ($P=0.009$) and diarrhea ($P=0.006$) were more severe in the 57-to-63-days group.

The frequency of adverse events declined significantly with increasing gravidity and parity (Table 2). Nulliparous women received significantly more analgesia ($P<0.001$), opiate analgesia ($P<0.001$), and medications for nausea ($P<0.001$) and diarrhea ($P<0.001$) than parous women. Chronologic age was not consistently related to the frequency of adverse events.

Other adverse events reported included headache (32 percent); dizziness, encompassing light-headedness and faintness (12 percent); back pain and fatigue (9 percent each); fever, vaginitis, and viral infections (4 percent each); rigors and dyspepsia (3 percent each); and asthenia, leg pain, anxiety, insomnia, anemia, syncope, leukorrhea, and sinusitis (2 percent each). Endometritis occurred in 19 women; it was considered study-related in 10, in 1 of whom it was severe.

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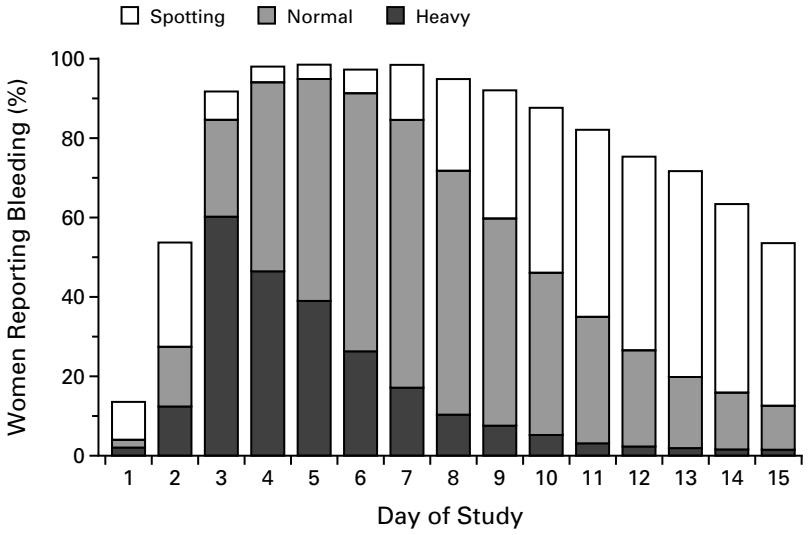

Figure 3. Types of Vaginal Bleeding as Recorded by the Women from Day 1 (Administration of Mifepristone) to Day 15.

The data are from 1506 women who did not undergo surgical termination of pregnancy and who recorded the types of bleeding they had from study day 1 to day 15 on menstrual-diary cards. Bleeding was characterized as spotting, as similar to normal menstrual bleeding (normal), or as heavier than normal menstrual bleeding (heavy).

TABLE 2. INCIDENCES OF ABDOMINAL PAIN, NAUSEA, VOMITING, AND DIARRHEA ACCORDING TO GESTATIONAL GROUP, GRAVIDITY, AND PARITY.

VARIABLE	NO. OF WOMEN	ABDOMINAL PAIN	NAUSEA	VOMITING	DIARRHEA
		number (percent)			
Gestational group					
≤49 days	859	827 (96)	528 (61)	222 (26)	174 (20)
50 to 56 days	722	704 (98)	512 (71)*	277 (38)*	169 (23)
57 to 63 days	540	529 (98)	388 (72)*	220 (41)*	142 (26)†
Gravidity					
1	568	555 (98)	395 (70)‡	236 (42)‡	148 (26)‡
2	527	519 (98)‡	378 (72)‡	205 (39)‡	131 (25)‡
≥3	1026	986 (96)	655 (64)	278 (27)	206 (20)
Parity					
0	1163	1143 (98)	827 (71)	473 (41)	295 (25)
1	449	432 (96)§	280 (62)§	132 (29)§	94 (21)
≥2	509	485 (95)§	321 (63)§	114 (22)§	96 (19)§

*P<0.001 for the comparison with the ≤49-days group (by Fisher's exact test).

†P=0.01 for the comparison with the ≤49-days group (by Fisher's exact test).

‡0.001≤P≤0.03 for the comparison with the women who had had three or more pregnancies (by Fisher's exact test).

§0.001≤P≤0.004 for the comparison with the women who had had no children (by Fisher's exact test).

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DISCUSSION

In this large, multicenter U.S. trial, the success of medical termination of pregnancy decreased gradually with advancing gestational age. We confirmed the international experience that mifepristone and misoprostol can terminate pregnancies of up to 49 days' duration, although the success rate was lower than previously described.[7,10-12] As noted in other countries,[13] this lower success rate may be related to the lack of experience with medical abortion in the United States as well as to the design of our study. We considered the need for surgical intervention on day 15 as representing failure, but abortion might have occurred later.[13,14] Also, a surgical termination performed at the woman's request was classified as a failure instead of being excluded from the efficacy analysis.[10,12,13] Unexpectedly, success was also less frequent among women who had previous elective abortions. Although the reason is unknown, this factor could also have contributed to the differences, because 51 percent of the women in our study had had previous elective abortions, as compared with 25 to 27 percent in two British studies.[12,13]

Efficacy decreased after 49 days' gestation. A similar trend has previously been reported with misoprostol but not with gemeprost.[10-15] Thus, the lower success rates later in gestation are probably related to the prostaglandin component of the regimen. Such lower rates were not found when misoprostol was given by the vaginal route,[16,17] presumably because of greater tissue bioavailability.[18] Higher doses of oral misoprostol increase uterine contractility[19] and are also associated with improved results.[11,12,15] Efficacy is not, however, related to differences in the dose of mifepristone, and similarly good results have been reported with single doses as low as 200 mg.[11,14,20]

The incidence of adverse events rose with the duration of pregnancy.[7,10,13] These events included both subjective symptoms (abdominal pain, nausea, and vomiting) and more objective markers (hospitalizations and surgical interventions). The majority of hospitalizations and surgical interventions were for vaginal bleeding. With advancing pregnancy, the duration of bleeding increased, as did the administration of uterotonic drugs and intravenous fluids. Despite the increases in the numbers of failures and adverse events, the majority of the women in this study reported that they were satisfied with their medical abortions, regardless of whether the outcome was successful (Winikoff B, et al.: unpublished data).

One drawback of this method of pregnancy termination is the inconvenience of the four-hour clinic stay after the administration of misoprostol. In its favor is the fact that many adverse events, including those rated as severe, occurred during this period, as did almost half the expulsions, and some women may prefer to be in the clinic during these events. Moreover, in the women with pregnancies of longer duration, the majority of the hospitalizations or surgical interventions occurred on day 3, whereas in the women with pregnancies of shorter duration, these events were evenly distributed throughout the 15-day study period. Thus, the four-hour visit may be most appropriate for women with pregnancies of longer duration. Nonetheless, on the basis of the results of a small study, mifepristone combined with home application of vaginal misoprostol is a safe alternative in women with pregnancies of up to 56 days' duration.[17]

Careful medical follow-up is essential to ensure that surgical termination is performed in cases of failed medical abortion. In this study, 5 percent of the women did not return for final confirmation of the outcomes of their pregnancies, and five of these women had continuing pregnancies when last seen at visit 2. The ultimate outcome of these pregnancies is unknown, despite our repeated attempts to contact the women. In other studies, the loss to follow-up has ranged from 3 to 11 percent.[5-7,10,12,21] Although mifepristone is not teratogenic in rats, mice, or monkeys,[22,23] skull deformities attributed to uterine contractions occurred in rabbits.[24] Misoprostol, on the other hand, has been reported to be teratogenic in humans.[25,26]

Recently, other methods of medical abortion have been evaluated. Oral misoprostol alone is not effective.[19,27] The efficacy of vaginal misoprostol in the first trimester varies widely, from 47 to 94 percent,[28,29] but it is highly effective in the second trimester.[30] Success rates with methotrexate and vaginal misoprostol range from 83 to 98 percent.[31-35] As compared with mifepristone, this latter regimen has the advantage of being an effective treatment for ectopic pregnancy.[36] However, misoprostol has to be given three to seven days after methotrexate, delaying the abortion process.[35] Unlike mifepristone, methotrexate is cytotoxic to proliferating trophoblast tissue, and persisting pregnancies may represent a greater teratogenic risk.[28,32,33,35]

In conclusion, the regimen of mifepristone and misoprostol is safe and effective for women seeking medical abortions of pregnancies of 49 days' duration or less. With longer durations of pregnancy, the regimen is less effective and the incidence of adverse events is higher.

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APPENDIX

The participating principal investigators and their associated centers are listed below (at the investigator's request, Planned Parenthood of Greater Boston is listed by center only):

P. Blumenthal, Johns Hopkins Bayview Medical Center, Baltimore; L. Borgatta, Planned Parenthood of Westchester and Rockland, White Plains, N.Y.; M.D. Creinin, University of Pittsburgh, Pittsburgh; C.L. Dean, Washington University School of Medicine, St. Louis.; S. Haskell, Planned Parenthood of Greater Iowa, Des Moines; T.C. Malloy, Feminist Women's Health Center, Atlanta; D.R. Mishell, Jr., University of Southern California School of Medicine, Los Angeles; M. Nichols and E. Newhall, Oregon Health Sciences University, Portland; Planned Parenthood Clinic of Greater Boston, Boston; A.N. Poindexter, Planned Parenthood of Houston and Southeast Texas, Houston; S.T. Poppema, Aurora Medical Services, Seattle; E. Rothenberg, Planned Parenthood of Central New Jersey, Shrewsbury; K.L. Sheehan, Planned Parenthood of San Diego and Riverside Counties, San Diego, Calif.; L. Sogor, Preterm, Cleveland; J. Tyson, Planned Parenthood of Northern New England, Burlington, Vt.; P. Vargas, Planned Parenthood of the Rocky Mountains, Denver; and C. Westhoff, Columbia University College of Physicians and Surgeons, New York.

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BRIEF REPORT

Telehealth Medication Abortion in Primary Care: A Comparison to Usual in-Clinic Care

Silpa Srinivasulu, MPH, Deyang Nyandak, MD, Anna E. Fiastro, PhD, MPH, MEM, Honor MacNaughton, MD, Amy Tressan, MD, and Emily M. Godfrey, MD, MPH

Introduction: **Providing abortion in primary care expands access and alleviates delays. The 2020 COVID-19 public health emergency (PHE) led to the expansion of telehealth, including medication abortion (MAB). This study evaluates the accessibility of novel telehealth MAB (teleMAB) initiated during the PHE, with the lifting of mifepristone restrictions, compared with traditional in-clinic MAB offered before the PHE at a Massachusetts safety-net primary care organization.**

Methods: **We conducted a retrospective electronic medical record review of 267 MABs. We describe sociodemographic, care access, and complete abortion characteristics and compare differences between teleMAB and in-clinic MABs using Chi-squared test, fisher's exact test, independent *t* test, and Wilcoxon rank sum. We conducted logistic regression to examine differences in time to care (6 days or less vs 7 days or more).**

Results: **184 MABs were eligible for analysis (137 in-clinic, 47 teleMAB). Patients were not significantly more likely to receive teleMAB versus in-clinic MAB based on race, ethnicity, language, or payment. Completed abortion did not significantly differ between groups ($P = .187$). Patients received care more quickly when accessing teleMAB compared with usual in-clinic MAB (median 3 days, range 0 to 20 vs median 6 days, range 0 to 32; $P < .001$). TeleMAB patients had 2.29 times the odds of having their abortion appointment within 6 days compared with in-clinic (95% CI: 1.13, 4.86).**

Conclusion: **TeleMAB in primary care is as effective, timelier, and potentially more accessible than in-clinic MAB when in-person mifepristone regulations were enforced. TeleMAB is feasible and can promote patient-centered and timely access to abortion care. (J Am Board Fam Med 2024;37:295–302.)**

Keywords: **Abortion-Induced, Access to Health Care, Logistic Regression, Mifepristone, Patient-Centered Care, Primary Health Care, Quantitative Research, Reproductive Health, Retrospective Studies, Telehealth, Women's Health**

Introduction

The *Dobbs v Jackson Women's Health Organization* US Supreme Court decision (*Dobbs*) ended the federal protection to abortion, curtailing access for more than 35 million women and pregnancy-capable people who now live in 18 states that have banned or severely restricted provision.[1,2] Decades of research demonstrates that when abortion is restricted, those seeking care experience significant delays due to challenges navigating limited appointment availability and increased travel distances.[3–5] Medication abortion (MAB) in primary care has the potential to meaningfully increase access to care.[6–8] Early abortion is within the scope of primary care, and family physicians routinely provide safe and effective medication and aspiration abortion in outpatient settings.[9–13] Some patients prefer obtaining abortion care with primary care because of the trust, privacy, and continuity of care it affords and are

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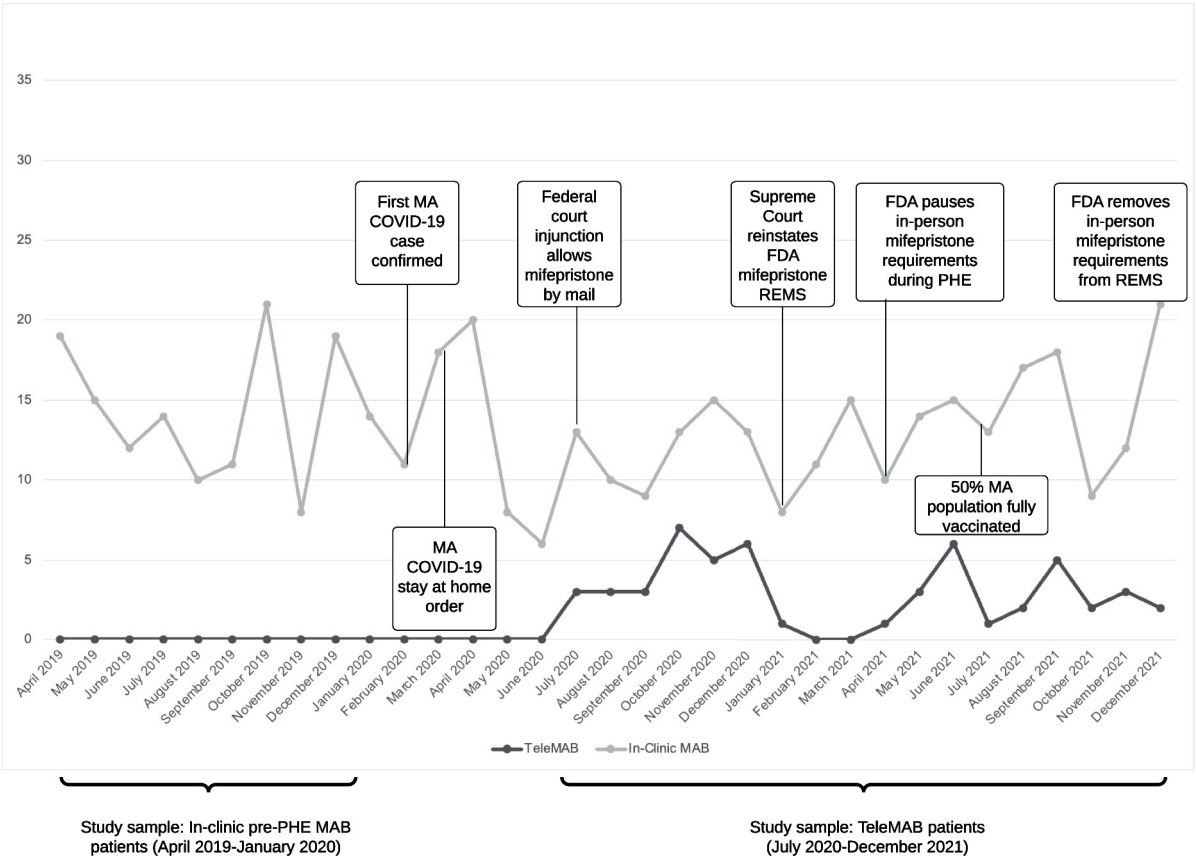
highly satisfied with this care.[14,15] Yet, as of 2018 only 3% of family physicians reported providing abortion, although before its Food and Drug Administration (FDA) approval, 45% of family physicians anticipated offering MAB in their practices.[16,17] Despite its proven safety, since its approval the FDA has restricted mifepristone, the first of a 2-drug MAB regimen, under a "Risk Evaluation and Mitigation Strategy" (REMS), requiring clinicians to physically assess patients' pregnancies and dispense the medication in-clinic, until the COVID-19 Public Health Emergency (PHE).[18]

The PHE led to sustained changes in health care delivery, expanding telehealth services, including in primary care.[19] A temporary injunction on the FDA REMS and dissemination of evidence-based protocols supporting remote clinical assessment of patients allowed for telehealth MAB (teleMAB).[18,20,21] Although some clinics successfully adapted to the changing environment, few safety-net primary care clinics transitioned from in-clinic MAB to teleMAB with medication delivery. Barriers to novel abortion provision include unsupportive leadership, community or professional stigma, and burdensome systems, federal, and state regulations, including pre-*Dobbs* restrictions on teleMAB in 19 states.[22–24]

Although teleMAB can alleviate geographic barriers to abortion, medically underserved communities are impacted by harmful economic and social policies and conditions—poor broadband infrastructure, low access to education and job opportunities, residential segregation, and more—that impede their abilities to use telehealth, resulting in further inequities.[7,25] The extent to which primary care settings can meet the needs of diverse populations by offering teleMAB compared with usual in-clinic MAB is unclear. This study evaluates the accessibility of novel primary care teleMAB, initiated during the PHE with the lifting of mifepristone FDA restrictions, compared with traditional in-clinic MAB offered before the PHE.

Figure 1. Total medication abortions per month at Massachusetts primary care health system before and during public health emergency (April 2019–December 2021).



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Methods

Study Design and Setting

We conducted a retrospective electronic medical record (EMR) review at a large primary care safety-net health system in Massachusetts. This organization serves an economically and culturally diverse population of 120,000 patients across 15 primary care clinics. Many identify as immigrants, the majority hold public or subsidized insurance, and 42% have limited English proficiency requiring professional interpretation in more than 60 languages. The organization has routinely provided MAB since 2003, providing on average 14 MABs per month (2019) and does not publicly advertise their abortion services.

In response to the PHE and temporary lifting of FDA restrictions, the organization expanded MAB to offer synchronous telehealth consultations, remote consent signing, and medications delivered to patients via courier from July 28, 2020 to present, except from January to April 2021 when the Supreme Court reinstated FDA enforcement of the in-person requirements (Figure 1).[18] Patients up to 11 weeks' gestation could choose between in-person and teleMAB appointments, though access to in-person appointments was severely curtailed during the PHE due to temporary clinic closures, staffing changes, and backlogs of appointments leading to health care delays for an extended time. Still, in-clinic visits were required for patients with contraindications to remote care, like symptoms of potential ectopic pregnancy. The in-clinic pre-PHE sample best represents the organization's abortion-seeking patient population during the same months as examined for teleMAB to account for seasonal tendencies in abortion.[26,27] MAB protocols changed in March 2020; first requiring ultrasound and recommending lab work, then only requiring ultrasound and labs when indicated, consistent with published standards of care.[21]

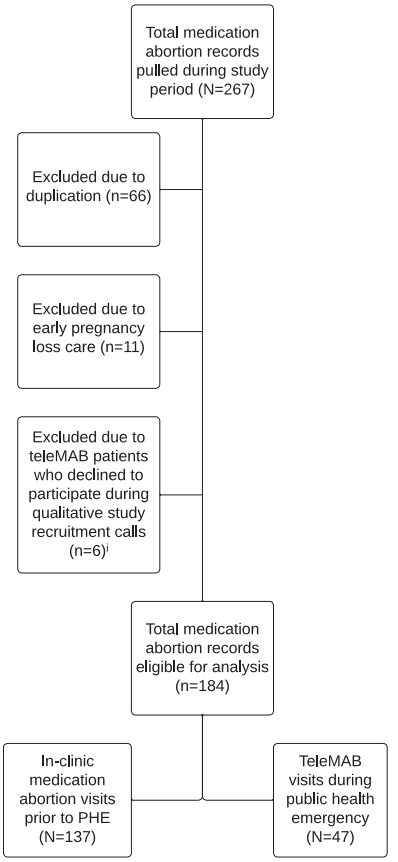
We extracted EMR data for eligible patients (n = 267): in-clinic MAB (April 12, 2019-January 12, 2020) and teleMAB (July 28, 2020-December 31, 2021). Figure 2 illustrates exclusion criteria.

Data Collection

DN, HM, and AT developed an encrypted Google Forms chart abstraction tool to systematically summarize sociodemographic, care access, and relevant medical information in a deidentified dataset. Sociodemographics included race (self-report, predetermined categories), ethnicity (self-report, open-ended), form of payment (private, public, missing), language of care, and whether a patient was an established patient at time of MAB. Race, ethnicity, payment, and language were included to explore racial, ethnic, and income-related differences in teleMAB access and serve as proxy measurements for systemic social, economic, and political barriers to accessing care.[28]

Care access measures included gestational age at time of MAB appointment and time to MAB appointment, calculated in days from when a patient first requested MAB (phone call or visit) to their MAB appointment date. We dichotomized time to MAB appointment as 6 days or less versus seven days or more based on an analysis of the 2014 Abortion Patient Survey, which found an average abortion

Figure 2. Flow diagram of inclusion criteria into study.



[i]Due to institutional review board requirements, eligible patients who declined to participate in an complementary qualitative study were excluded from this chart review (n= 6)

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Table 1. Sociodemographic and Access Characteristics of Patients Receiving Medication Abortion in a Primary Care Health System Before and During the COVID-19 Public Health Emergency

	In-Clinic MAB Pre-PHE (n = 137)	TeleMAB during PHE (n = 47)	P-Value
Established Patient at Time of MAB*	124 (91.2%)	43 (91.5%)	1.0
Race			0.19
Asian	9 (6.6%)	6 (12.8%)	
Black	52 (37.9%)	13 (27.7%)	
White	22 (16.1%)	12 (25.5%)	
Other	50 (36.5%)	15 (31.9%)	
Unknown/Preferred not to Share	4 (2.9%)	1 (2.1%)	
Ethnicity±			0.46
African American	16 (11.8%)	6 (13.9%)	
Hispanic	19 (14.1%)	6 (13.9%)	
Brazilian/Portuguese	24 (17.8%)	9 (20.9%)	
Haitian	25 (18.5%)	3 (6.9%)	
Other	51 (37.8%)	19 (44.2%)	
Primary Language‡			0.18
English	110 (80.3%)	42 (89.4%)	
Portuguese	12 (8.8%)	3 (6.4%)	
Other	15 (10.9%)	2 (4.3%)	
Form of Payment			0.95
Private Insurance	24 (17.5%)	14 (29.8%)	
Public Insurance§	76 (55.5%)	33 (70.2%)	
Not documented in EMR‖	37 (27.0%)	0 (0%)	
Gestational Age in Days at Time of MAB Appointment¶	48.1 (28 to 68)	45.3 (30 to 75)	0.049#
41 days and under	32 (23.7%)	20 (42.6%)	
42 to 56 days	79 (58.5%)	20 (42.6%)	
57 to 69 days	24 (17.8%)	5 (10.6%)	
70 to 77 days	0 (0%)	2 (4.3%)	
Completed Abortion**	130 (94.9%) 95% CI: 89.8%, 97.9%	42 (89.4%) 95% CI: 76.9%, 96.5%	0.187

*1 in-clinic patient missing (n = 136).
±Ethnicity was self-reported by patients. "Other" category includes ethnicities such as: Nepali, Moroccan, Nigerian, American, Korean, etc.
‡χ^2 test compared English and non-English speaking. Other languages included: Spanish, Haitian Creole, Nepali, and Arabic. Patients used phone interpreters, face-to-face interpreters, or spoke English during their visits.
§Includes payment by public insurance, grant, or out of pocket.
‖37 visits' form of payment not documented in EMR due to a technology issue during specific segment of time. Assigned missing in fisher's exact test.
¶2 in-clinic cases missing due to pregnancy of unknown location, medication abortion complete by drop in hcg; n = 135; mean, range, and independent *t* test for statistical differences reported here.
#significant results at $P = .05$.
**Complete abortions without additional doses of medication; no patients lost to follow-up as in-person appointments or phone calls were required to confirm completed abortion.

appointment delay of 7.6 days.[29] Complete abortion was dichotomized to describe MAB completions per protocol 1 to 28 days after abortion.

Data Analysis

We reported sociodemographic, care access, and complete abortion measures using descriptive statistics and compare differences between in-clinic and telehealth groups using c^2, fisher's exact test, independent *t* test, and Wilcoxon rank sum. We conducted logistic regression to examine time to care differences. We used R (4.1.1, R Core Team 2022) to conduct analyses. We set significance at $P = .05$; unknown responses were assigned missing. This study was approved by the two organizations' institutional review boards.

Results

Of 267 medical records extracted, 184 were eligible for analysis, of which 137 (74.5%) MABs occurred in-clinic pre-PHE and 47 (25.5%) were teleMAB encounters during the PHE (Table 1). The vast majority in both groups (91%) were established patients. Patients were not significantly more likely to receive teleMAB versus in-clinic MAB based on race, ethnicity, language, or form of payment. Completed abortion did not significantly differ between teleMAB and in-clinic MABs ($P = .187$).

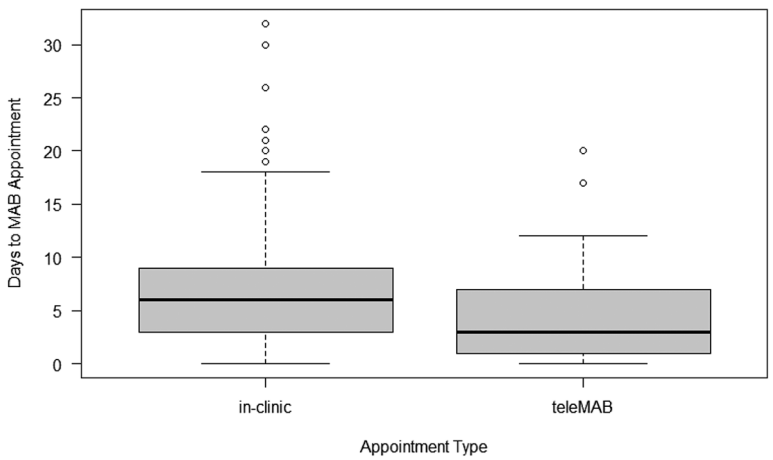
In-clinic visits had a mean gestational age at time of appointment of 48.1 days compared with 45.3 days for teleMAB ($P = .049$). Patients received care more quickly when accessing teleMAB compared with in-clinic services (median 3 days to teleMAB, range 0 to 20 days vs median 6 days to in-clinic, range 0 to 32; $P < .001$, Figure 3). TeleMAB patients had 2.29 times the odds of having their abortion appointment within 6 days compared with in-clinic (95% CI: 1.13, 4.86).

Discussion

In a safety-net primary care system we found that teleMAB was as effective, timelier, and potentially more accessible than in-clinic care (when the FDA enforced in-person assessment and medication acquisition). This demonstrates the feasibility of primary care organizations to integrate novel abortion services to meet their patients' needs. In addition, timely clinical visits is an important indicator of quality abortion care.[30,31] Reducing delays enhances patient-centeredness, reflecting a health system's responsiveness to patients' preferences, needs, and values.[30] Increasing access in primary care is critical as *Dobbs* and other abortion restrictions have increased demand at remaining facilities, contributing to delays and prolonged care.[4,32–35]

We found no differences in sociodemographic characteristics or complete abortion between in-clinic and teleMAB patients. Although we cannot draw conclusions regarding MAB safety due to the study's small sample, our findings are within the range of other studies evaluating complete abortion after MAB in primary care.[36–38] And, although not statistically significant, we found a smaller percentage of teleMAB patients were Black, Haitian, and non-English speaking. Studies during the PHE have found racial, ethnic, and language inequities in broad telehealth utilization.[39–42] Structural barriers drive these inequities, including challenges integrating interpretation into video visits, reimbursement for audio-only visits, and systematic disinvestment in predominantly Black and/or low-income communities and consequences on access to and comfort using digital health infrastructure.[41] Like other telehealth services, teleMAB may not be as accessible due to this digital divide.[25,42] Employing strategies to increase abortion access in community-based settings where and how underserved communities obtain their usual health care is critical. Beyond telehealth, primary care organizations should prioritize access to timely in-person

Figure 3. Days between first contact for medication abortion and appointment between in-clinic pre-PHE visits and teleMAB visits during the PHE. *Abbreviation:* PHE, public health emergency.



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appointments for patients who cannot or do not want to use telehealth. Research is needed to ensure introducing teleMAB does not exacerbate access disparities.

This study has limitations. We sought to collect comprehensive demographics but were limited by IRB requirements that restricted collecting age, parity, and other clinical data. Although time-related factors comparing in-clinic pre-PHE MAB with teleMAB during the PHE may have created systematic differences in the study's abortion-seeking population, this comparison is appropriate given the reduced in-person appointment and staff availability during the PHE, and the need to compare newly introduced teleMAB to usual in-clinic care. As the FDA permanently revised the mifepristone REMS in December 2021 by removing in-person requirements and allowing a pharmacy certification process, future research should compare access to and timeliness of primary care teleMAB to in-clinic MAB, as both are now similarly available in unrestricted states. Further study of the feasibility and effectiveness of primary care teleMAB may motivate more clinics to offer this care, thus reducing delays and improving access. And although the Supreme Court prepares to hear *Alliance for Hippocratic Medicine v FDA*, which may reverse the FDA's REMS modifications that enabled remote mifepristone dispensing, misoprostol-only teleMAB protocols will still be available.[43,44]

Novel teleMAB was comparable to in-clinic services historically provided in a primary care safety-net health care system. TeleMAB seems feasible and can promote timely access to abortion care. Primary care settings should consider implementing teleMAB provision to facilitate timely, patient-centered access to care.

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Original research article

Acceptability of home use of mifepristone for medical abortion ☆

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Abstract

Background: Most medical abortion protocols require women to take mifepristone in the doctor's office. We assessed the acceptability of home use of mifepristone among women and their providers.
Study Design: In this multicenter trial, eligible women requesting termination of early pregnancy (n=301) chose whether to take mifepristone in the office or at home. Data on safety, efficacy, acceptability and disability were collected.
Results: One hundred thirty-nine women (46%) chose to take mifepristone at home, and 162 (54%) chose office administration. Ninety-five percent of home users said that they would take the mifepristone in the same place in the future. Home users were not more likely to call the doctor's office or make an unplanned visit, and providers would recommend home use again for 95% of patients who chose home use.
Conclusions: Home administration of mifepristone was safe and acceptable to women and providers in our study. Women should be offered this choice to allow more flexibility, comfort and privacy in their abortion experiences.
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Keywords: Medical abortion; Mifepristone; Home use

1. Introduction

Due to the politicized nature of abortion in the United States, mifepristone is distributed and dispensed in a highly unusual manner. Mifepristone is supplied only to physicians who sign an agreement with the distributor and is not available in pharmacies. In addition, mifepristone is generally administered under the direct observation of a physician or nurse. These conditions are specified in the manufacturer's label approved by the Food and Drug Administration [1]; however, there is a long history of off-label use in the US for other aspects of mifepristone provision where supportive data exist. Despite the fact that mifepristone has few to no side effects for most women, no data have been gathered on mifepristone use outside the constraints of office provision in the US. A descriptive study of women overseas who acquired both mifepristone and misoprostol from the Women on the Web website and self-administered the tablets reported a success rate similar to rates reported for other outpatient settings (93%) [2].

Women considering medical abortion may assume incorrectly that the abortion will occur on the day of their appointment and accordingly plan their visit around the demands of childcare, work and school. However, the most severe bleeding and cramping usually occur 1 to 3 days after the appointment, after the woman takes the misoprostol. Therefore, requiring women to take mifepristone in the doctor's office can interfere with patients' ability to plan how the abortion will fit into their lives because it forces them to

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initiate the bleeding process at a time when it may be costly or inconvenient. Appointments are often not available at the most convenient times for patients. By contrast, if a woman were sent home with both medications, she could plan to experience bleeding over the weekend or at another time that is suitable for her so that she can avoid schedule disruption or loss of income. Offering women the option to take mifepristone at home may also enhance patient choice for those women who come to the doctor's office intending to have a medical abortion but ultimately choose to have a surgical abortion because of scheduling issues. Lastly, home use of mifepristone has the potential to increase patient satisfaction for those women who wish to start the medical abortion process in the privacy of their homes, with their partners or families.

Many studies of medical abortion have sought to increase acceptability by giving women greater flexibility and autonomy [3–21]. Similarly, the objective of this study was to assess the acceptability of home use of mifepristone for termination of pregnancy among women who choose it and their providers. We also aimed to compare the experiences of women using mifepristone at home to those of women taking mifepristone in the doctor's office and to estimate the proportion of women who might be interested in this new option.

2. Methods

Women presenting for termination of pregnancies up to 63 days of gestation were recruited for this prospective, nonrandomized multicenter trial. The study was conducted from May 2009 through November 2010 at four urban, demographically diverse clinical sites in New York City, Philadelphia and Atlanta. Ethical approval for the study was obtained from the Allendale Institutional Review Board, as well as the institutional review boards of the Montefiore Medical Center, the Institute for Family Health and the University of Pennsylvania. All participants gave written informed consent.

Study participation was generally offered to women after they had made the decision to have a medical abortion, although at three of the sites, the study was mentioned to some women during options counseling. Gestational age was determined according to clinical protocols (two sites by transvaginal ultrasound, one site by first day of last menstrual period (LMP) plus bimanual examination and one site by either or both methods). Participants were given a choice between taking the mifepristone at home or in the office setting. Since one of our primary objectives was to evaluate the acceptability of home use of mifepristone, participant preference was important.

At enrollment, study staff completed a questionnaire with each participant, which included questions about mifepristone administration location choice, pregnancy history and employment status. Women were also asked open-ended questions about their reasons for choosing to take the mifepristone where they did. Those who chose home use were asked to provide a date and time for when they planned to take the mifepristone. Providers counseled women to select a date within the 63-day gestational limit and within 1 week of their abortion appointment. Participants were then given 200-mg mifepristone to take orally either at home or in the doctor's office, depending on their stated choice. Each participant was given four 200-mcg pills of misoprostol to be taken 6 to 48 h after mifepristone per their site's medical abortion protocol. Women also received a home study card with instructions to record the time and date of mifepristone and misoprostol administration, number of missed days of work and/or school and hours of paid childcare needed due to the abortion. Pain, antidiarrheal and antinausea medications were recommended according to each site's standard clinical protocol.

Participants returned to the doctor's office 1 to 2 weeks after mifepristone administration for a follow-up visit. If a clinician determined that the abortion was complete (based on clinical history, examination and/or vaginal ultrasound, as per clinical protocol), an exit interview was administered to collect data on aspects of participant satisfaction. Responses on the home study card regarding time of medication administration and days of missed work, school or childcare needed due to the abortion were also reviewed with the participant during the follow-up visit. If the participant was unable to return for her follow-up visit, this information was obtained over the phone by study staff when possible. For participants requiring additional follow up or a surgical completion, the exit interview was conducted once the abortion was complete. After a participant was discharged from the study, providers answered a hypothetical question about whether or not they would recommend this participant take mifepristone at home in the future.

Studies have demonstrated that 87–97% of women find home use of misoprostol acceptable [7,22,23]. We wished to show that the satisfaction rate for home use of mifepristone is comparable to reported satisfaction rates for home use of misoprostol, which is now standard in the US. We chose 87% as the minimum value that would be regarded as consistent with the conclusion that home use of mifepristone is as acceptable as standard care. Enrolling 114 women in the home-use group would allow us to estimate an acceptability rate of 92% with a confidence interval of ±5%. Since the study was not randomized, we could not know a priori what proportion of women were going to choose the home-mifepristone regimen. Therefore, we planned to enroll participants until at least 114 women were followed up in the home-use group and at least 100 women in the office-use group so as to be able to provide adequate descriptive data for women in both groups.

When analyzing our results, we used Fisher's Exact Test to determine differences in proportions, and for continuous variables, we used the Student's *t* test to assess differences in means. In our analysis of primary and secondary outcomes,

we considered two-tailed p values of less than .05 to be statistically significant. We calculated 95% confidence intervals for rates as exact binomial confidence intervals. We analyzed data using Statistical Package for the Social Sciences (SPSS) 17.0 (SPSS, Chicago, IL, USA).

3. Results

Between May 2009 and November 2010, the study sites enrolled 301 women, 139 (46.2%) who chose home use of mifepristone and 162 (53.8%) who chose office use. The proportion of women who chose home use ranged from 41%–54% among the four study sites. Thirteen women (9.4%) in the home-use group and 25 women (15.4%) in the office-use group were lost to follow up (p=.11). Outcome data were available for a total of 260 participants, and success rates did not differ between groups (96.7% for home users vs. 95.6% for office users, p=.75). Four women in the home-use group and five women in the office-use group reported visiting the emergency room (ER) for care related to their abortion. Only one of the women who visited the ER received a surgical completion as part of her care; she was also the only one who was subsequently admitted to the hospital (the other women received fluids, pain and antinausea medication). Besides that case, no serious adverse events occurred among the study participants.

Despite the nonrandomized sample, baseline characteristics, including age, gravidity and employment status, were similar for the two groups (Table 1). Home users were more likely to have had a previous abortion, but this difference was not statistically significant. Women were asked to provide reasons for their choice of where to take the mifepristone; more than half of home users cited the flexibility in schedule, and more than one fourth felt that it would be more comfortable (Table 2). Office users also reported comfort as a common reason for their choice; 28% reported that they wanted to start the process immediately, and 26% answered that they had already planned their schedule accordingly, reflecting the extensive phone counseling that precedes many medical abortion appointments.

Table 1
Participant characteristics

	Home mifepristone users n=139	Office mifepristone users n=162	p value
Age, years (mean, range)	28.0 (16–42)	27.4 (14–48)	.51
Gravidity, mean (range)	2.5 (1–9)	2.5 (1–9)	.93
Gestational age, days (mean, range)	47.3 (28–64)	47.4 (28–66)	.85
Had previous abortion, %	51.4	40.1	.06
Had previous medical abortion, %	25.5	26.1	1.0
Doing paid work, %	68.3	69.8	.80
Student, %	31.9	35.8	.54
Part-time student, %	9.4	9.9	1.0
Full-time student, %	22.5	25.9	.50

Table 2
Top five reasons for choosing mifepristone location

Home mifepristone users, n=139	Office mifepristone users, n=161
More flexibility in schedule (62%)	More comfortable (35%)
More comfortable (28%)	Want to start abortion
More private (17%)	immediately (28%)
Miss less work/school (15%)	Already planned timing (26%)
More compatible with household duties (14%)	Less anxiety (16%)
	Like provider presence (14%)

Women could give more than 1 answer.

Among participants in the home user group who returned for follow up and recorded a date and time of mifepristone administration, 74% took mifepristone at the scheduled time (defined as within a window of 12 h around the time they had recorded with the provider). Three women decided to keep the pregnancy and opted not to take the mifepristone. Of the 31 women who took the mifepristone at a time different from what they scheduled, 9 took it before, and 22 took it after their scheduled time (Table 3). For those women who delayed taking the mifepristone, the median delay was 25 h. Reasons women provided for not taking the mifepristone at the scheduled time included work/school conflicts, family schedule conflicts, wanting more time to consider the abortion and greater convenience. No participant took the mifepristone after 63 days' LMP.

Over 90% of women in both groups took the misoprostol at the scheduled time (Table 3). Participants in the home-use group were slightly more likely to take the misoprostol on a Saturday or Sunday (41% vs. 35%), but this difference was not significant. All participants took the misoprostol within 72 h of taking the mifepristone, including those women who did not take mifepristone at the scheduled time.

Nearly all women who chose home use said that they would choose to take the mifepristone at home again if they needed another abortion (95.0%), whereas 81.7% of office users said that they would choose office use again (p=.001) (Table 4). Most home users (97.5%) and 75% of office users would recommend home use to a friend (p=.001).

Participants in both groups were asked to report the best and worst features of taking the mifepristone where they did (Table 4). Home users most valued being able to schedule the bleeding around their responsibilities and found home use comfortable. Almost three fourths of home users could not cite a single worst feature; however, 11% did report feeling anxious. Office users also reported comfort as a key best feature, and about a third valued the presence of a provider when they administered the mifepristone. Four in five office users

Table 3
Timing of mifepristone and misoprostol administration

	Home mifepristone n=117	Office mifepristone n=124	p value
Mifepristone administration[a]			
Took mifepristone at scheduled time, % (n)	73.5 (86)	n/a	n/a
Took mifepristone before scheduled time, % (n)	7.7 (9)	n/a	n/a
Took mifepristone after scheduled time, % (n)	18.8 (22)	n/a	n/a
Median delay, h (range)	25 h (7 h–9 d)	n/a	n/a
Misoprostol administration			
Took misoprostol at the scheduled time, % (n)[b]	94.2 (81/86)	91.1 (113/124)	.59
Took misoprostol on the weekend, % (n)	41.0 (48/117)	35.4 (45/127)	.43
Median mifepristone–misoprostol interval, h (range)[c]	24 (6–49 h)	24 (5–69 h)	n/a

n/a=not applicable.
[a] Among women who returned for follow up and completed a patient diary.
[b] Excludes women who did not take mifepristone at the scheduled time.
[c] Clinical protocols at two sites allowed for mifepristone–misoprostol intervals as short as 6 h. Home mifepristone group is n=117 and n=125 for office mifepristone group.

could also not cite a worst feature of taking the mifepristone in the doctor's office.

There were no significant differences in the mean number of days of work missed, school missed and hours of paid childcare needed due to the abortion between study groups, although the associations are in the hypothesized directions (Table 5). Most women made no additional calls (85% for home users and 90% for office users) or unscheduled visits to the doctor's office (96% for home users and 99% for office users). Providers recommended home use in the future for over 90% of participants in both groups (95.1% for home users and 90.2% for office users).

4. Discussion

Our study shows that women are able to administer mifepristone safely and properly outside of the doctor's office and that administration under direct medical supervision is unnecessary. There were no differences in rates of efficacy or complications between participants who took the mifepristone at home or in the office. All women who opted for home use of mifepristone took it within 63 days' LMP, which is the current evidence-based gestational age limit for use, and all study participants took the misoprostol within 72 h of mifepristone administration, regardless of mifepristone

Table 4
Participant satisfaction and best/worst features of taking mifepristone at the chosen location

	Home mifepristone	Office mifepristone
Would take mifepristone in same place again, % (n)[a]	95.0 (114/120)	81.7 (103/126)
Would recommend home use to a friend, % (n)[b]	97.5 (115/118)	75.0 (93/124)
Best features (%):	n=120	n=132
Scheduled around responsibilities/flexibility	55.8	19.7
Comfortable	39.2	43.2
Private	34.2	4.5
Chose bleeding time	30.0	3.8
Partner/Friend present	13.3	0.0
Provider present	0.0	32.6
Not anxious	4.2	14.4
Not confusing	2.5	9.1
Worst features (%):		
None	74.2	81.8
Anxious	10.8	2.3
Confusing	4.2	0.8
Could not schedule around responsibilities	0.8	4.5
Opportunity for 2nd thoughts/delay	3.3	0.0

[a] p=.001.
[b] p<.001.

Table 5
Lost productivity[a] and service delivery burden

	Home mifepristone	Office mifepristone	p value
	n=85	n=95	
Mean days work missed (range)	0.51 (0–5)	0.81 (0–7)	
Missed 0 days, %	71.8	60.6	.16
	n=36	n=41	
Mean school days missed (range)	0.56 (0–7)	0.59 (0–5)	
Missed 0 days, %	77.8	65.9	.32
	n=49	n=53	
Mean h of paid childcare needed (range)	0.73 (0–24)	0.98 (0–16)	
Needed no paid childcare, %	95.9	88.7	.27
	n=138	n=161	
Unscheduled visits, # (range)	7 (0–2)	2 (0–1)	
Women making no unscheduled visits, %	96.4	98.8	.26
Total doctor's office calls, # (range)	40 (0–8)	25 (0–4)	
Women making no calls, %	84.8	90.1	.22

[a] Participants who were not employed, not in school or did not have children were excluded from the respective analyses.

administration location. Women who took the mifepristone at home were very satisfied with their experiences, and offering this option did not result in increased burden on clinical services in the form of calls and extra visits.

Regardless of where participants chose to take the mifepristone, many reported that the ability to plan when the abortion would occur was important to them. The option of home use enhances women's ability to plan their abortion experiences. Although it is reassuring that 74% of the participants in the home-use group took the mifepristone when they said they would during their initial visit, those women who took the mifepristone at a different time made good use of their greater autonomy; some took it earlier, some later, and several women used the flexibility as an opportunity to reflect further on their abortion decision. None of these women took the mifepristone and misoprostol in a nontherapeutic manner or in a way that was inconsistent with current guidelines.

A strength of our study is that our results are readily applicable to current clinical practice. Because our study design permitted participants to choose the place of mifepristone administration, we are able to report acceptability based on choice of where to initiate the abortion. Had we randomized participants to office versus home use, we would not have been able to describe this important outcome. Some providers reported improved counseling as an unanticipated benefit of the study. The process of talking through when and where women would take the abortion pills led to a greater understanding of the participants' privacy issues and support networks.

Our study has several limitations. We cannot predict with accuracy the future uptake of home use of mifepristone among all women seeking abortion because our study sites mainly offered the option of home use to those women who had already expressed interest in medical abortion. In addition, some women may have been interested in the option of home use but did not want to enroll in a research study to be able to have the opportunity. However, as almost half of participants chose home use, it is a fair conclusion that a substantial number of women would be interested in this option if it were incorporated into regular clinical practice.

Another potential limitation of our study is that more than half of our cases came from sites that offered medical abortion on Fridays and Saturdays. Because of the large number of participants who could take mifepristone in the office and still have weekend bleeding, we were likely unable to describe adequately the potential of home use for reducing childcare costs and the number of missed days of work or school for women undergoing medical abortion.

Home use of mifepristone is an innovation that stands to improve women's abortion experiences. In states where laws require women to receive inperson counseling 24 h or more before their abortion, home use has the potential to make medical abortion more accessible to women by eliminating a doctor's visit. Women who chose home use overwhelmingly approved of it, and taking the mifepristone at home did not result in increased complications or burden on clinicians. Our results support the use of home use of mifepristone, and this option should be offered to all women who undergo medical abortion.

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Telemedicine Abortion in Primary Care: An Exploration of Patient Experiences

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ABSTRACT

PURPOSE The purpose of the study was to explore patients' experiences and perspectives obtaining telemedicine medication abortion (TeleMAB) through their primary care health system.

METHODS We conducted in-depth telephone interviews with 14 English-, Spanish-, and/or Portuguese-speaking patients who received a TeleMAB between July 2020 and December 2021, within a large primary care safety-net community health system in Massachusetts. We created and piloted a semistructured interview guide informed by patient-clinician communication frameworks and prior studies on patient experiences with TeleMAB. We analyzed data using reflexive thematic analysis and summarized main themes.

RESULTS Overall, participants found TeleMAB services in their primary care health system acceptable, positive, and easy. Participants discussed how TeleMAB supported their ability to exercise control, autonomy, and flexibility, and decreased barriers experienced with in-clinic care. Many participants perceived their primary care health system as the place to go for any pregnancy-related health care need, including abortion. They valued receiving abortion care from their established health care team within the context of ongoing social and medical concerns.

CONCLUSIONS Patients find TeleMAB from their primary care health system acceptable and beneficial. Primary care settings can integrate TeleMAB services to decrease care silos, normalize abortion as a part of comprehensive primary care, and improve access through remote care offerings. TeleMAB supports patients' access and autonomy, with the potential to benefit many people of reproductive age.

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INTRODUCTION

Decades of abortion restrictions decrease equitable access to care, contribute to America's growing maternal mortality crisis, and exacerbate abortion stigma.[1-5] State-specific restrictions have singled out abortion providers and patients, enacting laws that are medically unnecessary and politically motivated. Laws include complete abortion bans, gestational duration limits, waiting periods, insurance coverage, unnecessary ultrasounds, need for specialized ambulatory surgical centers, and restrictions on telemedicine.[6] Restrictions further marginalize underserved communities, disproportionately affecting people who identify as Black, Indigenous, and people of color (BIPOC) who make up about 70% of those who obtain abortion services.[7,8] These inequities have worsened since June 2022 with the U S Supreme Court decision in *Dobbs v. Jackson Women's Health Organization* (*Dobbs*) with almost one-half of all US states subsequently severely restricting or banning abortion care altogether.[9]

Primary care plays a critical role caring for the most underserved populations in the US health care system.[10-12] Yet, before the *Dobbs* ruling few primary care practices offered abortion; 95% of abortions occurred in stand-alone clinics outside of where patients get their usual medical care.[13-16] Importantly, abortion in primary care settings has been shown to be safe, feasible, and effective.[17-20] In addition, some patients prefer abortion within primary care, compared with independent abortion clinics, for reasons of trust, familiarity, privacy, and provider comfort.[21-23]

During the 2019 coronavirus pandemic (COVID-19), several primary care practices initiated direct-to-patient telemedicine medication abortion (TeleMAB)

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and mailed pills to patients.[24] Research shows that TeleMAB by primary care is feasible and efficient.[25,26] To date, however, no studies have evaluated patients' experiences regarding obtaining TeleMAB through their regular primary care health system.[27,28] Patient experience is an important aspect of patient-centered care and to thus understanding their perceptions enhances the delivery of care.[29] Therefore, we interviewed patients who completed TeleMAB through their primary care health system to understand their experiences.

METHODS

Study Design, Setting, and Sample

From March-May 2022, we interviewed a convenience sample of patients who received TeleMAB within a large primary care safety-net community health system in Massachusetts. This health system cares for a culturally diverse patient population of approximately 120,000 patients who mostly hold public or subsidized health insurance. Eligibility criteria included patients who received a TeleMAB between July 28, 2020 and December 31, 2021, had medications delivered, and spoke and understood English, Spanish, and/or Portuguese (n = 47). Using electronic medical records, D.N. generated a list of eligible participants. Interviewers called patients via encrypted teleconferencing software up to 5 times over 2 weeks and shared study information. Consent forms were e-mailed in the participant's language or patients provided verbal consent. D.N. did not call any patient for whom she had provided care and only identified as a researcher and not a physician. The 2 Institutional Review Boards of the involved institutions, University of Washington and Cambridge Health Alliance, approved this study. We followed the Consolidated Criteria for Reporting Qualitative Research (COREQ) reporting guidelines.[30]

Telemedicine Medication Abortion Workflow

Primary care clinics in this health system began providing in-clinic medication abortion (MAB) in 2003. In July 2020 the health system implemented direct-to-patient, TeleMAB services, which entailed the use of video visits or synchronous telephone calls between the clinician and patient. When patients expressed the need for a medication abortion, the health system offered them in-clinic or TeleMAB appointments. For patients who chose TeleMAB, the clinician assessed eligibility for remote care including patient location in Massachusetts at time of visit and assessment of gestational dating and ectopic pregnancy risk based on clinical history. The clinician counseled eligible patients on expected process, e-mailed consent forms for electronic signature, and placed a pharmacy order to send a package which was delivered by the health system's courier with mifepristone, misoprostol, anti-nausea medications, analgesics, a urine pregnancy test, and an instruction printout. The clinic scheduled each patient for a 1- to 2-week follow-up telemedicine appointment. Patients could choose to have any or all aspects of care via telemedicine or in-clinic.

Data Collection

We created a semistructured interview guide (Supplemental Appendix, 1.0 - 2.0) informed by the Miller patient-provider communication framework, prior studies on patient experiences with TeleMAB, and the research team's ongoing work exploring patients' experiences with TeleMAB at a primary care–based reproductive health clinic.[31-34] We chose Miller's framework because it includes key components of patient-centered communication and the medium of communication used, ie, telemedicine. Interviewers (D.N., S.S., A.E.F.) each pre-tested the guide with people of reproductive age and refined the questions based on their feedback (Supplemental Appendix, 3.0). All interviews were audio recorded, transcribed, and quality checked.[35,36] After the interview, participants self reported sociodemographic characteristics (Supplemental Appendix, 4.0) and received a $50 gift card.

Analysis

S.S. and A.E.F. performed the study analysis using reflexive thematic analysis.[37] They read transcripts, made conceptual notes, met to discuss potential codes, developed a codebook, and considered how the constructs related to a broader framework of patient experience. S.S. and A.E.F. used Dedoose software (SocioCultural Research Consultants) to manage, sort, and code data. They simultaneously coded 4 transcripts, discussed discrepancies in coding after each one, and refined the codebook accordingly. They coded the remaining transcripts independently (5 each) and met to refine study findings. The analytic team reached data saturation on key themes.[38]

Research Team and Reflexivity

D.N., A.T., and H.M. are family physicians who provided primary care including abortion at the study site. H.M. spearheaded TeleMAB implementation at the study site in June 2020. H.M., A.T., and D.N. were mentored and trained in key concepts of qualitative research by A.E.F. at the beginning of this study. S.S. is an MPH graduate and is a PhD student with a focus on reproductive health research with 4 years of experience conducting qualitative research. A.E.F. is a PhD graduate in public health with experience working in abortion policy and qualitative research. E.M.G. is a complex Family Planning Fellowship–trained practicing physician with master-level training in qualitative research. In terms of reflexivity, the team used Miller's framework which is based in patient-centered communication to shape the collected data and analysis. The analysts incorporated a reflexive process that deepened interpretations of the data and helped build cohesive and structured findings while reflecting on their own biases. A.E.F. is pro-telehealth and medication abortion, and A.F., D.N., H.M., and E.M.G. are pro-primary care, which may have influenced our interpretation of the data and the summary of findings.

RESULTS

Of 47 eligible patients, 14 (30%) agreed to an interview, 9 declined, 9 hung up after our introduction, 1 did not remember their appointment and was not interviewed, and 14 did not respond. One participant did not provide demographic information due to limited time. The other 13 participants identified as female, aged 26 to 42 years, and 10 (71.4%) were parents to children aged 8 months to 15 years. Six (42.8%) identified as African American/Black, 3 (21.4%) as Asian/Pacific Islander/Native Hawaiian, 2 (14.3%) as White and Black, 1 (7%) as White, and 1 as Hispanic/Latino. Eleven were interviewed in English, 2 in Portuguese, and 1 in Spanish.

Ease of Process of Obtaining TeleMAB in Primary Care

Overall, participants found TeleMAB in primary care acceptable, beneficial, and straightforward (Table 1). Participants felt provider counseling prepared them well and expressed confidence in having necessary information to successfully complete their abortion. One noted, "I was very confident and relaxed that everything was going to go right. They made me feel good about it. I wasn't scared" (ID 10, age unknown). They received clear instructions regarding medication use, expected side effects, and contact information for questions. Additionally, participants highlighted how caring interactions with staff amplified the ease of the process. For example, one participant, who initially felt overwhelmed by their pregnancy-related decisions, ultimately felt the experience was easy because of the support they received from their clinician and support staff.

Participants felt comfortable calling the health system or using their online patient portal to contact their providers to schedule appointments or ask questions. They shared having positive experiences with the medication delivery system, noting the simplicity and reliability of the service: " [The

Table 1. Excerpts Illustrating Patient Experience With TeleMAB Within Primary Care

Theme	Description	Illustrative Quotes
Ease of process of obtaining telemedicine medication abortion in primary care		
Patient-centered counseling and preparation	Participants reflected on having effective, patient-centered counseling throughout their TeleMAB experience and having clearly communicated instructions on how to use the medications and what to expect. Clinicians were also perceived as kind and non-judgmental. This enhanced participants' comfort and confidence with their TeleMAB.	#1 "Everything went well, the support they gave me, the information they gave me was complete and the process was exactly like the doctor told me it was going to be and everything turned out fine." (ID 3, age 28) #2 "She called again, [after the initial consultation], offered me support and she guided me through the steps on how to take medicine, what I'd feel, any side effects, if there were any issues - that they're just a phone call away… Very friendly. And again, they were great as far as support and everything." (ID 10, unknown age) #3 "Just dealing with people, making medication easy and making it simple to understand how to take it, the whole experience for me, someone who didn't plan to be pregnant, it was the most easy experience I've ever been through. And I would never have ever expected to go through an abortion experience like that, to be so simple." (ID 33, age 26)
Simplicity of the service	Participants found the process of scheduling appointments, contacting providers, and using the medication delivery system familiar, simple, easy, and reliable.	#4 "So, every time I needed to speak to her or set up an appointment, I was able to get a hold of either her or the other doctor that was in my case. They were there when I needed help." (ID 48, age 31) #5 "They set up a date to send the medication to my home, and a person delivered it to my hand. I had to sign the form, and I did the procedure at night." (ID 15, age 31) #6 "I trusted [the primary care system] and I knew how the process went, and I knew some of the people, and how things would go… I know how to message them and how to call them. Things like that made it feel familiar and easy to engage in. … Versus, I've never actually talked to anyone at [an abortion clinic] ever. So I'd have to figure out how to even set it up. So, I didn't have to go through that process." (ID 46, age 34)
Familiarity and trust in primary care system	Existing relationships and familiarity within one's primary care system made participants feel more comfortable navigating their abortion care.	#7 "Yeah, so prior to my first pregnancy, [my primary care doctor is] who I see for everything. So I didn't have to worry about finding new doctors for anything. She's who I go to." (ID 48, age 31) #8 "I felt more comfortable because I've been here for a minute, it's not my first pregnancy scare [with this clinic], so I knew that I could trust in them and rely on them." (ID 33, age 26) #9 "I've always had my PCP [in the health system] and that's where I had my baby and got all my care around that pregnancy and had really great experiences." (ID 46, age 34)

continues

CPC = crisis pregnancy center; PCP = primary care physician; teleMAB = telemedicine medication abortion.

Note: Fourteen Massachusetts women of reproductive age were interviewed in 2022. Excerpts have been edited for clarity.

Table 1. Excerpts Illustrating Patient Experience With TeleMAB Within Primary Care *(continued)*

Theme	Description	Illustrative Quotes
Advantages of telemedicine		
Flexibility over where and when to take the appointment	Telemedicine allowed participants to take appointments in places and times that fit into their lives, reducing logistical, financial, health, and time-related burdens.	#10 "The televisit is convenient. It saves you time to move around. For instance, I have kids, so honestly, everywhere I will be going, I will be going with them, because I have no one to stay with them… And also the transport fare. I don't drive, so I have to transport myself to the hospital. Then the stress of looking after the kids, while I, at the same time, see the doctor, and all the examination processes. So [telemedicine] was quite convenient for me." (ID 53, age 34) #11 "It was fine. It was actually a slow day [at work], so thankfully I was able to talk to my doctor and get everything that I needed… I had my headphones in so nobody really got to hear the conversation. I was able to answer the questions that needed to be answered, and just be able to take those next four steps." (ID 33, age 26) #12 "They gave me the option of going to the clinic or having the appointment over the phone and I felt really comfortable doing it over the phone." (ID 3, age 28)
Autonomy and control	Telemedicine options afforded participants greater autonomy and control over their space, emotions, and overall experience. They felt more comfortable taking care of their needs in the comfort of their homes.	#13 "I was actually really sick during that pregnancy. I was vomiting the whole time up until the end of the abortion. So that was definitely a plus of not having to leave the house and be able to be in the comfort of my home and have the visits there" (ID 10, age unknown). #14 "You could just be transparent and bare and not have to worry about being stripped in front of someone…Having done both, I would go virtual again a billion times over… I was able to be more free with [my clinician]… And I could light a cigarette or if I needed to pace around or move or get ice water or anything, it was all at my disposal right there… They gave me control of a situation that was uncontrollable to me and was freaking me out … I felt very in the driver's seat." (ID 9, age 32)
Primary care normalizes abortion care		
Continuity of care	Participants felt more comfortable having abortion care in the primary care setting because their provider knew them and their needs and could take care of them in the full context of their health and social histories.	#15 "Yes, I like [abortion services provided at a primary care center]. It's a great clinic, where you can get treatment for everything. It's nice. It's because when you see an abortion clinic, it feels like a strange place. A place dedicated to abortions. It sounds strange. However, when it's a hospital where they treat all kinds of diseases and offer many treatments, it sounds better." (ID 15, age 31)
Primary care as a protective force	Participants felt their primary care providers helped reduce feelings of isolation, affirm their decisions, and mitigate difficult situations.	#16 "I'm a very traumatized person. I had a lot of childhood trauma and they just put ease in my life for the first time. I was just so appreciative. Because kindness isn't owed to you, it's something given as a gift… [the clinician] didn't have judgment on me." (ID 9, age 32) #17 "I didn't know that it was going to go so bad… but I kept my cries in and I was able to talk to [the primary care doctor] about it. I just told him that I totally appreciate him being there for me because, besides the boyfriend, I had nobody else that I could speak to about everything that I went through." (ID 54, age 33) #18 "I was being pressured (by the CPC) to make a different decision than what I came here for, but they want to try to tell me that they understand me and that they feel my emotion. You don't feel my emotion or understand my decision, if you're trying to force me to do something that I've even planned to come here to do." (ID 33, age 26)

CPC = crisis pregnancy center; PCP = primary care physician; teleMAB = telemedicine medication abortion.

Note: Fourteen Massachusetts women of reproductive age were interviewed in 2022. Excerpts have been edited for clarity.

medications] came at the time and date that it was supposed to come" (ID 10, age unknown). When asked what one participant liked about the delivery service, they responded, "All I had to do was just sit back at home and wait. It was great. It was the best part" (ID 15, age 31).

Existing relationships within the participants' primary care network made them feel comfortable navigating their care. While some participants were cared for by their own primary care physicians (PCPs), many participants received care by providers who were not necessarily their primary care doctor. Their trust extended from their provider to the health system. Participants felt more comfortable reaching out to their primary care network than to unfamiliar abortion clinics (Table 1, #6). While some felt comfortable asking their provider about pregnancy options because of existing relationships (Table 1, 7), others knew the health system provided abortion from prior pregnancy experiences (Table 1, #8 & #9). Despite being cared for by multiple

individuals—administrative staff, nurses, and physicians—participants described smooth transitions of care.

Advantages of Telemedicine

Participants discussed how TeleMAB supported their ability to exercise control, autonomy, and flexibility (Table 1). In particular, patients described decreased interruptions to their daily lives, increased agency over their chosen surroundings and access to preferred coping mechanisms. For example, one participant shared that they completed their appointment while at work. Another participant noted a sense of agency by having their appointment at their desired location. One participant felt too sick from pregnancy symptoms to travel and valued staying home during the appointment. One shared, "It just made it an overall easy experience, and I didn't even have to go to my doctor for this. I'm doing this in my own time, my own energy, in my own home" (ID 33, age 26). Being in their own space gave participants greater access to coping strategies that helped decrease their anxiety and helped them feel safer expressing emotions and private information, "I could be a lot more vulnerable because I was right in my bed. And then you didn't have to worry about crying or wiping your face up and seeing people after that. Or people overhearing you in the office or something. You were just at home so you could just be like… this is worrying me" (ID 9, age 32).

Primary Care Normalizes Abortion Care

Many participants perceived their primary care system as the place to go for pregnancy-related needs, including abortion. Their first instinct when they missed their period was "to call [their] PCP" (ID 54, age 33). Participants felt abortion should be part of routine primary care, whereas an independent abortion clinic seemed more isolating and "strange." Participants felt comfortable knowing that their abortion providers had access to their medical histories: "It was just comforting knowing I know the person [doing the abortion care] and we've seen each other multiple times before and she knows a little bit of my history and what I was going through at the time, so we had a good relationship as far as communication" (ID 10, age unknown). Another participant shared how their physician considered their history of gastrointestinal issues and the potential interaction of their chronic medications, noting, "she actually probably saved me from an overdose, too" (ID 9, age 32). They appreciated that their provider delivered care in the full context of their health and social needs.

Although complications from MABs are extremely rare, when medical or social challenges did arise participants reported their PCPs helped assuage difficult situations (Table 1). One participant had excessive bleeding after taking the medications and visited the emergency department, but felt relieved to talk to their PCP throughout the complication. Another participant inadvertently initially visited a crisis pregnancy center where they felt pressured to continue the pregnancy despite being certain about wanting an abortion. They subsequently had an overall affirming abortion experience with their PCP, however, as "I feel like my doctor did a really good job of giving me my options, but also giving me the opportunity to choose what I want to do, regardless of what they believe or regardless of what they feel is right," highlighting the importance of a trusted PCP relationship as a protective force in difficult situations (ID 33, age 26).

DISCUSSION

Overall, participants who received TeleMABs within their primary care health system appreciated the ease of process, clear communication, non-judgmental interactions, continuity of care, and familiarity and trust with the system. Participants' TeleMAB experience contributed to increased feelings of autonomy, flexibility, and comfort. Participants noted a positive experience regardless of whether their PCP or another primary care clinician within the health system provided abortion care, but when difficult situations arose, established relationships with one's PCP helped mitigate the impact. Our findings highlight the ability of a primary care system to provide safe and positive abortion experiences in a high-quality, patient-centered way.

The more abortion is integrated into routine health care, the more normalized it becomes.[39] In our study, participants highlighted how familiarity with the system, ongoing patient-provider relationships, and being cared for in the context of their overall health made the abortion process more normal. Prior studies have found that providing emotional support and having a supportive patient-provider relationship reduces individual-level abortion stigma.[40] Though further research is needed on the link between normalizing care and decreasing stigma, we hypothesize that the factors found in our study which are unique to primary care may also destigmatize abortion care.

Although first trimester abortion care falls within the skill set of PCPs, significant barriers to providing abortion services remain. Barriers include limited abortion education within clinical training, policy restrictions limiting its provision in Federally Qualified Health Centers, onerous regulations around mifepristone prescribing, and state-level abortion bans.[41-43] There are limitations of implementing new abortion care models in states with complete bans. In states where access is protected or with limited restrictions, however, primary care systems can increase abortion access by implementing TeleMAB services, restructuring pay scale and reimbursement models, and partnering with abortion funds. In states where abortion bans exist, primary care providers can advocate with their state legislatures to remove state-level abortion restrictions.

Our study has several limitations. Because we interviewed participants 4 to 22 months after receiving TeleMAB (average of 7.7), our findings may be susceptible to limited recall. Our findings may reflect more positive patient experiences as people with negative experiences may have been less

willing to participate. Our patient population resided in Massachusetts, a state with better abortion access compared with other states, decreasing its generalizability.[44] Additionally, the majority of patients were English speaking, which may have biased our findings toward the English-speaking subgroup. We did not track if the participants received TeleMAB from their regular PCPs or whether appointments were via telephone or video. Future research could explore primary care patients' experiences prospectively, in more languages, telehealth modality, and with a larger sample size to address these limitations. While we hypothesize that integrating TeleMAB into primary care would increase abortion equity particularly for historically marginalized populations who have experienced racism and discrimination within medicine, this should be investigated further in future research.[45]

Findings from our study support primary care clinicians in advocating for TeleMAB implementation in ways that best address patients' needs. Since primary care clinicians vastly outnumber obstetrician-gynecologists in the United States and are more likely to practice in underserved and rural communities, barriers must be addressed to increase access and improve patient experience. Ultimately, a collaborative effort across state Departments of Health, primary care practices, and reproductive rights and justice organizations is needed to begin dismantling barriers to primary care provision of MAB, increasing access to care for millions.[46]


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Key words: abortion; telemedicine; primary care; patient experience; acceptability; normalize; access

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Supplemental materials

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EXHIBIT B-6

APPENDIX TO PETITIONER GENBIOPRO, INC.'S CITIZEN PETITION DATED JULY 3, 2025[1]

Source	Appendix Starting Page
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FDA U.S. FOOD & DRUG ADMINISTRATION

ANDA 091178

ANDA APPROVAL

(b) (6), (b) (4)
GenBioPro, Inc.
(b) (6), (b) (4)
Attention: (b) (6), (b) (4)

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on February 3, 2009, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Mifepristone Tablets, 200 mg.

Reference is also made to the complete response letter issued by this office on February 23, 2018, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is **approved**, effective on the date of this letter. The (b) (6) has determined your Mifepristone Tablets, 200 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Mifeprex Tablets, 200 mg, of Danco Laboratories, LLC.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under section 505(j) is subject to certain elements of the REMS required for the applicable listed drug.

The details of the REMS requirements were outlined in our letter dated June 15, 2011. In that letter, you were also notified that pursuant to section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA and the listed drug it references must use a single, shared system for elements to assure safe use (ETASU), unless FDA waives that requirement.

Your REMS, known as the Mifepristone REMS Program, submitted on May 30, 2017; is approved, and will be posted on the FDA REMS website: http://www.fda.gov/rems

The REMS consists of ETASU and an implementation system.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Your REMS must be fully operational before you introduce Mifepristone Tablets, 200 mg, into interstate commerce.

The Mifepristone REMS uses a single, shared system for the ETASU. This single, shared system REMS Program currently includes the products listed on the FDA REMS website, available at http://www.fda.gov/rems. Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

We remind you that you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FD&C Act.

We also remind you that section 505-1(f)(8) of the FD&C Act prohibits holders of an approved covered application from using any element to assure safe use to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing a REMS assessment or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

ANDA 091178 REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 091178/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 091178/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 091178/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES
SUBMITTED IN SUPPLEMENT XXX

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR ANDA 091178

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

In addition to submitting the proposed REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS submission.

For more information on submitting REMS in SPL format, please email REMSWebsite@fda.hhs.gov

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

(b) (6)

Center for Drug Evaluation and Research

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[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

(b) (6)

Digitally signed by (b) (6)
Date: 4/11/2019 02:22:21PM
GUID: 54078879000a1b9e15dd31ed6f0343ca

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020687Orig1s025

Trade Name:	Mifeprex Tablets 200 mg
Generic or Proper Name:	Mifepristone
Sponsor:	Danco Laboratories, LLC
Approval Date:	January 3, 2023
Indication:	For modification to the approved single, shared system (SSS) risk evaluation and mitigation strategy (REMS) for mifepristone 200 mg tablets, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation, as well as corresponding labeling revisions to the prescribing information and the Medication Guide to align with the modification to the Mifepristone REMS Program.

CENTER FOR DRUG EVALUATION AND RESEARCH

020687Orig1s025

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Cross Discipline Team Leader Review	
Clinical Review(s)	
Product Quality Review(s)	
Non-Clinical Review(s)	
Statistical Review(s)	
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s025

APPROVAL LETTER

U.S. FOOD & DRUG ADMINISTRATION

NDA 020687/S-025

SUPPLEMENT APPROVAL

Danco Laboratories, LLC
(b) (4), (b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6):

Please refer to your supplemental new drug application (sNDA) dated and received June 22, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets, 200 mg.

This Prior Approval sNDA provides for modification to the approved single, shared system (SSS) risk evaluation and mitigation strategy (REMS) for mifepristone 200 mg tablets, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation, as well as corresponding labeling revisions to the prescribing information and the Medication Guide to align with the modification to the Mifepristone REMS Program. This SSS REMS is known as the Mifepristone REMS Program.

APPROVAL & LABELING

We have completed our review of the supplemental application, as amended. It is approved effective the date of this letter.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The Mifepristone REMS Program, of which Mifeprex is a member, was originally approved on April 11, 2019, and the most recent REMS modification was approved on May 14, 2021. The Mifepristone REMS Program consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In order to ensure the benefits of Mifeprex outweigh its risks and to minimize burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the REMS modifications outlined in our REMS Modification

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Notification letter dated December 16, 2021. In addition the following modifications were communicated during the course of the review:

- Revisions to the REMS goal to align with the updated REMS requirements.
- Replacing serial number with recording of NDC and lot number of mifepristone dispensed.
- Additional edits for clarification and consistency in the REMS Document and REMS materials (*Prescriber Agreement Forms, Patient Agreement Form,* and *Pharmacy Agreement Forms*).

Your proposed modified REMS, received on June 22, 2022, amended and appended to this letter, is approved. The modified REMS consists of the elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

The modification of the approved REMS must be fully implemented within 120 calendar days of this letter.

This shared system REMS, known as the Mifepristone REMS Program, currently includes those products listed on the FDA REMS website[3].

Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS must be revised to one year from the date of the approval of the modified SSS REMS (1/3/2023) and annually thereafter.

The revised REMS assessment plan must include, but is not limited to, the following:

Program Implementation and Operations

1. REMS Certification Statistics
   a. Prescribers
      i. Number of certified prescribers who have certified with the Sponsor's distributor(s) and number who have submitted *Prescriber Agreement Forms* to Certified Pharmacies
      ii. Number and percentage of newly certified prescribers
      iii. Number and percentage of active certified prescribers (i.e., who ordered mifepristone or submitted a prescription during the reporting period)

   b. Pharmacies

[3] https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

i. Number of certified pharmacies
ii. Number and percentage of newly certified pharmacies
iii. Number and percentage of active certified pharmacies (i.e., that dispensed mifepristone during the reporting period)

c. Wholesalers/Distributors
i. Number of authorized wholesalers/distributors
ii. Number and percentage of newly authorized wholesalers/distributors
iii. Number and percentage of active authorized wholesalers/distributors (i.e. that shipped mifepristone during the reporting period)

2. Utilization Data
a. Total number of tablets shipped by wholesalers/distributors, stratified by Certified Prescriber or Certified Pharmacy location
b. Number of prescriptions dispensed from pharmacies

3. REMS Compliance Data
a. Audits: Summary of audit activities for each stakeholder (i.e., certified pharmacies and wholesalers/distributors) including but not limited to:
i. A copy of the final audit plan for each stakeholder type (provide for the current reporting period)
ii. The number of audits expected, and the number of audits performed
iii. The number and type of deficiencies noted
iv. For those with deficiencies noted, report the corrective and preventive actions (CAPAs) required, if any, to address the deficiencies, including the status (e.g., completed, not completed, in progress) (provide for the current reporting period)
v. For any stakeholders that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken (provide for the current reporting period)
vi. A summary report of all resulting changes to processes and procedures necessary to ensure compliance with the REMS requirements (provide for the current reporting period)

b. A summary report of non-compliance, associated corrective action plans (CAPAs), and the status of CAPAs including but not limited to:
i. A copy of the final non-compliance plans for Pharmacies and Distributors (provide for the current reporting period)
ii. For each instance of noncompliance below (iii-v), report the following information (provide for the current reporting period):
1. A unique, anonymized ID for the stakeholder(s) associated with the non-compliance event to enable tracking over time
2. The source of the non-compliance data (e.g., self-reported, audit, other)
3. A root cause analysis of the non-compliance

4. Actions to prevent future occurrences and outcomes of such actions

iii. Prescriber compliance

1. Number and percentage of certified prescribers who became decertified as a result of non- compliance
   - Provide a summary of reasons for decertification (provide for the current reporting period)
2. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

iv. Pharmacy compliance

1. Number and percentage of prescriptions dispensed that were written by prescriber(s) who did not submit a Prescriber Agreement to the dispensing Certified Pharmacy
2. Number and percentage of mifepristone tablets dispensed by non-certified pharmacies
3. Number and percentage of pharmacies that became decertified as a result of non- compliance
   - Provide a summary of reasons for decertification (provide for the current reporting period)
4. An assessment of prescription delivery timelines, including percentage delivered more than four days after receipt of the prescription, duration and causes for delay. A proposal for this assessment will be submitted within 60 days of the approval of the REMS Modification.
5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

v. Wholesaler/distributor compliance

1. Number of healthcare providers who successfully ordered mifepristone who were not certified
2. Number of non-certified pharmacies that successfully ordered mifepristone
3. Number of shipments sent to non-certified prescriber receiving locations
4. Number of shipments sent to non-certified pharmacy receiving locations
5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

Overall Assessment of REMS Effectiveness

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a

proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively,

updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g.,
ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 020687 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 020687/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 020687/S-000/
PRIOR APPROVAL SUPPLEMENT

PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 020687/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 020687

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov
.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call (b) (6)

Sincerely,

{See appended electronic signature page}

(b) (6)

Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - REMS Document
  - Prescriber Agreement
  - Patient Agreement Form
  - Pharmacy Agreement Form

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (6)

01/03/2023 05:35:41 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s025

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MIFEPREX safely and effectively. See full prescribing information for MIFEPREX.

MIFEPREX® (mifepristone) tablets, for oral use
Initial U.S. Approval: 2000

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

See full prescribing information for complete boxed warning.

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use.

- **Atypical Presentation of Infection. Patients with serious bacterial infections and sepsis can present without fever, bacteremia or significant findings on pelvic examination. A high index of suspicion is needed to rule out serious infection and sepsis. (5.1)**
- **Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. (5.2)**

MIFEPREX is only available through a restricted program called the mifepristone REMS Program (5.3).

Before prescribing MIFEPREX, inform the patient about these risks. Ensure the patient knows whom to call and what to do if they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort or general malaise for more than 24 hours after taking misoprostol.

----------INDICATIONS AND USAGE----------

MIFEPREX is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. (1)

----------DOSAGE AND ADMINISTRATION----------

- 200 mg MIFEPREX on Day 1, followed 24-48 hours after MIFEPREX dosing by 800 mcg buccal misoprostol. (2.1)
- Instruct the patient what to do if significant adverse reactions occur. (2.2)
- Follow-up is needed to confirm complete termination of pregnancy. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card (3)

----------CONTRAINDICATIONS----------

- Confirmed/suspected ectopic pregnancy or undiagnosed adnexal mass (4)
- Chronic adrenal failure (4)
- Concurrent long-term corticosteroid therapy (4)
- History of allergy to mifepristone, misoprostol, or other prostaglandins (4)
- Hemorrhagic disorders or concurrent anticoagulant therapy (4)
- Inherited porphyria (4)
- Intrauterine device (IUD) in place (4)

----------WARNINGS AND PRECAUTIONS----------

- Ectopic pregnancy: Exclude before treatment. (5.4)
- Rhesus immunization: Prevention needed as for surgical abortion. (5.5)

----------ADVERSE REACTIONS----------

Most common adverse reactions (>15%) are nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Danco Laboratories, LLC at 1-877-432-7596 or medicaldirector@earlyoptionpill.com or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- CYP3A4 inducers can lower mifepristone concentrations. (7.1)
- CYP3A4 inhibitors can increase mifepristone concentrations. Use with caution. (7.2)
- CYP3A4 substrate concentrations can be increased. Caution with coadministration of substrates with narrow therapeutic margin. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Risk of fetal malformations in ongoing pregnancy if not terminated is unknown. (8.1)

See 17 for PATIENT COUNSELING INFORMATION, Medication Guide.

Revised: 01/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use. No causal relationship between the use of MIFEPREX and misoprostol and these events has been established.

- **Atypical Presentation of Infection. Patients with serious bacterial infections (e.g., *Clostridium sordellii*) and sepsis can present without fever, bacteremia, or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis *[see Warnings and Precautions (5.1)]*.**
- **Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding *[see Warnings and Precautions (5.2)]*.**

Because of the risks of serious complications described above, MIFEPREX is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the mifepristone REMS Program *[see Warnings and Precautions (5.3)]*.

Before prescribing MIFEPREX, inform the patient about the risk of these serious events. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting, or diarrhea) for more than 24 hours after taking misoprostol.

1 INDICATIONS AND USAGE

MIFEPREX is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Regimen

For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period. The duration of pregnancy may be determined from menstrual history and clinical examination. Assess the pregnancy by ultrasonographic scan if the duration of pregnancy is uncertain or if ectopic pregnancy is suspected.

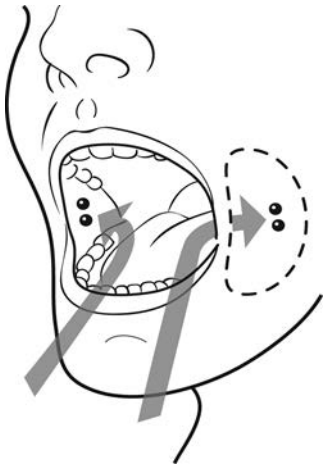
Remove any intrauterine device (“IUD”) before treatment with MIFEPREX begins [*see Contraindications (4)*].

The dosing regimen for MIFEPREX and misoprostol is:

- MIFEPREX 200 mg orally + misoprostol 800 mcg buccally
  - *Day One:* MIFEPREX Administration
    One 200 mg tablet of MIFEPREX is taken in a single oral dose.
  - *Day Two or Three:* Misoprostol Administration (minimum 24-hour interval between MIFEPREX and misoprostol)
    Four 200 mcg tablets (total dose 800 mcg) of misoprostol are taken by the buccal route.

    Tell the patient to place two 200 mcg misoprostol tablets in each cheek pouch (the area between the cheek and gums) for 30 minutes and then swallow any remnants with water or another liquid (see Figure 1).

    Figure 1

    2 pills between cheek and gum on left side + 2 pills between cheek and gum on right side

Patients taking MIFEPREX must take misoprostol within 24 to 48 hours after taking MIFEPREX. The effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours or more than 48 hours after mifepristone administration.

Because most women will expel the pregnancy within 2 to 24 hours of taking misoprostol *[see Clinical Studies (14)]*, discuss with the patient an appropriate location for them to be when taking the misoprostol, taking into account that expulsion could begin within 2 hours of administration.

2.2 Patient Management Following Misoprostol Administration

During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms *[see Adverse Reactions (6)].*

Give the patient:

- Instructions on what to do if significant discomfort, excessive vaginal bleeding or other adverse reactions occur
- A phone number to call if the patient has questions following the administration of the misoprostol
- The name and phone number of the healthcare provider who will be handling emergencies.

2.3 Post-treatment Assessment: Day 7 to 14

Patients should follow-up with their healthcare provider approximately 7 to 14 days after the administration of MIFEPREX. This assessment is very important to confirm that complete termination of pregnancy has occurred and to evaluate the degree of bleeding. Termination can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan. Lack of bleeding following treatment usually indicates failure; however, prolonged or heavy bleeding is not proof of a complete abortion.

The existence of debris in the uterus (e.g., if seen on ultrasonography) following the treatment procedure will not necessarily require surgery for its removal.

Patients should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of women may experience some type of bleeding for more than 30 days. Persistence of heavy or moderate vaginal bleeding at the time of follow-up, however, could indicate an incomplete abortion.

If complete expulsion has not occurred, but the pregnancy is not ongoing, patients may be treated with another dose of misoprostol 800 mcg buccally. There have been rare reports of uterine rupture in women who took MIFEPREX and misoprostol, including women with prior uterine rupture or uterine scar and women who received multiple doses of misoprostol within 24 hours. Patients who choose to use a repeat dose of misoprostol should have a follow-up visit with their healthcare provider in approximately 7 days to assess for complete termination.

Surgical evacuation is recommended to manage ongoing pregnancies after medical abortion *[see Use in Specific Populations (8.1)]*. Advise the patient whether you will provide such care or will refer them to another provider as part of counseling prior to prescribing MIFEPREX.

2.4 Contact for Consultation

For consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4 Early Option (1-877-432-7596).

3 DOSAGE FORMS AND STRENGTHS

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card. MIFEPREX tablets are light yellow, cylindrical, and bi-convex tablets, approximately 11 mm in diameter and imprinted on one side with “MF.”

4 CONTRAINDICATIONS

- Administration of MIFEPREX and misoprostol for the termination of pregnancy (the “treatment procedure”) is contraindicated in patients with any of the following conditions:
  - Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy) *[see Warnings and Precautions (5.4)]*
  - Chronic adrenal failure (risk of acute adrenal insufficiency)
  - Concurrent long-term corticosteroid therapy (risk of acute adrenal insufficiency)
  - History of allergy to mifepristone, misoprostol, or other prostaglandins (allergic reactions including anaphylaxis, angioedema, rash, hives, and itching have been reported *[see Adverse Reactions (6.2)]*)
  - Hemorrhagic disorders or concurrent anticoagulant therapy (risk of heavy bleeding)

- Inherited porphyrias (risk of worsening or of precipitation of attacks)

- Use of MIFEPREX and misoprostol for termination of intrauterine pregnancy is contraindicated in patients with an intrauterine device ("IUD") in place (the IUD might interfere with pregnancy termination). If the IUD is removed, MIFEPREX may be used.

5 WARNINGS AND PRECAUTIONS

5.1 Infection and Sepsis

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of MIFEPREX *[see Boxed Warning]*. Healthcare providers evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. A sustained (> 4 hours) fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (e.g., from *Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting, or diarrhea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. No causal relationship between MIFEPREX and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

5.2 Uterine Bleeding

Uterine bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications, and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock. Counsel patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion *[see Boxed Warning]*.

Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of all subjects may experience some type of bleeding for 30 days or more. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.

Decreases in hemoglobin concentration, hematocrit, and red blood cell count may occur in patients who bleed heavily.

Excessive uterine bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, surgical uterine evacuation, administration of saline infusions, and/or blood transfusions. Based on data from several large clinical trials, vasoconstrictor drugs were used in 4.3% of all subjects, there was a decrease in hemoglobin of more than 2 g/dL in 5.5% of subjects, and blood transfusions were administered to ≤ 0.1% of subjects. Because heavy bleeding requiring surgical uterine evacuation occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

5.3 Mifepristone REMS Program

MIFEPREX is available only through a restricted program under a REMS called the mifepristone REMS Program, because of the risks of serious complications *[see Warnings and Precautions (5.1, 5.2)]*.

Notable requirements of the mifepristone REMS Program include the following:

- Prescribers must be certified with the program by completing the Prescriber Agreement Form.
- Patients must sign a Patient Agreement Form.
- MIFEPREX must only be dispensed to patients by or under the supervision of a certified prescriber, or by certified pharmacies on prescriptions issued by certified prescribers.

Further information is available at 1-877-4 Early Option (1-877-432-7596).

5.4 Ectopic Pregnancy

MIFEPREX is contraindicated in patients with a confirmed or suspected ectopic pregnancy because MIFEPREX is not effective for terminating ectopic pregnancies *[see Contraindications (4)].* Healthcare providers should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy because some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed MIFEPREX.

Patients who became pregnant with an IUD in place should be assessed for ectopic pregnancy.

5.5 Rhesus Immunization

The use of MIFEPREX is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Infection and sepsis *[see Warnings and Precautions (5.1)]*
- Uterine bleeding *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Information presented on common adverse reactions relies solely on data from U.S. studies, because rates reported in non-U.S. studies were markedly lower and are not likely generalizable to the U.S. population. In three U.S. clinical studies totaling 1,248 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally, women reported adverse reactions in diaries and in interviews at the follow-up visit. These studies enrolled generally healthy women of reproductive age without contraindications to mifepristone or misoprostol use according to the MIFEPREX product label. Gestational age was assessed prior to study enrollment using the date of the woman's last menstrual period, clinical evaluation, and/or ultrasound examination.

About 85% of patients report at least one adverse reaction following administration of MIFEPREX and misoprostol, and many can be expected to report more than one such reaction. The most commonly reported adverse reactions (>15%) were nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness (see Table 1). The frequency of adverse reactions varies between studies and may be dependent on many factors, including the patient population and gestational age.

Abdominal pain/cramping is expected in all medical abortion patients and its incidence is not reported in clinical studies. Treatment with MIFEPREX and misoprostol is designed to induce uterine bleeding and cramping to cause termination of an intrauterine pregnancy. Uterine bleeding and cramping are expected consequences of the action of MIFEPREX and misoprostol as used in the treatment procedure. Most patients can expect bleeding more heavily than they do during a heavy menstrual period *[see Warnings and Precautions (5.2)]*.

Table 1 lists the adverse reactions reported in U.S. clinical studies with incidence >15% of women.

Table 1
Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. Clinical Studies

Adverse Reaction	# U.S. studies	Number of Evaluable Women	Range of frequency (%)	Upper Gestational Age of Studies Reporting Outcome
Nausea	3	1,248	51-75%	70 days
Weakness	2	630	55-58%	63 days
Fever/chills	1	414	48%	63 days
Vomiting	3	1,248	37-48%	70 days
Headache	2	630	41-44%	63 days
Diarrhea	3	1,248	18-43%	70 days
Dizziness	2	630	39-41%	63 days

One study provided gestational-age stratified adverse reaction rates for women who were 57-63 and 64-70 days; there was little difference in frequency of the reported common adverse reactions by gestational age.

Information on serious adverse reactions was reported in six U.S. and four non-U.S. clinical studies, totaling 30,966 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally. Serious adverse reaction rates were similar between U.S. and non-U.S. studies, so rates from both U.S. and non-U.S. studies are presented. In the U.S. studies, one studied women through 56 days gestation, four through 63 days gestation, and one through 70 days gestation, while in the non-U.S. studies, two studied women through 63 days gestation, and two through 70 days gestation. Serious adverse reactions were reported in <0.5% of women. Information from the U.S. and non-U.S. studies is presented in Table 2.

Table 2
Serious Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. and Non-U.S. Clinical Studies

Adverse Reaction	U.S.			Non-U.S.		
	# of studies	Number of Evaluable Women	Range of frequency (%)	# of studies	Number of Evaluable Women	Range of frequency (%)
Transfusion	4	17,774	0.03-0.5%	3	12,134	0-0.1%
Sepsis	1	629	0.2%	1	11,155	<0.01%*
ER visit	2	1,043	2.9-4.6%	1	95	0
Hospitalization Related to Medical Abortion	3	14,339	0.04-0.6%	3	1,286	0-0.7%
Infection without sepsis	1	216	0	1	11,155	0.2%
Hemorrhage	NR	NR	NR	1	11,155	0.1%

NR= Not reported
* This outcome represents a single patient who experienced death related to sepsis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of MIFEPREX and misoprostol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and infestations: post-abortal infection (including endometritis, endomyometritis, parametritis, pelvic infection, pelvic inflammatory disease, salpingitis)
Blood and the lymphatic system disorders: anemia
Immune system disorders: allergic reaction (including anaphylaxis, angioedema, hives, rash, itching)
Psychiatric disorders: anxiety
Cardiac disorders: tachycardia (including racing pulse, heart palpitations, heart pounding)
Vascular disorders: syncope, fainting, loss of consciousness, hypotension (including orthostatic), light-headedness
Respiratory, thoracic and mediastinal disorders: shortness of breath
Gastrointestinal disorders: dyspepsia
Musculoskeletal, connective tissue and bone disorders: back pain, leg pain
Reproductive system and breast disorders: uterine rupture, ruptured ectopic pregnancy, hematometra, leukorrhea
General disorders and administration site conditions: pain

7 DRUG INTERACTIONS

7.1 Drugs that May Reduce MIFEPREX Exposure (Effect of CYP 3A4 Inducers on MIFEPREX)

CYP450 3A4 is primarily responsible for the metabolism of mifepristone. CYP3A4 inducers such as rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (such as phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum concentrations of mifepristone). Whether this action has an impact on the efficacy of the dose

regimen is unknown. Refer to the follow-up assessment *[see Dosage and Administration (2.3)]* to verify that treatment has been successful.

7.2 Drugs that May Increase MIFEPREX Exposure (Effect of CYP 3A4 Inhibitors on MIFEPREX)

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum concentrations of mifepristone). MIFEPREX should be used with caution in patients currently or recently treated with CYP 3A4 inhibitors.

7.3 Effects of MIFEPREX on Other Drugs (Effect of MIFEPREX on CYP 3A4 Substrates)

Based on *in vitro* inhibition information, coadministration of mifepristone may lead to an increase in serum concentrations of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

MIFEPREX is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Risks to pregnant patients are discussed throughout the labeling.

Refer to misoprostol labeling for risks to pregnant patients with the use of misoprostol.

The risk of adverse developmental outcomes with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol is unknown; however, the process of a failed pregnancy termination could disrupt normal embryo-fetal development and result in adverse developmental effects. Birth defects have been reported with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol. In animal reproduction studies, increased fetal losses were observed in mice, rats, and rabbits and skull deformities were observed in rabbits with administration of mifepristone at doses lower than the human exposure level based on body surface area.

Data

Animal Data

In teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure based on body surface area), because of the antiprogestational activity of mifepristone,fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from inhibition of progesterone action.

8.2 Lactation

MIFEPREX is present in human milk. Limited data demonstrate undetectable to low levels of the drug in human milk with the relative (weight-adjusted) infant dose 0.5% or less as compared to maternal dosing. There is no information on the effects of MIFEPREX in a regimen with

misoprostol in a breastfed infant or on milk production. Refer to misoprostol labeling for lactation information with the use of misoprostol. The developmental and health benefits of breast-feeding should be considered along with any potential adverse effects on the breast-fed child from MIFEPREX in a regimen with misoprostol.

8.4 Pediatric Use

Safety and efficacy of MIFEPREX have been established in pregnant females. Data from a clinical study of MIFEPREX that included a subset of 322 females under age 17 demonstrated a safety and efficacy profile similar to that observed in adults.

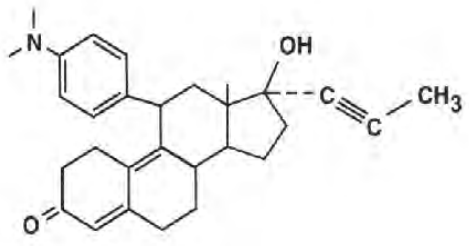
10 OVERDOSAGE

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than 1800 mg (ninefold the recommended dose for medical abortion). If a patient ingests a massive overdose, the patient should be observed closely for signs of adrenal failure.

11 DESCRIPTION

MIFEPREX tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical, and bi-convex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11ß-[*p*-(Dimethylamino)phenyl]-17ß-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is $C_{29}H_{35}NO_2$. Its structural formula is:



The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 192-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit, and monkey), the compound inhibits the activity of endogenous or exogenous progesterone, resulting in effects on the uterus and cervix that, when combined with misoprostol, result in termination of an intrauterine pregnancy.

During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity

of prostaglandins.

12.2 Pharmacodynamics

Use of MIFEPREX in a regimen with misoprostol disrupts pregnancy by causing decidual necrosis, myometrial contractions, and cervical softening, leading to the expulsion of the products of conception.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women.

Antiglucocorticoid and antiandrogenic activity: Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity. The activity of the glucocorticoid dexamethasone in rats was inhibited following doses of 10 to 25 mg/kg of mifepristone. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotropic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

12.3 Pharmacokinetics

Mifepristone is rapidly absorbed after oral ingestion with non-linear pharmacokinetics for Cmax after single oral doses of 200 mg and 600 mg in healthy subjects.

Absorption

The absolute bioavailability of a 20 mg mifepristone oral dose in females of childbearing age is 69%. Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 ± 1.0 mg/L occurring approximately 90 minutes after ingestion.

Following oral administration of a single dose of 200 mg in healthy men (n=8), mean Cmax was 1.77 ± 0.7 mg/L occurring approximately 45 minutes after ingestion. Mean $AUC_{0-\infty}$ was 25.8 ± 6.2 mg*hr/L.

Distribution

Mifepristone is 98% bound to plasma proteins, albumin, and α_1-acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance.

Elimination

Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11ß; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Excretion

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum concentrations are undetectable by 11 days.

Specific Populations

The effects of age, hepatic disease and renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed.

Mutagenesis

Results from studies conducted *in vitro* and in animals have revealed no genotoxic potential for mifepristone. Among the tests carried out were: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pompe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; *in vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice.

Impairment of Fertility

In rats, administration of 0.3 mg/kg mifepristone per day caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effects on reproductive performance were observed.

14 CLINICAL STUDIES

Safety and efficacy data from clinical studies of mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally through 70 days gestation are reported below. Success was defined as the complete expulsion of the products of conception without the need for surgical intervention. The overall rates of success and failure, shown by reason for failure based on 22 worldwide clinical studies (including 7 U.S. studies) appear in Table 3.

The demographics of women who participated in the U.S. clinical studies varied depending on study location and represent the racial and ethnic variety of American females. Females of all reproductive ages were represented, including females less than 18 and more than 40 years of age; most were 27 years or younger.

Table 3
Outcome Following Treatment with Mifepristone (oral) and Misoprostol (buccal) Through 70 Days Gestation

	U.S. Trials	Non-U.S. Trials
N	16,794	18,425
Complete Medical Abortion	97.4%	96.2%
Surgical Intervention*	2.6%	3.8%
Ongoing Pregnancy**	0.7%	0.9%

* Reasons for surgical intervention include ongoing pregnancy, medical necessity, persistent or heavy bleeding after treatment, patient request, or incomplete expulsion.
** Ongoing pregnancy is a subcategory of surgical intervention, indicating the percent of women who have surgical intervention due to an ongoing pregnancy.

The results for clinical studies that reported outcomes, including failure rates for ongoing pregnancy, by gestational age are presented in Table 4.

Table 4
Outcome by Gestational Age Following Treatment with Mifepristone and Misoprostol (buccal) for U.S. and Non-U.S. Clinical Studies

	≤49 days			50-56 days			57-63 days			64-70 days		
	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies
Complete medical abortion	12,046	98.1	10	3,941	96.8	7	2,294	94.7	9	479	92.7	4
Surgical intervention for ongoing pregnancy	10,272	0.3	6	3,788	0.8	6	2,211	2	8	453	3.1	3

One clinical study asked subjects through 70 days gestation to estimate when they expelled the pregnancy, with 70% providing data. Of these, 23-38% reported expulsion within 3 hours and over 90% within 24 hours of using misoprostol.

16 HOW SUPPLIED/STORAGE AND HANDLING

is only available through a restricted program called the Mifepristone REMS Program *[see Warnings and Precautions (5.3)].*

MIFEPREX is supplied as light yellow, cylindrical, and bi-convex tablets imprinted on one side with “MF.” Each tablet contains 200 mg of mifepristone. One tablet is individually blistered on one blister card that is packaged in an individual package (National Drug Code 64875-001-01).

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide), included with each package of MIFEPREX. Additional copies of the Medication Guide are available by contacting Danco Laboratories at 1-877-4 Early Option (1-877-432-7596) or from www.earlyoptionpill.com.

Serious Infections and Bleeding

- Inform the patient that uterine bleeding and uterine cramping will occur [*see Warnings and Precautions (5.2)*].
- Advise the patient that serious and sometimes fatal infections and bleeding can occur very rarely [*see Warnings and Precautions (5.1, 5.2)*].
- MIFEPREX is only available through a restricted program called the Mifepristone REMS Program [*see Warnings and Precautions (5.3)*]. Under the mifepristone REMS Program:
    - Patients must sign a Patient Agreement Form.
    - MIFEPREX is only dispensed by or under the supervision of certified prescribers or by certified pharmacies on prescriptions issued by certified prescribers.

Provider Contacts and Actions in Case of Complications

- Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, or if the patient experiences complications including prolonged heavy bleeding, severe abdominal pain, or sustained fever *[see Boxed Warning]*.
-

Compliance with Treatment Schedule and Follow-up Assessment

- Advise the patient that it is necessary to complete the treatment schedule, including a follow-up assessment approximately 7 to14 days after taking MIFEPREX *[see Dosage and Administration (2.3)]*.
- Explain that
    - prolonged heavy vaginal bleeding is not proof of a complete abortion,
    - if the treatment fails and the pregnancy continues, the risk of fetal malformation is unknown,
    - it is recommended that ongoing pregnancy be managed by surgical termination *[see Dosage and Administration (2.3)]*. Advise the patient whether you will provide such care or will refer them to another provider.

Subsequent Fertility

- Inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses.
- Inform the patient that contraception can be initiated as soon as pregnancy expulsion has been confirmed, or before resuming sexual intercourse.

MIFEPREX is a registered trademark of Danco Laboratories, LLC.

Manufactured for:
Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

01/2023

MEDICATION GUIDE

Mifeprex (MIF-eh-prex) (mifepristone tablets, for oral use

Read this information carefully before taking Mifeprex and misoprostol. It will help you understand how the treatment works. This Medication Guide does not take the place of talking with your healthcare provider.

What is the most important information I should know about Mifeprex?

What symptoms should I be concerned with? Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Seeking medical attention as soon as possible is needed in these circumstances. Serious infection has resulted in death in a very small number of cases. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your healthcare provider. You can write down your healthcare provider's telephone number here _____.

Be sure to contact your healthcare provider promptly if you have any of the following:

- **Heavy Bleeding.** Contact your healthcare provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C).
- **Abdominal Pain or "Feeling Sick."** If you have abdominal pain or discomfort, or you are "feeling sick," including weakness, nausea, vomiting, or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your healthcare provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).
- **Fever.** In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your healthcare provider right away. Fever may be a symptom of a serious infection or another problem.

If you cannot reach your healthcare provider, go to the nearest hospital emergency room.

What to do if you are still pregnant after Mifeprex with misoprostol treatment. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy. In many cases, this surgical procedure can be done in the office/clinic. The chance of birth defects if the pregnancy is not ended is unknown.

Talk with your healthcare provider. Before you take Mifeprex, you should read this Medication Guide and you and your healthcare provider should discuss the benefits and risks of your using Mifeprex.

What is Mifeprex?

Mifeprex is used in a regimen with another prescription medicine called misoprostol, to end an early pregnancy. Early pregnancy means it is 70 days (10 weeks) or less since your last menstrual period began. Mifeprex is not approved for ending pregnancies that are further along. Mifeprex blocks a hormone needed for your pregnancy to continue. When you use Mifeprex on Day 1, you also need to take another medicine called misoprostol 24 to 48 hours after you take Mifeprex, to cause the pregnancy to be passed from your uterus.

The pregnancy is likely to be passed from your uterus within 2 to 24 hours after taking Mifeprex and misoprostol. When the pregnancy is passed from the uterus, you will have bleeding and cramping that will likely be heavier than your usual period. About 2 to 7 out of 100 women taking Mifeprex will need a surgical procedure because the pregnancy did not completely pass from the uterus or to stop bleeding.

Who should not take Mifeprex?

Some patients should not take Mifeprex. Do not take Mifeprex if you:

- Have a pregnancy that is more than 70 days (10 weeks). Your healthcare provider may do a clinical examination, an ultrasound examination, or other testing to determine how far along you are in pregnancy.
- Are using an IUD (intrauterine device or system). It must be taken out before you take Mifeprex.
- Have been told by your healthcare provider that you have a pregnancy outside the uterus (ectopic pregnancy).
- Have problems with your adrenal glands (chronic adrenal failure).
- Take a medicine to thin your blood.
- Have a bleeding problem.
- Have porphyria.
- Take certain steroid medicines.
- Are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Ask your healthcare provider if you are not sure about all your medical conditions before taking this medicine to find out if you can take Mifeprex.

What should I tell my healthcare provider before taking Mifeprex?

Before you take Mifeprex, tell your healthcare provider if you:

- cannot follow-up within approximately 7 to 14 days of your first visit
- are breastfeeding. Mifeprex can pass into your breast milk. The effect of the Mifeprex and misoprostol regimen on the breastfed infant or on milk production is unknown.
- are taking medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
  Mifeprex and certain other medicines may affect each other if they are used together. This can cause side effects.

How should I take Mifeprex?

- Mifeprex will be given to you by a healthcare provider or pharmacy.
- You and your healthcare provider will plan the most appropriate location for you to take the misoprostol, because it may cause bleeding, cramps, nausea, diarrhea, and other symptoms that usually begin within 2 to 24 hours after taking it.
- Most women will pass the pregnancy within 2 to 24 hours after taking the misoprostol tablets.

Follow the instruction below on how to take Mifeprex and misoprostol:

<u>Mifeprex (1 tablet) orally + misoprostol (4 tablets) buccally</u>

Day 1:

- Take 1 Mifeprex tablet by mouth.

24 to 48 hours after taking Mifeprex:

- Take 4 misoprostol tablets by placing 2 tablets in each cheek pouch (the area between your teeth and cheek - see Figure A) for 30 minutes and then swallow anything left over with a drink of water or another liquid.
- The medicines may not work as well if you take misoprostol sooner than 24 hours after Mifeprex or later than 48 hours after Mifeprex.
- Misoprostol often causes cramps, nausea, diarrhea, and other symptoms. Your healthcare provider may send you home with medicines for these symptoms.

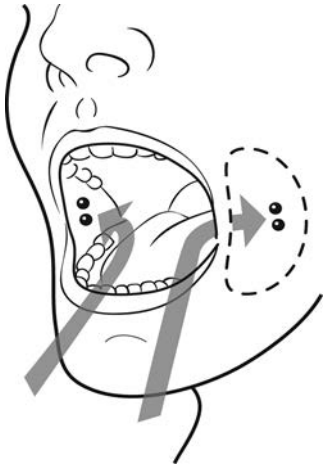


Figure A (2 tablets between your left cheek and gum and 2 tablets between your right cheek and gum).

Follow-up Assessment at Day 7 to 14:

- This follow-up assessment is very important. You must follow-up with your healthcare provider about 7 to 14 days after you have taken Mifeprex to be sure you are well and that you have had bleeding and the pregnancy has passed from your uterus.
- Your healthcare provider will assess whether your pregnancy has passed from your uterus. If your pregnancy continues, the chance that there may be birth defects is unknown. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy.
- If your pregnancy has ended, but has not yet completely passed from your uterus, your provider will talk with you about other choices you have, including waiting, taking another dose of misoprostol, or having a surgical procedure to empty your uterus.

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

What should I avoid while taking Mifeprex and misoprostol?

Do not take any other prescription or over-the-counter medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your healthcare provider about them because they may interfere with the treatment. Ask your healthcare provider about what medicines you can take for pain and other side effects.

What are the possible side effects of Mifeprex and misoprostol?

Mifeprex may cause serious side effects. See "What is the most important information I should know about Mifeprex?"

Cramping and bleeding. Cramping and vaginal bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must follow-up with your healthcare provider approximately 7 to 14 days after taking Mifeprex. See "How should I take Mifeprex?" for more information on your follow-up assessment. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take 24 to 48 hours after Mifeprex. Bleeding or spotting can be expected for an average of 9 to16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of passing the pregnancy.

The most common side effects of Mifeprex treatment include: nausea, weakness, fever/chills, vomiting, headache, diarrhea and dizziness. Your provider will tell you how to manage any pain or other side effects. These are not all the possible side effects of Mifeprex.

Call your healthcare provider for medical advice about any side effects that bother you or do not go away. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Mifeprex.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about Mifeprex. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider for information about Mifeprex that is written for healthcare professionals.

For more information about Mifeprex, go to www.earlyoptionpill.com or call 1-877-4 Early Option (1-877-432-7596).

Manufactured for: *Danco Laboratories, LLC*
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596) www.earlyoptionpill.com

This Medication Guide has been approved by the U.S. Food and Drug Administration. Approval 01/2023

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s025

REMS

Initial Shared System REMS approval: 04/2019
Most Recent Modification: 01/2023

Mifepristone Tablets, 200 mg
Progestin Antagonist

RISK EVALUATION AND MITIGATION STRATEGY (REMS)
SINGLE SHARED SYSTEM FOR MIFEPRISTONE 200 MG

I. GOAL

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.

b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.

c) Informing patients about the risk of serious complications associated with mifepristone.

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe mifepristone must be specially certified.
   a. To become specially certified to prescribe mifepristone, healthcare providers must:
      i. Review the Prescribing Information for mifepristone.
      ii. Complete a *Prescriber Agreement Form*. By signing[1] a *Prescriber Agreement Form*, prescribers agree that:
         1) They have the following qualifications:
            a) Ability to assess the duration of pregnancy accurately
            b) Ability to diagnose ectopic pregnancies
            c) Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
         2) They will follow the guidelines for use of mifepristone (see b.i-vii below).
   b. As a condition of certification, prescribers must follow the guidelines for use of mifepristone described below:
      i. Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
      ii. Ensure that the healthcare provider and patient sign the *Patient Agreement Form.*

[1] In this REMS, the terms "sign" and "signature" include electronic signatures.

Reference ID: 5103833

iii. Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.

iv. Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.

v. Ensure that any deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

vi. If mifepristone will be dispensed by a certified pharmacy:

1) Provide the certified pharmacy a signed *Prescriber Agreement Form*.

2) Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.

3) Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of the patient.

vii. The certified prescriber who dispenses mifepristone or who supervises the dispensing of mifepristone must:

1) Provide an authorized distributor with a signed *Prescriber Agreement Form*.

2) Ensure that the NDC and lot number from each package of mifepristone dispensed are recorded in the patient's record.

3) Ensure that healthcare providers under their supervision follow guidelines i.-v.

c. Mifepristone Sponsors must:

i. Ensure that healthcare providers who prescribe their mifepristone are specially certified in accordance with the requirements described above and de-certify healthcare providers who do not maintain compliance with certification requirements.

ii. Ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*:

1) Within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies.

2) Within one year after approval of this modification, if previously certified and ordering from an authorized distributor.

iii. Ensure that healthcare providers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy.

iv. Provide the Prescribing Information and their *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.

v. Ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date.

The following materials are part of the Mifepristone REMS Program:

- *Prescriber Agreement Form for Danco Laboratories, LLC*
- *Prescriber Agreement Form for GenBioPro, Inc.*
- *Patient Agreement Form*

2. Pharmacies that dispense mifepristone must be specially certified
    a. To become specially certified to dispense mifepristone, pharmacies must:
        i. Be able to receive *Prescriber Agreement Forms* by email and fax.
        ii. Be able to ship mifepristone using a shipping service that provides tracking information.
        iii. Designate an authorized representative to carry out the certification process on behalf of the pharmacy.
        iv. Ensure the authorized representative oversees implementation and compliance with the Mifepristone REMS Program by doing the following:
            1) Review the Prescribing Information for mifepristone.
            2) Complete a *Pharmacy Agreement Form*. By signing a *Pharmacy Agreement Form*, the authorized representative agrees that the pharmacy will put processes and procedures in place to ensure the following requirements are completed:
                a) Verify that the prescriber is certified by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with the pharmacy.
                b) Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in c) below.
                c) Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
                d) Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.
                e) Track and verify receipt of each shipment of mifepristone.
                f) Dispense mifepristone in its package as supplied by the Mifepristone Sponsor.
                g) Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to the Mifepristone Sponsor that provided the mifepristone. Notify the Mifepristone Sponsor that provided the dispensed mifepristone that the pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
                h) Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
                i) Maintain records of *Prescriber Agreement Forms*.
                j) Maintain records of dispensing and shipping.
                k) Maintain records of all processes and procedures including compliance with those processes and procedures.
                l) Maintain the identity of the patient and prescriber as confidential, including limiting access to patient and prescriber identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes.
                m) Train all relevant staff on the Mifepristone REMS Program requirements.

n) Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

b. Mifepristone Sponsors must:

i. Ensure that pharmacies are specially certified in accordance with the requirements described above and de-certify pharmacies that do not maintain compliance with certification requirements.

ii. Ensure that pharmacies can complete the certification process by email and fax to an authorized distributor.

i. Verify annually that the name and contact information for the pharmacy's authorized representative corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, require the pharmacy to recertify with the new authorized representative.

The following materials are part of the Mifepristone REMS Program:

- *Pharmacy Agreement Form for Danco Laboratories, LLC*
- *Pharmacy Agreement Form for GenBioPro, Inc.*

3. Mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions as ensured by the certified prescriber in signing the *Prescriber Agreement Form*.

a. The patient must sign a *Patient Agreement Form* indicating that the patient has:

i. Received, read and been provided a copy of the *Patient Agreement Form*.

ii. Received counseling from the healthcare provider regarding the risk of serious complications associated with mifepristone.

B. Implementation System

1. Mifepristone Sponsors must ensure that their mifepristone is only distributed to certified prescribers and certified pharmacies by:

a. Ensuring that distributors who distribute their mifepristone comply with the program requirements for distributors.

i. The distributors must put processes and procedures in place to:

1) Complete the certification process upon receipt of a *Prescriber Agreement Form* or *Pharmacy Agreement Form*.

2) Notify healthcare providers and pharmacies when they have been certified by the Mifepristone REMS Program.

3) Ship mifepristone only to certified pharmacies or locations identified by certified prescribers.

4) Not ship mifepristone to pharmacies or prescribers who become de-certified from the Mifepristone REMS Program.

5) Provide the Prescribing Information and their Prescriber Agreement Form to healthcare providers who (1) attempt to order mifepristone and are not yet certified, or (2) inquire about how to become certified.

ii. Put processes and procedures in place to maintain a distribution system that is secure,

confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, NDC and lot numbers, proof of delivery and controlled returns of mifepristone.

iii. Train all relevant staff on the Mifepristone REMS Program requirements.

iv. Comply with audits by Mifepristone Sponsors or a third party acting on behalf of Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed for the Mifepristone REMS Program. In addition, distributors must maintain appropriate documentation and make it available for audits.

b. Ensuring that distributors maintain secure and confidential distribution records of all shipments of mifepristone.

2. Mifepristone Sponsors must monitor their distribution data to ensure compliance with the Mifepristone REMS Program.

3. Mifepristone Sponsors must ensure that adequate records are maintained to demonstrate that the Mifepristone REMS Program requirements have been met, including, but not limited to records of mifepristone distribution; certification of prescribers and pharmacies; and audits of pharmacies and distributors. These records must be readily available for FDA inspections.

4. Mifepristone Sponsors must audit their new distributors within 90 calendar days and annually thereafter after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their distributor compliance if noncompliance is identified.

5. Mifepristone Sponsors must audit their certified pharmacies within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter audit certified pharmacies that have ordered mifepristone in the previous 12 months, to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their pharmacy compliance if noncompliance is identified.

6. Mifepristone Sponsors must take reasonable steps to improve implementation of and compliance with the requirements of the Mifepristone REMS Program based on monitoring and assessment of the Mifepristone REMS Program.

7. Mifepristone Sponsors must report to FDA any death associated with mifepristone whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the Mifepristone Sponsor. This requirement does not affect the sponsors' other reporting and follow-up requirements under FDA regulations.

C. Timetable for Submission of Assessments

The NDA Sponsor must submit REMS assessments to FDA one year from the date of the approval of the modified REMS (1/3/2023) and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 90 calendar days before the submission date for that assessment. The NDA Sponsor must submit each assessment so that it will be received by the FDA on or before the due date.

MIFEPREX® (Mifepristone) Tablets, 200 mg

PRESCRIBER AGREEMENT FORM

Mifeprex* (Mifepristone) Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To ***become a certified prescriber***, you must:

- **If you submit Mifeprex prescriptions for dispensing from certified pharmacies**:
  - Submit this form to each certified pharmacy to which you intend to submit Mifeprex prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order Mifeprex for dispensing by you or healthcare providers under your supervision:**
  - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
  - Healthcare settings, such as medical offices, clinics, and hospitals, where Mifeprex will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free), or by visiting www.earlyoptionpill.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received Mifeprex are reported to Danco Laboratories, LLC, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of Mifeprex that was dispensed to the patient.

*MIFEPREX is a registered trademark of Danco Laboratories, LLC
P.O. Box 4816-New York, NY 10185
1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

Ensure that healthcare providers under your supervision follow the guidelines listed above.

- If Mifeprex will be dispensed through a certified pharmacy:
  - Assess appropriateness of dispensing Mifeprex when contacted by a certified pharmacy about patients who will receive Mifeprex more than 4 calendar days after the prescription was received by the certified pharmacy.
  - Obtain the NDC and lot number of the package of Mifeprex the patient received in the event the prescriber becomes aware of the death of a patient.
- If Mifeprex will be dispensed by you or by healthcare providers under your supervision:
  - Ensure the NDC and lot number from each package of Mifeprex are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.

Approved 01/2023 [Doc control ID]

Mifepristone Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To ***become a certified prescriber***, you must:

- **If you submit mifepristone prescriptions for dispensing from certified pharmacies**:
  - Submit this form to each certified pharmacy to which you intend to submit mifepristone prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order mifepristone for dispensing by you or healthcare providers under your supervision:**
  - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
  - Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855—643-3463 toll-free), or by visiting www.MifeInfo.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received mifepristone are reported to GenBioPro, Inc. that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

Ensure that healthcare providers under your supervision follow the guidelines listed above.

- If mifepristone will be dispensed through a certified pharmacy:
  - Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.
  - Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of a patient.
- If mifepristone will be dispensed by you or by healthcare providers under your supervision:
  - Ensure the NDC and lot number from each package of mifepristone are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to **RxAgreements@GenBioPro.com** or fax to 1-877-239-8036

Approved 01/2023 [Doc control ID]

PATIENT AGREEMENT FORM Mifepristone Tablets, 200 mg

Healthcare Providers: *Counsel the patient on the risks of mifepristone. Both you and the patient must provide a written or electronic signature on this form.*

Patient Agreement:

1. I have decided to take mifepristone and misoprostol to end my pregnancy and will follow my healthcare provider's advice about when to take each drug and what to do in an emergency.
2. I understand:
   - **a.** I will take mifepristone on Day 1.
   - **b.** I will take the misoprostol tablets 24 to 48 hours after I take mifepristone.
3. My healthcare provider has talked with me about the risks, including:
   - heavy bleeding
   - infection
4. I will contact the clinic/office/provider right away if in the days after treatment I have:
   - a fever of 100.4°F or higher that lasts for more than four hours
   - heavy bleeding (soaking through two thick full-size sanitary pads per hour for two hours in a row)
   - severe stomach area (abdominal) pain or discomfort, or I am “feeling sick,” including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol
     — these symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

   My healthcare provider has told me that these symptoms listed above could require emergency care. If I cannot reach the clinic/office/provider right away, my healthcare provider has told me who to call and what to do.
5. I should follow up with my healthcare provider about 7 to 14 days after I take mifepristone to be sure that my pregnancy has ended and that I am well.
6. I know that, in some cases, the treatment will not work. This happens in about 2 to 7 out of 100 women who use this treatment. If my pregnancy continues after treatment with mifepristone and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy.
7. If I need a surgical procedure because the medicines did not end my pregnancy or to stop heavy bleeding, my healthcare provider has told me whether they will do the procedure or refer me to another healthcare provider who will.
8. I have the MEDICATION GUIDE for mifepristone.
9. My healthcare provider has answered all my questions.

Patient Signature: _____ **Patient Name** (print): _____ **Date**: _____

Provider Signature: _____ **Provider Name** (print): _____ **Date**: _____

Patient Agreement Forms may be provided, completed, signed, and transmitted in paper or electronically.

01/2023

MIFEPREX®(Mifepristone) Tablets, 200mg

PHARMACY AGREEMENT FORM

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense Mifeprex is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense Mifeprex is able to ship Mifeprex using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for Mifeprex. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free) or online at www.earlyoptionpill.com; and
- Each location of my pharmacy that will dispense Mifeprex will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting Mifeprex orders.
  - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
  - Dispense Mifeprex such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
  - Confirm with the prescriber the appropriateness of dispensing Mifeprex for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
  - Record in the patient's record the NDC and lot number from each package of Mifeprex dispensed.
  - Track and verify receipt of each shipment of Mifeprex.
  - Dispense mifepristone in its package as supplied by Danco Laboratories, LLC.
  - Report any patient deaths to the prescriber, including the NDC and lot number from the package of Mifeprex dispensed to the patient, and remind the prescriber of their obligation to report the deaths to Danco Laboratories, LLC. Notify Danco that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
  - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
  - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, and all processes and procedures including compliance with those processes and procedures.
  - Maintain the identity of Mifeprex patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance.
  - Train all relevant staff on the Mifepristone REMS Program requirements.
  - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____

DANCO
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*MIFEPREX is a registered trademark of Danco Laboratories, LLC

P.O. Box 4816-New York, NY 10185
1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred __ email __ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.

PHARMACY AGREEMENT FORM **Mifepristone Tablets, 200 mg**

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense mifepristone is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense mifepristone is able to ship mifepristone using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855-643-3463 toll-free) or online at www.MifeInfo.com; and
- Each location of my pharmacy that will dispense mifepristone will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting mifepristone orders.
  - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
  - Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
  - Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
  - Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.
  - Track and verify receipt of each shipment of mifepristone.
  - Dispense mifepristone in its package as supplied by GenBioPro, Inc.
  - Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to GenBioPro, Inc. Notify GenBioPro that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
  - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
  - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, all processes and procedures including compliance with those processes and procedures.
  - Maintain the identity of mifepristone patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance purposes.
  - Train all relevant staff on the Mifepristone REMS Program requirements.
  - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred __ email __ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to **RxAgreements@GenBioPro.com** or fax to **1-877-239-8036.**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s025

SUMMARY REVIEW

[redacted] and [redacted]

Center for Drug Evaluation and Research (CDER)

Application Type	NDA and ANDA
Application Number	NDA 020687 and ANDA 091178
Supplement Number, Date Received	NDA Supplement-025 and ANDA Supplement-004 received June 22, 2022 (sequences 18 and 87 respectively) and amended October 19, 2022 (sequences 22 and 91 respectively), November 30, 2022 (sequences 24 and 92 respectively), December 9, 2022 (sequences 25 and 93 respectively) and December 16, 2022 (sequences 26 and 95 respectively). This supplement is on a 180-Day clock.
Targeted Action Date	December 19, 2022
[redacted] #	2022-1169
Reviewer Names	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Review Completion Date	January 3, 2023
Subject	Review of proposed Major REMS Modification
Established Name	Mifepristone REMS
Name of Sponsor	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablet

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EXECUTIVE SUMMARY

This is a review of the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178. The Sponsors submitted proposed modification to the Mifepristone REMS Program on June 22, 2022, and amended their submissions on October 19, 2022 (Danco), October 20, 2022 (GBP), November 30, 2022 (both), December 9, 2022 (both) and December 16, 2022 (both).

The Mifepristone REMS Program was originally approved on April 11, 2019, to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021.[a] The Mifepristone REMS Program consists of elements to assure safe use (ETASU) A, C and D, an implementation system, and a timetable for submission of assessments of the REMS.

The Sponsors submitted the proposed modification to the REMS in response to the Agency's REMS Modification Notification letters dated December 16, 2021, which required removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement") and the addition of certification of pharmacies that dispense the drug.

In addition, the following were addressed during the course of the review:

- revisions to the REMS goal to align with the updated REMS requirements.
- replacing serial number with recording of NDC and lot number of mifepristone dispensed.
- additional edits for clarification and consistency in the REMS Document and REMS materials (*Prescriber Agreement Forms*, *Patient Agreement Form*, and *Pharmacy Agreement Forms*).

The review team finds the proposed modification to the Mifepristone REMS Program last submitted on December 16, 2022, to be acceptable and recommends approval of the REMS modification. The proposed REMS modification includes changes to the REMS goal, additional REMS requirements for prescribers to incorporate dispensing from certified pharmacies and new REMS requirements for pharmacy certification.

The proposed goal of the modified REMS for mifepristone 200 mg is to mitigate the risk of serious complications associated with mifepristone by:

a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.

b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.

c) Informing patients about the risk of serious complications associated with mifepristone.

[a] The May 14, 2021 REMS modification approved the inclusion of gender neutral language in the Patient Agreement Form as well as corresponding minor changes to the REMS document to be consistent with the changes made to the Patient Agreement Form.

The timetable for submission of assessments of the REMS was modified to one year from the date of the approval of the modified REMS and annually thereafter. The assessment plan was revised to align with the changes to the REMS and capture additional metrics for drug utilization and REMS operations.

The modified REMS includes ETASU A, B and D, an implementation system, and a timetable for submission of assessments of the REMS. Mifepristone will no longer be required to be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to as the "in-person dispensing requirement" for brevity) and will be able to be dispensed from certified pharmacies.

1. Introduction

This review evaluates the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178.

The Sponsors initially submitted proposed modification to the Mifepristone REMS Program on June 22, 2022, in response to the Agency's REMS Modification Notification letters issued on December 16, 2021, to Danco and GBP, requiring the following modification to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks:

- removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement")
- addition of certification of pharmacies that dispense the drug

Per the Agency's December 16, 2021, REMS Modification Notification letters, the proposed REMS was required to include the following ETASU to mitigate the risk of serious complications associated with mifepristone, including at least the following:

- healthcare providers have particular experience or training, or are specially certified
- pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- the drug is dispensed to patients with evidence or other documentation of safe use conditions

The REMS was also required to include an implementation system and timetable for submission of assessments.

2. Background

2.1. Product Information and REMS Information

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifepristone is available as 200 mg tablets for oral use.

Mifeprex (mifepristone) was approved on September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (subpart H)[b] to ensure that the benefits of the drug outweighed

[b] NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

the risk of serious complications associated with mifepristone when used for medical abortion.[c] Mifeprex was deemed to have in effect an approved REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA), and the Mifeprex REMS was approved on June 8, 2011.

On March 29, 2016, FDA approved an efficacy supplement for Mifeprex, which included changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol, as well as a modification of the gestational age up to which Mifeprex has been shown to be safe and effective and a modification to the process for follow-up after administration of the drug. FDA also approved modification to the Mifeprex REMS that reflected the changes approved in the efficacy supplement.[1-5] On April 11, 2019, FDA approved ANDA 091178 and the Mifepristone REMS Program.[6-7] The Mifepristone REMS Program is a single, shared system REMS that includes NDA 020687 and ANDA 091178. The goal of the approved Mifepristone REMS Program is to mitigate the risk of serious complications associated with mifepristone by:

a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program (under ETASU A).
b) Ensuring that mifepristone is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber (under ETASU C).
c) Informing patients about the risk of serious complications associated with mifepristone (under ETASU D).

The Mifepristone REMS Program was last modified and approved in 2021 to revise the *Patient Agreement Form* to include gender-neutral language; however, the goal of the Mifepristone REMS Program has not changed since the initial approval in 2019.

Under ETASU A, to become specially certified to prescribe mifepristone, a healthcare provider must review the prescribing information, complete and sign the *Prescriber Agreement Form,* and agree to follow the guidelines for use of mifepristone. Under ETASU C, in the Mifepristone REMS Program as approved prior to today's action, mifepristone was required to be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. Under ETASU D, mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions (i.e., the patient must sign a *Patient Agreement Form*). The approved Mifepristone REMS Program includes an implementation system, and a timetable for assessments (one year from the date of the initial approval of the REMS on April 11, 2019, and every three years thereafter).

In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 public health emergency (PHE) regarding the in-person dispensing requirement in the Mifepristone REMS Program. Specifically, FDA communicated that provided all other requirements of the Mifepristone REMS Program are met, the Agency intended to exercise enforcement discretion with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the *Patient Agreement Form*, during the COVID-19 PHE. This determination, which FDA made on April 12, 2021, was effective immediately. We also note that from July 13, 2020, to January 12, 2021, per a court order, FDA was enjoined from enforcing the in-person dispensing requirement of the Mifepristone REMS Program.[8]

[c] Mifepristone is also approved in approximately 80 other countries. https://gynuity.org/assets/resources/biblio_ref_lst_mife_en.pdf

Further, and as we also communicated on April 12, 2021, to the extent all of the other requirements of the Mifepristone REMS Program are met, the Agency intended to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of Mifeprex or the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

2.2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 04/11/2019: Approval of the Mifepristone REMS Program, a single, shared system REMS that includes NDA 020687 and ANDA 091178.
- 04/12/2021: The Agency issued a General Advice letter to both the NDA and ANDA Applicants, explaining that FDA intended to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement in the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form.
- 05/07/2021: The Agency stated that it would be reviewing the elements of the Mifepristone REMS Program in accordance with section 505-1 of the FD&C Act.
- 12/16/2021: The Agency completed its review of the Mifepristone REMS Program and determined, among other things, that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification.[9]
- 12/16/2021: REMS Modification Notification letters were sent to both Sponsors stating that the approved Mifepristone REMS Program must be modified to minimize the burden on the healthcare system of complying with the REMS and ensure that the benefits of the drug outweigh the risks.
- 04/08/2022: Final written responses to a Type A meeting request were provided to Danco, the point of contact for the Mifepristone REMS Program. The questions pertained to the 12/16/2021 REMS Modification Notification letter requirements.
- 04/13/2022: The Sponsors requested an extension to 6/30/2022, to submit a proposed REMS modification in response to the Agency's 12/16/2021 REMS Modification Notification letters.
- 04/15/2022: The Agency granted the Sponsors' request for an extension to submit a proposed REMS modification and conveyed that the modification must be submitted no later than 06/30/2022.[10]
- 06/22/2022: Danco and GBP submitted a proposed REMS modification to their respective applications in response to the 12/16/2021 REMS Modification Notification letters.
- 07/22/2022: An Information Request was sent to the Sponsors requesting clarification of the proposed prescriber and dispenser requirements and additional rationale to support their proposal.
- 08/26/2022: Sponsors submitted responses to 07/22/2022 Information Request.
- 09/19/2022: Teleconference was held between Agency and Sponsors where the Agency communicated the REMS requirements that are necessary to support the addition of pharmacy

certification. The Agency proposed focusing on the pharmacy settings where a closed system[d] REMS could be implemented using the existing email and facsimile based system, (b) (4) , as the best strategy for an approvable modification by the goal date.

- 09/22/2022: An Information Request was sent to Sponsors requesting confirmation that the Sponsors agree with the pharmacy distribution approach outlined in the 09/19/2022 teleconference so that the Agency's feedback could be appropriately tailored.
- 09/23/2022: The Sponsors confirmed via email that they were willing to pursue (b) (4) , as discussed in the 09/19/2022 teleconference. The Sponsors also requested a teleconference to discuss the current modification (b) (4) .
- 09/27/2022: Comments from the 09/19/2022 teleconference sent to Sponsors with additional comments and requests regarding what will be necessary for pharmacy certification.
- 09/29/2022: An Information request was sent to the Sponsors asking for agenda items, questions, and a request to walk through their proposed system for pharmacy certification, including dispensing through mail-order or specialty pharmacies, at the 10/06/2022 scheduled teleconference.
- 10/04/2022: Sponsors emailed that they will focus the 10/06/2022 teleconference on the 09/27/2022 Agency comments and their mail order and specialty pharmacy distribution model.
- 10/06/2022: Teleconference was held between Agency and Sponsors where Sponsors outlined their proposal for pharmacy certification, including dispensing through mail order and specialty pharmacies, as well as their concerns with certain requirements and general timelines.
- 10/19/2022: Danco submitted a REMS amendment to their pending sNDA, which included a REMS document and REMS materials. They did not submit a REMS Supporting Document.
- 10/20/2022: GBP submitted a REMS amendment to their pending sANDA, which included a REMS document and REMS materials. They did not submit a REMS Supporting Document.
- 10/25/2022: Teleconference was held between Agency and Sponsors to discuss the *Patient Agreement Form* and timing related to shipping a mifepristone prescription from a certified pharmacy to the patient.
- 11/23/2022: An Information Request was sent to Sponsors with comments on their proposed REMS Document, submitted on 10/19/2022 (Danco) and 10/20/2022 (GBP).
- 11/30/2022: Danco and GBP submitted REMS amendments, which included the REMS Document, to their respective pending supplemental applications.
- 12/01/2022: Teleconference was held between Agency and Sponsors to discuss the REMS Document.
- 12/05/2022: An Information Request was sent to Sponsors with comments on their proposed REMS Document submitted on 11/30/2022 and discussed at the teleconference on 12/01/2022, and REMS materials submitted to their applications on 10/19/2022 and 10/20/2022.

[d] "Closed system" in this case refers to a system where prescribers, pharmacies, and distributors are certified or authorized in the REMS and the certification of the stakeholder must be verified prior to distribution or dispensing, as per the REMS.

- 12/07/2022: Teleconference was held between Agency and Sponsors to discuss the REMS Document and REMS materials the Agency sent to the Sponsors on 12/05/22.
- 12/08/2022: Danco and GBP submitted REMS amendments, including the REMS Document, *Prescriber Agreement Form, Pharmacy Agreement Form, Patient Agreement Form* and REMS Supporting Document, to their respective pending applications.
- 12/09/2022: An Information Request was sent to Sponsors with the Agency's comments on the REMS assessment plan.
- 12/14/2022: An Information Request was sent to Sponsors with the Agency's comments on the REMS Document, *Prescriber Agreement Form, Pharmacy Agreement Form*, and REMS Supporting Document.
- 12/15/2022: Two teleconferences were held between Agency and Sponsors to discuss the proposed REMS Document and REMS materials the Agency sent to the Sponsors on 12/14/22.
- 12/16/2022: Sponsors submitted a REMS amendment to their respective applications.

3. Review of Proposed REMS Modification

(b) (6) has discussed the Sponsors' proposed modification with the review team, which includes members of the (b) (6) and the (b) (6) ; hereafter referred to as the review team. This review includes their input and concurrence with the analysis and proposed changes to the Mifepristone REMS Program.

3.1. REMS Goal

The Sponsors proposed modification to the goal for the Mifepristone REMS Program to add that mifepristone can also be dispensed from certified pharmacies on prescriptions issued by certified prescribers. The proposed REMS goal is:

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.

b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.

c) Informing patients about the risk of serious complications associated with mifepristone.

Reviewer Comment: *We agree with the Sponsors' proposal.*

3.2. REMS Document

The proposed REMS Document is not in the format as outlined in the 2017 Draft Guidance for Industry, Format and Content of a REMS Document.[11]

Reviewer Comment: *To avoid the misperception that this REMS modification is making major changes to the REMS document that go beyond our December 16, 2021, determination that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification, CDER staff and management discussed whether to change the format of the REMS document to that described in the 2017 draft guidance.*[11] *After internal discussion, CDER staff and management aligned not to transition the REMS document at this time to the format described in the 2017 draft guidance.*

3.3. REMS Requirements

3.3.1. Addition and Removal of ETASU

The December 16, 2021, REMS Modification Notification letters specified that the ETASU must be modified to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure the benefits of the drug outweigh the risks by:

- Removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices and hospitals (i.e., the "in-person dispensing requirement"), and;
- Adding a requirement that pharmacies that dispense the drug be specially certified.

The Sponsors proposed changes to the REMS as reflected in the subsections below.

3.3.2. REMS Participant Requirements and Materials

3.3.2.1. Prescriber Requirements

Consistent with the approved Mifepristone REMS Program prescribers must be specially certified. To become specially certified to prescribe mifepristone, healthcare providers who prescribe must review the Prescribing Information for mifepristone and complete the *Prescriber Agreement Form*. In signing the *Prescriber Agreement Form*, prescribers agree they meet certain qualifications and will follow the guidelines for use of mifepristone. The guidelines for use include ensuring i) that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained; ii) that the healthcare provider (HCP) and the patient sign the *Patient Agreement Form*, iii) the patient receives a copy of the *Patient Agreement Form* and Medication Guide, iv) the *Patient Agreement Form* is placed in the patient's medical record; v) that any patient deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient. The language on the guidelines for use was revised from the Mifepristone REMS Program approved in 2021 to clarify that, if the certified prescriber supervises the dispensing of mifepristone, they must ensure the guidelines for use of mifepristone are followed by those under their supervision. This clarification reflects the ongoing implementation of the approved Mifepristone REMS Program. For example, consistent with the approved REMS, the *Patient Agreement Form* does not require the certified prescriber's signature, but rather the signature of the healthcare provider counseling the patient on the risks of mifepristone. Additional changes were made globally to provide consistency and clarity of the requirements for certified prescribers and healthcare providers who complete tasks under the supervision of certified prescribers.

A certified prescriber may submit the *Prescriber Agreement Form* to an authorized distributor if the certified prescriber wishes to dispense or supervise the dispensing of mifepristone; this is consistent with the current requirements of the Mifepristone REMS Program. Additional requirements were

added to incorporate mifepristone dispensing by a certified pharmacy. If a healthcare provider wishes to prescribe mifepristone by sending a prescription to a certified pharmacy for dispensing, the healthcare provider must become certified by providing the pharmacy a *Prescriber Agreement Form* signed by the provider. A certified prescriber must also assess the appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than four calendar days after the prescription was received by the certified pharmacy.

The NDC and lot number of the dispensed drug will be recorded in the patient's record when mifepristone is dispensed by or under the supervision of a certified prescriber, replacing the requirement that serial numbers from each package of mifepristone be recorded in the patient's record. If prescribers become aware of the death of a patient for whom the mifepristone was dispensed from a certified pharmacy, the prescribers will be required to obtain the NDC and lot number of the package of mifepristone the patient received from the pharmacy.

The following materials support prescriber requirements:

- *Prescriber Agreement Form* for Danco Laboratories, LLC
- *Prescriber Agreement Form* for GenBioPro, Inc.
- *Patient Agreement Form*

Reviewer Comment: *We agree with the Sponsors' proposal.*

Although certain activities (review of the Patient Agreement Form with patients and answering any questions about treatment, signing, providing a copy to the patient and retaining the Patient Agreement Form, providing a copy of the Medication Guide, and ensuring any deaths are reported to the Mifepristone Sponsor, recording the NDC and lot number from drug dispensed from the certified prescriber or those under their supervision) may be conducted by healthcare providers under the supervision of a certified prescriber, the certified prescriber remains responsible for ensuring compliance with the requirements of the Mifepristone REMS Program. We agree with the additional language to further clarify that the certified prescriber must ensure the guidelines for use of mifepristone are followed.

As proposed, certified prescribers may either, 1) continue to submit the Prescriber Agreement Form to an authorized distributor if the certified prescriber is dispensing or supervising the dispensing of the drug (as already required in the REMS), or 2) if the drug will be dispensed from a certified pharmacy, submit the Prescriber Agreement Form to the certified pharmacy that will dispense the drug (as proposed in the modification). Regarding #2, the pharmacy can only fill prescriptions written by a certified prescriber.

Based on our review of the proposed changes, the review team finds it acceptable for prescribers to submit their Prescriber Agreement Form directly to the certified pharmacy. Although certified prescribers still have the option of in-person dispensing of the drug, not all prescribers may want to stock mifepristone. Typically due to the number of drugs that are available and the expense associated with stocking prescription medications intended for outpatient use, most prescribers do not stock many medications, if they stock medications at all.

The proposal to submit a Prescriber Agreement Form to a certified pharmacy provides another option for dispensing mifepristone. The burden of providing the Prescriber Agreement Form prior to or when the prescription is provided to a certified pharmacy does not create unreasonable burden for prescribers. The burden of prescriber certification has been minimized to the extent possible. The Prescriber Agreement Form is designed to require minimal time to complete and requires that the prescriber submit it to the authorized distributor once, and if the prescriber chooses to use a certified pharmacy to dispense mifepristone, they will need to submit the form to the certified pharmacy.

There is an additional requirement added for certified pharmacies and certified prescribers in the event that a patient will not receive their medication from the certified pharmacy within four calendar days of the pharmacy's receipt of the prescription (for example, if the medication is not in stock). In this circumstance, the pharmacy will be required to contact the certified prescriber to make them aware of the delay and will be required to obtain from the prescriber confirmation that it is appropriate to dispense mifepristone to the patient even though they will receive mifepristone more than four calendar days after the prescription was received by the certified pharmacy. This confirmation is intended to ensure timeliness of delivery in light of the labeled indication and gestational age. Additional details and rationale on the pharmacy requirements to dispense and ship drug in a timely manner are described in section 3.3.2.3.

If a certified prescriber becomes aware of a patient death that occurs subsequent to the use of mifepristone dispensed from a pharmacy, the certified prescriber must obtain the NDC and lot number of the package of mifepristone the patient received from the pharmacy. This information will be reported to the appropriate Mifepristone Sponsor in the same manner prescribers have done previously. This additional requirement to obtain the NDC and lot number from the pharmacy is needed to ensure consistent adverse event reporting when mifepristone is dispensed from a certified pharmacy.

Prescriber Agreement Form

The Sponsors' proposed changes to the *Prescriber Agreement Form* aligned with those described above. The proposed *Prescriber Agreement Form* explains the two methods of certification which are: 1) submitting the form to the authorized distributor and 2) submitting the form to the dispensing certified pharmacy. Further clarification was added that healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification. The statement that certified prescribers are responsible for overseeing implementation and compliance with the REMS Program was also added. The following statement was added to the form: "I understand that the pharmacy may dispense mifepristone made by a different manufacturer than that stated on the Prescriber Agreement Form." The account set up information was removed and replaced with prescriber information response fields.

***Reviewer Comment**: We agree with the Sponsors' proposal. Changes in the above prescriber requirements were incorporated in the Prescriber Agreement Form.*

3.3.2.2. Patient Requirements

The *Patient Agreement Form* was updated to clarify that the signatures may be written or electronic, to reorganize the risk information about ectopic pregnancy, and to remove the statement that the Medication Guide will be taken to an emergency room or provided to a healthcare provider who did not prescribe mifepristone so that it is known that the patient had a medical abortion with mifepristone.

The following materials support patient requirements:

- *Patient Agreement Form*

***Reviewer Comment:** We agree with the Sponsors' proposal.*

The Patient Agreement Form continues to be an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients, and also provides the information in a brief and understandable format for patients. The requirement to counsel the

patient, to provide the patient with the Patient Agreement Form, and to have the healthcare provider and patient sign the Patient Agreement Form, ensures that each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care. The form is signed by the patient and the provider and placed in the patient's medical record, and a copy is provided to the patient, to document the patient's acknowledgment of receiving the information from the prescriber. The Agency agrees that the further clarification that signatures can be written or electronic is appropriate for the continued use of the form.

The reference to ectopic pregnancy has been reorganized in the document since it is not a risk of the drug. The signs and symptoms of an untreated ectopic pregnancy that may persist after mifepristone use have been clarified in the section of the form that explains the signs and symptoms of potential problems that may occur after mifepristone use.

The review team agrees with removing the patient's agreement to take the Medication Guide with them if they visit an emergency room or HCP who did not give them mifepristone so the emergency room or HCP will understand that the patient is having a medical abortion. Although this statement has been in the Medication Guide for a number of years, upon further consideration, the Agency has concluded that patients seeking emergency medical care are not likely to carry a Medication Guide with them, the Medication Guide is readily available online, and information about medical conditions and previous treatments can be obtained at the point of care.

3.3.2.3. Pharmacy Requirements

The Sponsors proposed that certified pharmacies, in addition to certified prescribers and HCPs under the supervision of certified prescribers, can dispense mifepristone. In order for a pharmacy to become certified, the pharmacy must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy. The Authorized Representative must certify that they have read and understood the Prescribing Information for mifepristone. Each location of the pharmacy must be able to receive *Prescriber Agreement Forms* by email and fax and be able to ship mifepristone using a shipping service that provides tracking information.

Additionally, each dispensing pharmacy location must put processes and procedures in place to fulfill the REMS requirements. Certified pharmacies must verify prescriber certification by confirming they have obtained a copy of the prescriber's signed *Prescriber Agreement Form* before dispensing. Certified pharmacies must dispense mifepristone such that it is received by the patient within four days from the day of prescription receipt by the pharmacy. If the pharmacy will not be able to deliver mifepristone to the patient within four days of receipt of the prescription, the pharmacy must contact the prescriber to confirm the appropriateness of dispensing mifepristone and document the certified prescriber's decision. The pharmacy must also record the NDC and lot number from each package of mifepristone dispensed in the patient's record, track and verify receipt of each shipment of mifepristone, dispense mifepristone in its original package, and only distribute, transfer, loan, or sell mifepristone to certified prescribers or between locations of the certified pharmacy. The pharmacy must also report any patient deaths to the prescriber, including the NDC and lot number from the package dispensed to the patient, and remind the prescriber of their obligation under the REMS to report patient deaths to the Sponsor that supplied the mifepristone; the certified pharmacy also must notify the Sponsor that supplied the mifepristone that the pharmacy submitted a report of a patient death to the prescriber and include the name and contact information for the prescriber as well as the NDC and lot number of the dispensed

product. Record-keeping requirements of the pharmacy include records of *Prescriber Agreement Forms*, mifepristone dispensing and shipping, and all processes and procedures and compliance with those processes and procedures. Pharmacies must train all relevant staff and participate in compliance audits. Pharmacies must also maintain the identity of patients and providers as confidential, including limiting access to patient and provider identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes. The requirement that mifepristone not be dispensed from retail pharmacies was removed.

The following materials support pharmacy requirements:

- *Pharmacy Agreement Form* for Danco Laboratories, LLC
- *Pharmacy Agreement Form* for GenBioPro, Inc.

Reviewer Comment: *We agree with the Sponsors' proposal. The Mifepristone REMS Program continues to require that mifepristone be prescribed only by certified prescribers. With the removal of the in-person dispensing requirement, however, mifepristone can be dispensed from a pharmacy, provided the product is prescribed by a certified prescriber and all other requirements of the REMS are met. Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies. Adding the pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Without pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber. Adding pharmacy certification ensures that the prescriber is certified prior to dispensing the product to a patient; certified prescribers, in turn, have agreed to meet all the conditions of the REMS, including ensuring that the Patient Agreement Form is completed. In addition, wholesalers and distributors can only ship to certified pharmacies. Based on our review and our consideration of the distribution model implemented by the Sponsors during the periods when the in-person dispensing requirement was not being enforced, as well as REMS assessment data and published literature, we conclude that provided all other requirements of the REMS are met, the REMS program, with the removal of the in-person dispensing requirement and the addition of a requirement for pharmacy certification, will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients.*

The requirement to maintain confidentiality, including limiting access to patient and provider identity only to those personnel necessary for dispensing under the Mifepristone REMS Program or as necessary for payment and/or insurance purposes, is included to avoid unduly burdening patient access.

The Sponsors proposed inclusion of this requirement because of concerns that patients may be reluctant or unwilling to seek to obtain mifepristone from pharmacies if they are concerned that confidentiality of their medical information could be compromised, potentially exposing them to intimidation, threats, or acts of violence by individuals opposed to the use of mifepristone for medical abortion.[e] *Further, unwillingness on the part of prescribers to participate in the Mifepristone REMS Program on the basis of*

[e] See e.g., *2020 Violence and Disruption Statistics,* National Abortion Federation (Dec. 16, 2021), https://prochoice.org/national-abortion-federation-releases-2020-violence-disruption-statistics/; Amanda Musa, CNN, *Wyoming Authorities Search for a Suspect Believed to Have Set an Abortion Clinic on Fire*, CNN WIRE (June 10, 2022), https://abc17news.com/news/2022/06/10/wyoming-authorities-search-for-a-suspect-believed-to-have-set-an-abortion-clinic-on-fire/.

Reference ID: 5103819

similar confidentiality concerns may unduly burden patient access by limiting the number of prescribers who are willing to send prescriptions to certified pharmacies. Addition of this requirement protects patient access by requiring the pharmacy to put processes and procedures in place to limit access to confidential information to only those individuals who are essential for dispensing mifepristone under the Mifepristone REMS Program or as necessary for payment or insurance purposes. Inclusion of this requirement for certified pharmacies is consistent with the requirement in the current Mifepristone REMS Program, that distributors maintain secure and confidential records.

Reference to mifepristone not being available in retail pharmacies was removed from the REMS. There is no single definition of the term "retail pharmacy" and therefore the scope of the exclusion in the REMS was not well defined. Including a restriction in the Mifepristone REMS Program that retail pharmacies cannot participate in the REMS may unintentionally prohibit the participation of mail order and specialty pharmacies that could, under one or more definitions, also be considered a "retail pharmacy."

After reconsideration of the term, "retail," the Agency concluded that a more appropriate approach was to articulate the specific requirements that would be necessary for pharmacy certification. As modified, the REMS will not preclude the participation of any pharmacy that meets the certification requirements. However, we acknowledge that the provision in the REMS related to pharmacies' verification of prescriber enrollment will likely limit the types of pharmacies that will choose to certify in the REMS. The REMS requires that pharmacies dispense mifepristone only after verifying that the prescriber is certified. The REMS further requires that pharmacies be able to receive the Prescriber Agreement Forms by email and fax. (b) (4)



The pharmacy certification requirements include that the drug reach patients within four days of the certified pharmacy receiving the prescription. During the course of the review, the review team concluded that requiring medication delivery to the patient within four days of the pharmacy's receipt of a prescription is acceptable based on the labeled indication and literature,[13] while taking into account practical shipping considerations (e.g., shipping over weekends and holidays). For patients who will not receive the drug within four calendar days of the date the pharmacy receives the prescription, the pharmacy must notify the certified prescriber and the certified prescriber must determine if it is still appropriate for the certified pharmacy to dispense the drug. The pharmacy must document the certified prescriber's decision. A prescriber's confirmation that it is appropriate to dispense mifepristone when it will not be delivered to the patient within the allotted four days is intended to ensure timeliness of delivery in light of the labeled indication and gestational age.

Pharmacy Agreement Form

The proposed *Pharmacy Agreement Form* is a new form and is the means by which a pharmacy becomes certified to dispense mifepristone. The form, which is submitted by an authorized representative on behalf of a pharmacy seeking certification, outlines all requirements proposed above. Clarification is included in the form that healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program, do not require pharmacy certification. Any new authorized representative must complete and submit the *Pharmacy Agreement Form*. Spaces for specific authorized representative information and pharmacy name and address are included. The completed form can be submitted by email or fax to the authorized distributor.

Reviewer Comment: *We agree with the Sponsors' proposal. The Pharmacy Agreement Form aligns with the pharmacy requirements discussed above.*

3.3.2.4. Distributor Requirements

The Sponsors proposed that the distributors' processes and procedures in the approved Mifepristone REMS Program be updated to ensure that mifepristone is only shipped to clinics, medical offices and hospitals identified by certified prescribers and to certified pharmacies. Distributors will continue to complete the certification process for any *Prescriber Agreement Forms* they receive and also will complete the certification process for pharmacies upon receipt of a *Pharmacy Agreement Form*, including notifying pharmacies when they become certified. FDA was removed as a potential auditor for distributors.

Reviewer Comment: *We agree with the Sponsors' proposal. At this time, FDA does not audit distributors directly, it carries out inspections of Sponsors to monitor industry compliance with REMS requirements.*

3.3.3. REMS Sponsor Requirements

3.3.3.1. Sponsor Requirements to Support Prescriber Certification

The Sponsors proposed additions to this section of the REMS document, including that Sponsors will ensure prescribers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy, and that Sponsors will ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date. Sponsors will also ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*: (1) within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies, or (2) within one year after approval of this modification, if previously certified and ordering from an authorized distributor.

Reviewer Comment: *We agree with the Sponsors' proposal. The requirement to confirm that the locations associated with the certified prescriber are current is parallel to the pharmacy requirement that the authorized representative's contact information is up to date. In determining the pharmacy requirement, which is necessary to ensure program compliance and is consistent with other approved REMS that include pharmacy certification, the Agency also concluded that a parallel requirement for certified prescribers should be added.*

With respect to recertification, it is important that active certified prescribers are informed of and agree to new REMS requirements to ensure the continued safe use of mifepristone. There is minimal burden to recertification and the timelines allow sufficient time to accomplish recertification.

3.3.3.2. Sponsor Requirements to Support Pharmacy Certification

The Sponsors proposed the addition of Sponsor requirements to support pharmacy certification and compliance, including ensuring that pharmacies are certified in accordance with the requirements in the Mifepristone REMS Program, de-certifying pharmacies that do not maintain compliance with the certification requirements, and ensuring that pharmacy certification can be completed by email and fax to an authorized distributor. Annually, the authorized representative's name and contact information will be verified to ensure it corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, a new authorized representative must certify for the pharmacy. All reference to the requirement in the 2021 Mifepristone REMS Program that mifepristone to be dispensed to patients only in clinics, medical offices and hospitals by or under the supervision of a certified prescriber, and not from retail pharmacies, was removed.

Reviewer Comment: *We agree with the Sponsors' proposal. Changes are in line with the REMS Modification Notification letters sent December 16, 2021. Refer to section 3.3.2.3 Reviewer Comments on Pharmacy Certification for rationale for removing the statement that mifepristone is not distributed to or dispensed from retail pharmacies. Ensuring that the authorized representative's contact information is up to date is necessary to ensure that there is always a point person who is responsible for implementing the Mifepristone REMS Program in their pharmacy and can address any changes that are needed if pharmacy audits identify a need for improvement.*

3.3.3.3. Sponsor Implementation Requirements

The Sponsors proposed that they will ensure that adequate records are maintained to demonstrate that REMS requirements have been met (including but not limited to records of mifepristone distribution, certification of prescribers and pharmacies, and audits of pharmacies and distributors), and that the records must be readily available for FDA inspections. The distributor audit requirement was updated to audit new distributors within 90 calendar days of becoming authorized and annually thereafter (a one-time audit requirement was previously required). The Sponsors also proposed a pharmacy audit requirement whereby certified pharmacies that order mifepristone are audited within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter for pharmacies that ordered in the previous 12 months.

Reviewer's Comment: *We agree with the Sponsors' proposal.*

The number of pharmacies that will certify in the REMS is uncertain; therefore, to obtain a reliable sample size for the audits, the Sponsors will need to audit all certified pharmacies within 180 calendar days after the pharmacy places its first order and annually thereafter for pharmacies that have ordered mifepristone in the previous 12 months. Audits performed at 180 days should allow time for establishment and implementation of audit protocols and for the Sponsors to perform the audits. With the addition of more stakeholders (i.e., certified pharmacies), it is also necessary to audit distributors annually to ensure the REMS requirements are followed. The requirement to conduct audits annually may be revisited if assessment data shows that the REMS is meeting its goal.

3.4. REMS Assessment Timetable

The Sponsors proposed that assessments must be submitted one year from the approval of the modified REMS and annually thereafter, instead of every three years as per the previous requirement.

Reviewer's Comment*: We agree with the Sponsors' proposal. With the addition of new pharmacy stakeholders and removal of the in-person dispensing requirement, more frequent assessment after this REMS modification is needed to ensure REMS processes are being followed and that the REMS is meeting its goal. The requirement can be revisited at a later date if assessment data shows that the modified REMS is meeting its goal. The NDA applicant is required to submit assessment reports as outlined in the timetable for submission of assessments. These reports address requirements for the Mifepristone REMS Program. The Sponsors have indicated that some data will be submitted as separate reports when Sponsor-specific information is needed to address the assessment metrics.*

4. Supporting Document

The Sponsors' REMS Supporting Document was substantially updated to include information regarding the proposed modification under review. Background and rationale from the 12/16/21 REMS Modification Notification letters was included. An updated description of the REMS goal and the ETASU was also included to align with the changes in the REMS Document and provide further clarification. Further explanation of prescriber requirements and rationale for various pharmacy requirements was also included.

Regarding implementation of the modified REMS, the Sponsors additionally proposed that pharmacies that received and shipped mifepristone during the Agency's exercise of enforcement discretion during the COVID-19 PHE, that wish to continue to dispense mifepristone, will be required to comply with the pharmacy certification requirements within 120 days of approval of the modified REMS.

The communication strategy to alert current and future prescriber and pharmacy stakeholders was outlined. Distributors, certified prescribers that purchased mifepristone in the last twelve months, and various professional organizations will receive information about REMS changes within 120 days of modification approval. The Sponsors proposed to list pharmacies that agree to be publicly disclosed on their respective product websites but disclosure of this nature is not a requirement of the REMS. The Sponsors indicated that they anticipate certified pharmacies that do not agree to public disclosure will communicate with the certified prescribers they wish to work with.

The REMS Assessment Plan is discussed in the following section.

Reviewer's Comment*: We agree with the Sponsors' proposal. The Supporting Document addresses all REMS requirements and provides sufficient clarification of implementation and maintenance of the REMS. The implementation requirements for pharmacies currently dispensing mifepristone under FDA's exercise of enforcement discretion during the COVID-19 PHE provide for continued use of these pharmacies without breaks in service. The communication strategy is also adequate given the efforts to reach both established certified prescribers and potentially new prescribers through professional organizations.*

The Sponsors' plan to communicate which pharmacies are certified to certified prescribers is adequate. For the reasons listed in section 3.3.2.3, confidentiality is a concern for REMS stakeholders. Disclosure of pharmacy certification status should be a choice made by individual certified pharmacies. The Sponsors have indicated that there will be some certified pharmacies that have agreed to publicly disclose their status, making this information available to certified prescribers who wish to use a pharmacy to dispense mifepristone.

5. REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document and will be included in the REMS Modification Approval letter.

The REMS Assessment Plan was revised to align with the modified REMS goal and objectives.

The goal of the Mifepristone REMS Program is to mitigate the risk of serious complications associated with mifepristone by:

a. Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
    - This objective will be assessed using REMS Certification Statistics and REMS Compliance metrics.

b. Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
    - This objective will be assessed using REMS Certification Statistics and REMS Compliance metrics.

c. Informing patients about the risk of serious complications associated with mifepristone.
    - This objective will be indirectly assessed using REMS Certification Statistics to avoid compromising patient and prescriber confidentiality. As part of the certification process, healthcare providers agree to:
        - Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained
        - Ensure that the *Patient Agreement Form* is signed by the healthcare provider and the patient
        - Ensure that the patient is provided with a copy of the *Patient Agreement Form* and the Medication Guide
        - Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record

The following revisions were made from the Mifepristone REMS Assessment Plan in the April 11, 2019, Supplement Approval letter:

The Assessment Plan Categories of 1) Program Implementation and Operations and 2) Overall Assessment of REMS Effectiveness were added.

REMS Certification Statistics metrics were added to capture certification numbers for program stakeholders to assess the first objective of requiring healthcare providers who prescribe mifepristone to be certified and the second objective of ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. The total number of certified prescribers who certified with the wholesaler/distributor and the total number of certified prescribers who submitted a *Prescriber Agreement Form* to certified pharmacies were added to capture the additional method of prescriber certification. The number of newly certified prescribers and the number of active certified prescribers (i.e., those who ordered mifepristone or submitted a prescription during the reporting period) were added. Metrics were also added to capture the total number of certified, newly certified, and active certified pharmacies as well as the total number of authorized, newly authorized, and active authorized wholesaler/distributors.

Drug Utilization Data metrics were added to obtain information on shipment and dispensing of mifepristone. Metrics were added to capture the total number of tablets shipped by the wholesaler/distributor and the number of prescriptions dispensed.

REMS Compliance Data metrics were added to assess the first objective of requiring healthcare providers who prescribe mifepristone to be certified and the second objective of ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. These metrics capture program deviations and evaluate overall if the REMS is operating as intended. Metrics include certified pharmacies and wholesaler/distributor audit results and a summary of instances of non-compliance and actions taken to address non-compliance. Prescriber compliance metrics were added to assess if prescribers are decertified along with reasons why. Pharmacy compliance metrics were added to assess if prescriptions were dispensed that were written by non-certified prescribers or if mifepristone tablets were dispensed by non-certified pharmacies as well as the number of pharmacies that were decertified along with reasons why. Wholesaler/distributor metrics were added to assess if shipments were sent to non-certified prescribers and non-certified pharmacies and corrective actions taken. The audit plan and non-compliance plans will be submitted for FDA review within 60 days after the REMS modification approval.

The Sponsors were asked to develop an assessment of prescription delivery timelines to determine what percentage of prescriptions were delivered on time (within four calendar days) and what percentage were delivered late (more than four calendar days) along with the length of the delay and reasons for the delay (e.g., mifepristone is out of stock shipment issues, other). The protocol for this assessment will be submitted for FDA review within 60 days after the REMS modification approval.

The revised REMS Assessment Plan is in the Appendix.

Reviewer's Comment*: We agree with the Sponsors' proposed REMS Assessment Plan.*

6. Discussion

The Sponsors submitted changes to the REMS to remove the requirement that mifepristone be dispensed only in certain healthcare settings (i.e., the "in-person dispensing requirement") and to add that certified pharmacies can dispense the drug in order to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks. The REMS goal was updated to this effect. Changes were required for prescriber requirements and Sponsors to support the change in ETASU, and new pharmacy requirements were introduced.

The qualifications to become a certified prescriber have not changed as a result of the modification to the Mifepristone REMS Program; however, clarification has been provided for certain prescriber requirements and new prescriber requirements have been added to support pharmacy dispensing. Although certain responsibilities may be conducted by staff under the supervision of a certified prescriber, the certified prescriber remains responsible for ensuring compliance with the requirements of the Mifepristone REMS Program. In order to clarify this, revisions were made throughout the prescriber requirements and REMS materials to reflect that the certified prescriber is responsible for ensuring that the prescriber requirements are met. Additionally, the review team finds it acceptable that certified prescribers who wish to use a certified pharmacy to dispense mifepristone submit their *Prescriber Agreement Form* to the dispensing certified pharmacy (b) (4) . The burden to prescriber and

pharmacy stakeholders of having certified prescribers submit the form directly to the certified pharmacy that will be dispensing the mifepristone is not unreasonable and has been minimized to the extent possible; it does not impact the safe use of the product. Prescriber requirements necessitated by the addition of some pharmacy requirements were added as well and include prescriber responsibilities in deciding whether or not mifepristone should be dispensed if the patient will receive the drug from the certified pharmacy more than four days after the pharmacy receives the prescription, and prescriber adverse event reporting requirements if a prescriber becomes aware of a patient death and the mifepristone was dispensed from a certified pharmacy. The addition of the latter requirements will ensure consistent adverse event data is relayed to the relevant Mifepristone Sponsor.

Changes were made to the *Patient Agreement Form.* Changes to the form were added to improve clarity of the safety messages. After further consideration, the patient's agreement to take the Medication Guide with them if they visit an emergency room or HCP who did not give them mifepristone so the emergency room or HCP will understand that the patient is having a medical abortion has been removed from the *Patient Agreement Form*. The Medication Guide is not typically carried by patients and this information can be obtained at the point of care. Changes align with updates to labeling submitted with this modification.[13, 14]

The Agency and Sponsors agreed during this modification to focus on certification of pharmacies that can receive *Prescriber Agreement Forms* via email or fax to complete the prescriber certification process. The proposed pharmacy certification requirements also support timely dispensing of mifepristone. If the mifepristone is shipped to the patient, the REMS requires that it must be delivered within four calendar days from the receipt of the prescription by the pharmacy; if the patient will receive the mifepristone more than four calendar days from pharmacy receipt of prescription, the REMS requires the pharmacist to confirm with the certified prescriber that it is still appropriate to dispense the drug to the patient. This allows prescribers to make treatment decisions based on individual patient situations. A requirement to maintain confidentiality was also added to avoid unduly burdening patient access since patients and prescribers may not utilize pharmacy dispensing if they believe their personal information is at risk. Ultimately, the addition of pharmacy distribution with the proposed requirements will offer another option for dispensing mifepristone, alleviating burden associated with the REMS.

(b) (4)

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The Agency reviewed the REMS in 2021, and per the review team's conclusions, a REMS modification was necessary to remove the in-person dispensing requirement and add a requirement that pharmacies that dispense the drug be specially certified; the review team concluded that these changes could occur without compromising patient safety. There have been no new safety concerns identified relevant to the REMS ETASUs that the applicants proposed modifying in their June 22, 2022 submissions since the REMS Modification Notification letters dated 12/16/2021. It is still the position of the review team that the proposed modification is acceptable.

Because the modification proposed include changes to the ETASU of the Mifepristone REMS Program, the assessment plan and timetable of assessments were changed. The assessment plan will capture information on pharmacy dispensing and provide valuable insight as to whether the program is operating as intended Annual assessments are consistent with other approved REMS modifications for major modifications necessitating extensive assessment plan changes.

As part of the REMS Assessment Plan, the REMS goal and objectives are assessed using Program Implementation and Operations Metrics, including REMS Certification Statistics and REMS Compliance Data. The metrics will provide information on the number of certified prescribers, certified pharmacies, and authorized wholesalers/distributors as well as if mifepristone is dispensed by non-certified prescribers or pharmacies. The Sponsors will use the indirect measure of healthcare provider certification to address the objective of informing patients of the risk of serious complications of mifepristone, due to concerns with prescriber and patient confidentiality. Although we typically assess whether patients are informed of the risks identified in a REMS through patient surveys and/or focus groups, we agree that the Sponsors' continued use of the indirect measure of healthcare provider certification adequately addresses the Mifepristone REMS Program objective of informing patients. In addition, because of these prescriber and patient confidentiality concerns, we believe it is unlikely that the Agency would be able to use the typical methods of assessment of patient knowledge and understanding of the risks and safe use of mifepristone.

7. Conclusions and Recommendations

The review team finds the proposed REMS modification for the Mifepristone REMS Program, as submitted on June 22, 2022, and amended on October 19, 2022 (Danco) and October 20, 2022 (GBP), November 30, 2022 (both), December 9 (both), and December 16 (both) acceptable. The REMS materials were amended to be consistent with the revised REMS document. The review team recommends approval of the Mifepristone REMS Program, received on June 22, 2022, and last amended on December 16, 2022, and appended to this review.

8. References

1. (b) (6) Clinical Review of SE-2 Efficacy Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909590.

2. (b) (6) Summary Review for Regulatory Action for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909594.

3. (b) (6) REMS Review for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909588.

4. (b) (6) REMS Review for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909587.

5. Approval Letter for SE-2 Efficacy Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909592.

6. (b) (6) REMS Review for mifepristone, NDA 020687. February 22, 2018. DARRTS Reference ID: 4224674.

7. Approval Letter for SE-20 REMS Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 4418041.

8. *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183, 233 (D. Md. July 13, 2020), order clarified, 2020 WL 8167535 (D. Md. Aug. 19, 2020) (preliminarily enjoining FDA from enforcing the in-person dispensing requirement and any other in-person requirements of the

Mifepristone SSS REMS); *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (Jan. 12, 2021) (staying the preliminary injunction imposed by the District Court).

9. (b) (6) REMS Modification Rationale Review for mifepristone, NDA 020687. December 16, 2021. DARRTS Reference ID: 4905882.

10. General Advice Letter for the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone, NDA 020687, April 15, 2022. DARRTS ID 4969358.

11. Format and Content of a REMS Document Guidance for Industry https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf. Accessed on December 18, 2022.

12. Grossman D, Raifman S, Morris N, et.al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. Contraception 2022; 107:36-41. https://doi.org/10.1016/j.contraception.2021.09.008. This article was included in the literature review for the December 16, 2021 REMS Modification Rationale Review, while the article was still in press.

9. Appendices

REMS Document

Prescriber Agreement Form for Danco Laboratories, LLC

Prescriber Agreement Form for GenBioPro, Inc.

Patient Agreement Form

Pharmacy Agreement Form for Danco Laboratories, LLC

Pharmacy Agreement Form for GenBioPro, Inc.

Mifepristone REMS Assessment Plan

Initial Shared System REMS approval: 04/2019
Most Recent Modification: 01/2023

Mifepristone Tablets, 200 mg
Progestin Antagonist

RISK EVALUATION AND MITIGATION STRATEGY (REMS)
SINGLE SHARED SYSTEM FOR MIFEPRISTONE 200 MG

I. GOAL

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.

b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.

c) Informing patients about the risk of serious complications associated with mifepristone.

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe mifepristone must be specially certified.
   a. To become specially certified to prescribe mifepristone, healthcare providers must:
      i. Review the Prescribing Information for mifepristone.
      ii. Complete a *Prescriber Agreement Form*. By signing[1] a *Prescriber Agreement Form*, prescribers agree that:
         1) They have the following qualifications:
            a) Ability to assess the duration of pregnancy accurately
            b) Ability to diagnose ectopic pregnancies
            c) Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
         2) They will follow the guidelines for use of mifepristone (see b.i-vii below).
   b. As a condition of certification, prescribers must follow the guidelines for use of mifepristone described below:
      i. Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
      ii. Ensure that the healthcare provider and patient sign the *Patient Agreement Form.*

[1] In this REMS, the terms "sign" and "signature" include electronic signatures.

Reference ID: 5103819

iii. Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.

iv. Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.

v. Ensure that any deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

vi. If mifepristone will be dispensed by a certified pharmacy:

1) Provide the certified pharmacy a signed *Prescriber Agreement Form*.

2) Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.

3) Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of the patient.

vii. The certified prescriber who dispenses mifepristone or who supervises the dispensing of mifepristone must:

1) Provide an authorized distributor with a signed *Prescriber Agreement Form*.

2) Ensure that the NDC and lot number from each package of mifepristone dispensed are recorded in the patient's record.

3) Ensure that healthcare providers under their supervision follow guidelines i.-v.

c. Mifepristone Sponsors must:

i. Ensure that healthcare providers who prescribe their mifepristone are specially certified in accordance with the requirements described above and de-certify healthcare providers who do not maintain compliance with certification requirements.

ii. Ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*:

1) Within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies.

2) Within one year after approval of this modification, if previously certified and ordering from an authorized distributor.

iii. Ensure that healthcare providers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy.

iv. Provide the Prescribing Information and their *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.

v. Ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date.

The following materials are part of the Mifepristone REMS Program:

- *Prescriber Agreement Form for Danco Laboratories, LLC*
- *Prescriber Agreement Form for GenBioPro, Inc.*
- *Patient Agreement Form*

2. Pharmacies that dispense mifepristone must be specially certified
    a. To become specially certified to dispense mifepristone, pharmacies must:
        i. Be able to receive *Prescriber Agreement Forms* by email and fax.
        ii. Be able to ship mifepristone using a shipping service that provides tracking information.
        iii. Designate an authorized representative to carry out the certification process on behalf of the pharmacy.
        iv. Ensure the authorized representative oversees implementation and compliance with the Mifepristone REMS Program by doing the following:
            1) Review the Prescribing Information for mifepristone.
            2) Complete a *Pharmacy Agreement Form*. By signing a *Pharmacy Agreement Form*, the authorized representative agrees that the pharmacy will put processes and procedures in place to ensure the following requirements are completed:
                a) Verify that the prescriber is certified by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with the pharmacy.
                b) Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in c) below.
                c) Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
                d) Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.
                e) Track and verify receipt of each shipment of mifepristone.
                f) Dispense mifepristone in its package as supplied by the Mifepristone Sponsor.
                g) Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to the Mifepristone Sponsor that provided the mifepristone. Notify the Mifepristone Sponsor that provided the dispensed mifepristone that the pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
                h) Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
                i) Maintain records of *Prescriber Agreement Forms*.
                j) Maintain records of dispensing and shipping.
                k) Maintain records of all processes and procedures including compliance with those processes and procedures.
                l) Maintain the identity of the patient and prescriber as confidential, including limiting access to patient and prescriber identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes.
                m) Train all relevant staff on the Mifepristone REMS Program requirements.

n) Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

b. Mifepristone Sponsors must:

i. Ensure that pharmacies are specially certified in accordance with the requirements described above and de-certify pharmacies that do not maintain compliance with certification requirements.

ii. Ensure that pharmacies can complete the certification process by email and fax to an authorized distributor.

i. Verify annually that the name and contact information for the pharmacy's authorized representative corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, require the pharmacy to recertify with the new authorized representative.

The following materials are part of the Mifepristone REMS Program:

- *Pharmacy Agreement Form for Danco Laboratories, LLC*
- *Pharmacy Agreement Form for GenBioPro, Inc.*

3. Mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions as ensured by the certified prescriber in signing the *Prescriber Agreement Form*.

a. The patient must sign a *Patient Agreement Form* indicating that the patient has:

i. Received, read and been provided a copy of the *Patient Agreement Form*.

ii. Received counseling from the healthcare provider regarding the risk of serious complications associated with mifepristone.

B. Implementation System

1. Mifepristone Sponsors must ensure that their mifepristone is only distributed to certified prescribers and certified pharmacies by:

a. Ensuring that distributors who distribute their mifepristone comply with the program requirements for distributors.

i. The distributors must put processes and procedures in place to:

1) Complete the certification process upon receipt of a *Prescriber Agreement Form* or *Pharmacy Agreement Form*.

2) Notify healthcare providers and pharmacies when they have been certified by the Mifepristone REMS Program.

3) Ship mifepristone only to certified pharmacies or locations identified by certified prescribers.

4) Not ship mifepristone to pharmacies or prescribers who become de-certified from the Mifepristone REMS Program.

5) Provide the Prescribing Information and their Prescriber Agreement Form to healthcare providers who (1) attempt to order mifepristone and are not yet certified, or (2) inquire about how to become certified.

ii. Put processes and procedures in place to maintain a distribution system that is secure,

confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, NDC and lot numbers, proof of delivery and controlled returns of mifepristone.

iii. Train all relevant staff on the Mifepristone REMS Program requirements.

iv. Comply with audits by Mifepristone Sponsors or a third party acting on behalf of Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed for the Mifepristone REMS Program. In addition, distributors must maintain appropriate documentation and make it available for audits.

b. Ensuring that distributors maintain secure and confidential distribution records of all shipments of mifepristone.

2. Mifepristone Sponsors must monitor their distribution data to ensure compliance with the Mifepristone REMS Program.

3. Mifepristone Sponsors must ensure that adequate records are maintained to demonstrate that the Mifepristone REMS Program requirements have been met, including, but not limited to records of mifepristone distribution; certification of prescribers and pharmacies; and audits of pharmacies and distributors. These records must be readily available for FDA inspections.

4. Mifepristone Sponsors must audit their new distributors within 90 calendar days and annually thereafter after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their distributor compliance if noncompliance is identified.

5. Mifepristone Sponsors must audit their certified pharmacies within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter audit certified pharmacies that have ordered mifepristone in the previous 12 months, to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their pharmacy compliance if noncompliance is identified.

6. Mifepristone Sponsors must take reasonable steps to improve implementation of and compliance with the requirements of the Mifepristone REMS Program based on monitoring and assessment of the Mifepristone REMS Program.

7. Mifepristone Sponsors must report to FDA any death associated with mifepristone whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the Mifepristone Sponsor. This requirement does not affect the sponsors' other reporting and follow-up requirements under FDA regulations.

C. Timetable for Submission of Assessments

The NDA Sponsor must submit REMS assessments to FDA one year from the date of the approval of the modified REMS (1/3/2023) and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 90 calendar days before the submission date for that assessment. The NDA Sponsor must submit each assessment so that it will be received by the FDA on or before the due date.

MIFEPREX® (Mifepristone) Tablets, 200 mg

PRESCRIBER AGREEMENT FORM

Mifeprex* (Mifepristone) Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To ***become a certified prescriber***, you must:

- **If you submit Mifeprex prescriptions for dispensing from certified pharmacies**:
  - Submit this form to each certified pharmacy to which you intend to submit Mifeprex prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order Mifeprex for dispensing by you or healthcare providers under your supervision:**
  - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
  - Healthcare settings, such as medical offices, clinics, and hospitals, where Mifeprex will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free), or by visiting www.earlyoptionpill.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received Mifeprex are reported to Danco Laboratories, LLC, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of Mifeprex that was dispensed to the patient.

*MIFEPREX is a registered trademark of Danco Laboratories, LLC
P.O. Box 4816-New York, NY 10185
1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

Ensure that healthcare providers under your supervision follow the guidelines listed above.

- If Mifeprex will be dispensed through a certified pharmacy:
  - Assess appropriateness of dispensing Mifeprex when contacted by a certified pharmacy about patients who will receive Mifeprex more than 4 calendar days after the prescription was received by the certified pharmacy.
  - Obtain the NDC and lot number of the package of Mifeprex the patient received in the event the prescriber becomes aware of the death of a patient.
- If Mifeprex will be dispensed by you or by healthcare providers under your supervision:
  - Ensure the NDC and lot number from each package of Mifeprex are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.

Approved 01/2023 [Doc control ID]

PRESCRIBER AGREEMENT FORM Mifepristone Tablets, 200 mg

Mifepristone Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To ***become a certified prescriber***, you must:

- **If you submit mifepristone prescriptions for dispensing from certified pharmacies**:
  - Submit this form to each certified pharmacy to which you intend to submit mifepristone prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order mifepristone for dispensing by you or healthcare providers under your supervision:**
  - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
  - Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855—643-3463 toll-free), or by visiting www.MifeInfo.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received mifepristone are reported to GenBioPro, Inc. that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

Ensure that healthcare providers under your supervision follow the guidelines listed above.

- If mifepristone will be dispensed through a certified pharmacy:
  - Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.
  - Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of a patient.
- If mifepristone will be dispensed by you or by healthcare providers under your supervision:
  - Ensure the NDC and lot number from each package of mifepristone are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to **RxAgreements@GenBioPro.com** or fax to 1-877-239-8036

Approved 01/2023 [Doc control ID]

PATIENT AGREEMENT FORM Mifepristone Tablets, 200 mg

Healthcare Providers: *Counsel the patient on the risks of mifepristone. Both you and the patient must provide a written or electronic signature on this form.*

Patient Agreement:

1. I have decided to take mifepristone and misoprostol to end my pregnancy and will follow my healthcare provider's advice about when to take each drug and what to do in an emergency.
2. I understand:
   - **a.** I will take mifepristone on Day 1.
   - **b.** I will take the misoprostol tablets 24 to 48 hours after I take mifepristone.
3. My healthcare provider has talked with me about the risks, including:
   - heavy bleeding
   - infection
4. I will contact the clinic/office/provider right away if in the days after treatment I have:
   - a fever of 100.4°F or higher that lasts for more than four hours
   - heavy bleeding (soaking through two thick full-size sanitary pads per hour for two hours in a row)
   - severe stomach area (abdominal) pain or discomfort, or I am “feeling sick,” including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol
     — these symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

   My healthcare provider has told me that these symptoms listed above could require emergency care. If I cannot reach the clinic/office/provider right away, my healthcare provider has told me who to call and what to do.
5. I should follow up with my healthcare provider about 7 to 14 days after I take mifepristone to be sure that my pregnancy has ended and that I am well.
6. I know that, in some cases, the treatment will not work. This happens in about 2 to 7 out of 100 women who use this treatment. If my pregnancy continues after treatment with mifepristone and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy.
7. If I need a surgical procedure because the medicines did not end my pregnancy or to stop heavy bleeding, my healthcare provider has told me whether they will do the procedure or refer me to another healthcare provider who will.
8. I have the MEDICATION GUIDE for mifepristone.
9. My healthcare provider has answered all my questions.

Patient Signature: _____ **Patient Name** (print): _____ **Date**: _____

Provider Signature: _____ **Provider Name** (print): _____ **Date**: _____

Patient Agreement Forms may be provided, completed, signed, and transmitted in paper or electronically.

01/2023

MIFEPREX®(Mifepristone) Tablets, 200mg

PHARMACY AGREEMENT FORM

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense Mifeprex is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense Mifeprex is able to ship Mifeprex using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for Mifeprex. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free) or online at www.earlyoptionpill.com; and
- Each location of my pharmacy that will dispense Mifeprex will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting Mifeprex orders.
  - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
  - Dispense Mifeprex such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
  - Confirm with the prescriber the appropriateness of dispensing Mifeprex for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
  - Record in the patient's record the NDC and lot number from each package of Mifeprex dispensed.
  - Track and verify receipt of each shipment of Mifeprex.
  - Dispense mifepristone in its package as supplied by Danco Laboratories, LLC.
  - Report any patient deaths to the prescriber, including the NDC and lot number from the package of Mifeprex dispensed to the patient, and remind the prescriber of their obligation to report the deaths to Danco Laboratories, LLC. Notify Danco that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
  - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
  - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, and all processes and procedures including compliance with those processes and procedures.
  - Maintain the identity of Mifeprex patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance.
  - Train all relevant staff on the Mifepristone REMS Program requirements.
  - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____

DANCO
Support • Progress • Options

*MIFEPREX is a registered trademark of Danco Laboratories, LLC

P.O. Box 4816-New York, NY 10185
1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred __ email __ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.

PHARMACY AGREEMENT FORM **Mifepristone Tablets, 200 mg**

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense mifepristone is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense mifepristone is able to ship mifepristone using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855-643-3463 toll-free) or online at www.MifeInfo.com; and
- Each location of my pharmacy that will dispense mifepristone will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting mifepristone orders.
  - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
  - Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
  - Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
  - Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.
  - Track and verify receipt of each shipment of mifepristone.
  - Dispense mifepristone in its package as supplied by GenBioPro, Inc.
  - Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to GenBioPro, Inc. Notify GenBioPro that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
  - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
  - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, all processes and procedures including compliance with those processes and procedures.
  - Maintain the identity of mifepristone patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance purposes.
  - Train all relevant staff on the Mifepristone REMS Program requirements.
  - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred __ email __ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to **RxAgreements@GenBioPro.com** or fax to **1-877-239-8036.**

The REMS Assessment Plan must include but is not limited to the following items.

Program Implementation and Operations

1. REMS Certification Statistics
   a. Prescribers
      i. Number of certified prescribers who have certified with the Sponsor's distributor(s) and number who have submitted *Prescriber Agreement Forms* to Certified Pharmacies
      ii. Number and percentage of newly certified prescribers
      iii. Number and percentage of active certified prescribers (i.e., who ordered mifepristone or submitted a prescription during the reporting period)

   b. Pharmacies
      i. Number of certified pharmacies
      ii. Number and percentage of newly certified pharmacies
      iii. Number and percentage of active certified pharmacies (i.e., that dispensed mifepristone during the reporting period)
   c. Wholesalers/Distributors
      i. Number of authorized wholesalers/distributors
      ii. Number and percentage of newly authorized wholesalers/distributors
      iii. Number and percentage of active authorized wholesalers/distributors (i.e. that shipped mifepristone during the reporting period)

2. Utilization Data
   a. Total number of tablets shipped by wholesalers/distributors, stratified by Certified Prescriber or Certified Pharmacy location
   b. Number of prescriptions dispensed from pharmacies

3. REMS Compliance Data
   a. Audits: Summary of audit activities for each stakeholder (i.e., certified pharmacies and wholesalers/distributors) including but not limited to:
      i. A copy of the final audit plan for each stakeholder type (provide for the current reporting period)
      ii. The number of audits expected, and the number of audits performed
      iii. The number and type of deficiencies noted
      iv. For those with deficiencies noted, report the corrective and preventive actions (CAPAs) required, if any, to address the deficiencies, including the status (e.g., completed, not completed, in progress) (provide for the current reporting period)
      v. For any stakeholders that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken (provide for the current reporting period)

vi. A summary report of all resulting changes to processes and procedures necessary to ensure compliance with the REMS requirements (provide for the current reporting period)

b. A summary report of non-compliance, associated corrective action plans (CAPAs), and the status of CAPAs including but not limited to:

i. A copy of the final non-compliance plans for Pharmacies and Distributors (provide for the current reporting period)

ii. For each instance of noncompliance below (iii-v), report the following information (provide for the current reporting period):

1. A unique, anonymized ID for the stakeholder(s) associated with the non-compliance event to enable tracking over time
2. The source of the non-compliance data (e.g., self-reported, audit, other)
3. A root cause analysis of the non-compliance
4. Actions to prevent future occurrences and outcomes of such actions

iii. Prescriber compliance

1. Number and percentage of certified prescribers who became decertified as a result of non- compliance
   - Provide a summary of reasons for decertification (provide for the current reporting period)
2. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

iv. Pharmacy compliance

1. Number and percentage of prescriptions dispensed that were written by prescriber(s) who did not submit a Prescriber Agreement to the dispensing Certified Pharmacy
2. Number and percentage of mifepristone tablets dispensed by non-certified pharmacies
3. Number and percentage of pharmacies that became decertified as a result of non-compliance
   - Provide a summary of reasons for decertification (provide for the current reporting period)
4. An assessment of prescription delivery timelines, including percentage delivered more than four days after receipt of the prescription, duration and causes for delay. A proposal for this assessment will be submitted within 60 days of the approval of the REMS Modification.
5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

v. Wholesaler/distributor compliance

1. Number of healthcare providers who successfully ordered mifepristone who were not certified
2. Number of non-certified pharmacies that successfully ordered mifepristone
3. Number of shipments sent to non-certified prescriber receiving locations
4. Number of shipments sent to non-certified pharmacy receiving locations

5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

Reference ID: 5103819

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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Center for Drug Evaluation and Research (CDER)

[redacted]

Application Type	NDA and ANDA
Application Number	020687 and 91178
Reviewer Names	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Review Completion Date	December 16, 2021

Subject	REMS Modification Rationale Review
Established Name	Mifepristone REMS
Name of Applicants	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablets

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EXECUTIVE SUMMARY

This review provides the [redacted] rationale and conclusions regarding modifications to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178.

ANDA 91178 was approved with the approval of the Mifepristone REMS Program on April 11, 2019 to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021. The REMS consists of elements to assure safe use (ETASU) under ETASU A, C and D, an implementation system, and a timetable for submission of assessments. To determine whether a modification to the REMS was warranted, FDA undertook a comprehensive review of the published literature; safety information collected during the COVID-19 public health emergency (PHE); the one-year REMS assessment report of the Mifepristone REMS Program; adverse event data; and information provided by advocacy groups, individuals and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation discussed below.

The modifications to the REMS will consist of:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to here as the "in-person dispensing requirement" for brevity)
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified

A REMS Modification Notification letter will be sent to both Applicants in the Single Shared System.

1. Introduction

In connection with the *Chelius v. Becerra* litigation, FDA agreed to undertake a full review of the Mifepristone REMS Program, in accordance with the REMS assessment provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[a] This review provides the analysis of the (b) (6) ((b) (6) and the (b) (6) ((b) (6) regarding whether any changes are warranted to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone (hereafter referred to as the Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178. The Mifeprex REMS was initially approved in 2011; the single, shared system REMS for mifepristone 200 mg, known as the Mifepristone REMS Program, was approved in 2019.

The last time the existing REMS elements to assure safe use (under ETASU A, C and D) were reviewed was in the context of our review of supplement S-020 to NDA 20687; these ETASU were updated following review and approval of supplement S-020 on March 29, 2016. The key changes approved in 2016 are summarized below.

Changes to labeling included:

- Changing the dosing of Mifeprex to 200 mg orally x 1
- Extension of maximum gestational age through 70 days
- Inclusion of misoprostol in the indication statement
- Replacing the term “physician” with “licensed healthcare provider”
- Removal of the phrase “Under Federal Law”

The Mifeprex REMS and REMS materials were updated to reflect the changes above, and additional changes were made including:

- Removing the Medication Guide as part of the REMS but retaining it as part of labeling.

2. Background

2.1. PRODUCT AND REMS INFORMATION

[a] Section 505-1(g)(2) of the FD&C Act (21 U.S.C. § 355-1(g)(2)).

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifepristone is available as 200 mg tablets for oral use.

Mifeprex (mifepristone) was approved on September 28, 2000 with a restricted distribution program under 21 CFR 314.520 (subpart H)[b] to ensure that the benefits of the drug outweighed the risk of serious complications associated with mifepristone when used for medical abortion. Mifeprex was deemed to have a REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007, and the Mifeprex REMS was approved on June 8, 2011. On March 29, 2016, as noted above, a supplemental application and REMS modification was approved for Mifeprex. On April 11, 2019, ANDA 091178 was approved, and the Mifepristone REMS Program was approved. The Mifepristone REMS Program is a single, shared system REMS that includes NDA 020687 and ANDA 91178.

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

a. Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program (under ETASU A).
b. Ensuring that mifepristone is only dispensed in certain healthcare settings, by or under the supervision of a certified prescriber (under ETASU C).
c. Informing patients about the risk of serious complications associated with mifepristone (under ETASU D).

Under ETASU A, to become specially certified to prescribe mifepristone, a healthcare provider must review the prescribing information, complete and sign the *Prescriber Agreement Form,* and follow the guidelines for use of mifepristone. Under ETASU C, mifepristone must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. Under ETASU D, mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions (i.e., the patient must sign a *Patient Agreement Form*). The Mifepristone REMS Program also includes an implementation system, and a timetable for assessments (one year from the date of the initial approval of the REMS on April 11, 2019, and every three years thereafter).

[b] NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

2.2. REGULATORY HISTORY AND EVENTS RELEVANT TO THIS REMS MODIFICATION RATIONALE REVIEW

The following is a summary of significant regulatory history since approval of the REMS modification on March 29, 2016:

- 03/29/2016: FDA approved an efficacy supplement (S-020) that, among other things, provided a new dosing regimen (200 mg mifepristone, followed in 24 to 48 hours by 800 mcg buccal misoprostol), increased the gestational age (GA) to which mifepristone may be used (through 70 days gestation), and modified the REMS.

- 03/29/2019: A Citizen Petition was received requesting that FDA revise the product labeling to reflect pre-2016 provisions (including limiting GA to 49 days and requiring patients to make 3 office visits) and that FDA maintain the REMS.

- 04/11/2019: ANDA 91178 was approved along with the Single Shared System REMS for Mifepristone 200 mg (Mifepristone REMS Program) for NDA 20687 and ANDA 91178.

- 01/31/2020: the COVID-19 public health emergency (PHE) was declared by the Secretary of Health and Human Services (HHS) as having existed since January 27, 2020.[c]

- 7/13/2020: The United States (US) District Court of Maryland granted a preliminary injunction in the *ACOG v. FDA* litigation to temporarily bar enforcement of the Mifepristone REMS Program in-person dispensing requirement during the COVID-19 PHE.

- 1/12/2021: US Supreme Court granted a stay of that injunction.

- 04/12/2021: FDA issued a General Advice Letter to both the NDA and ANDA Applicants, stating that provided that all other requirements of the Mifepristone REMS Program are met, and given that in-person dispensing of mifepristone for medical termination of early pregnancy may present additional COVID-related risks to patients and healthcare

[c] *See* Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued January 31, 2020, and subsequently renewed), available at https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx

personnel because it may involve a clinical visit solely for this purpose, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement in the Mifepristone REMS Program, including any in-person requirements that may be related to the *Patient Agreement Form.* FDA further stated that to the extent all of the other requirements of the Mifepristone REMS Program are met, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of mifepristone through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

- 05/07/2021: FDA stated that it would be reviewing the elements of the Mifepristone REMS Program in accordance with the REMS assessment provisions of section 505-1 of the FD&C Act.

- 05/14/2021: A modification was approved for the Mifepristone REMS Program. This modification was to revise the *Patient Agreement Form* to include gender-neutral language.

- 06/30/2021: An Information Request (IR) was sent to the Applicants for additional information on shipments and any program deviations, adverse events, or noncompliance with the REMS that occurred during the period from April 1, 2021 through September 30, 2021.

- 7/15/2021: An IR was sent to the Applicants to provide the total number of shipments during the period from April 1, 2021 to September 30, 2021 and details on whether any of those shipments were involved in any program deviation or non-compliance.

- 8/5/2021: An IR was sent to the Applicants for additional clinical and other information (e.g., adverse events and units of mifepristone shipped) for the period of March 29, 2016 through June 30, 2021, to be provided by August 31, 2021. This IR also requested information covering the period of July 1, 2021 through September 30, 2021 and an

aggregate summary (for the period of March 29, 2016 through September 30, 2021), to be provided by October 12, 2021.[d]

- 8/26/2021: The ANDA Applicant submitted a response to the IR issued on 8/5/2021.
- 08/27/2021: The NDA Applicant submitted a response to the IR issued on 8/5/2021.
- 10/08/2021: The NDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR. The NDA Applicant also included a follow-up to their initial response provided on August 27, 2021 to the August 5, 2021 IR.
- 10/12/2021: The ANDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR.
- 10/16/2021: The ANDA Applicant revised their Oct 12, 2012 response to provide a correction to the number of mifepristone tablets.
- (b) (4)
- 11/02/2021: A (b) (6) ((b) (6) meeting was convened to obtain CDER concurrence on the removal of the in-person dispensing requirement and the addition of a certification requirement for pharmacies. The (b) (6) (b) (6) and senior CDER leadership concurred with removing the in-person dispensing and adding pharmacy certification.

3. Rationale for Proposed REMS Modification

[d] Multiple Information Requests were issued to obtain additional information on drug shipments, any program deviations or noncompliance, and use of alternative methods for drug distribution during the COVID-19 PHE. These IRs are referenced as appropriate in this document and the one-year REMS Assessment Review of the Mifepristone REMS Program, December 16, 2021.

3.1. CURRENT REQUIREMENTS FOR THE APPROVED REMS

The Mifepristone REMS Program includes elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. Elements to assure safe use in the current REMS include a prescriber certification requirement (ETASU A), a requirement that mifepristone be dispensed only in certain healthcare settings by or under the supervision of a certified prescriber (ETASU C), and a requirement that mifepristone be dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions under ETASU D consists of a *Patient Agreement Form* between the prescriber and the patient indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with mifepristone 200 mg for medical termination of early pregnancy.

3.2. EVALUATION OF THE EVIDENCE

We reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation. Below is an overview of how information relevant to the current Mifepristone REMS Program was retrieved, analyzed, and applied to each of the individual ETASUs to determine if further changes should be considered.

Methods for the literature search

(b) (6) conducted a literature search in PubMed and Embase to retrieve publications relevant to this review. The time period used for this literature search was between March 29, 2016 (when the Mifeprex labeling and REMS were last substantially revised) through July 26, 2021. The search terms used were “medical abortion” and “mifepristone” and “pregnancy termination and mifepristone.”

The search retrieved 306 publications from PubMed and 613 from Embase, respectively; the search yielded 646 unique publications after eliminating duplications between the two databases. The result of our literature search was also supplemented by an examination of literature references provided by advocacy groups, individuals, plaintiffs in the *Chelius* litigation, and the Applicants, as well as letters from healthcare providers and researchers.

References included in these letters were considered for inclusion in this review using identical selection criteria to the (b) (6) literature search (outlined below).

For this review of the REMS, (b) (6) focused on publications containing safety data related to outcomes of medical abortion (objective safety data) obtained from our literature search and from the references provided to us relevant to the REMS ETASUs. We excluded systematic reviews and meta-analyses because these publications did not include original safety data related to the outcomes of medical abortion. The following are examples of materials that were excluded from our literature search:

- Information from survey studies or qualitative studies that evaluated perspectives on and/or satisfaction with medical abortion procedures from patients, pharmacists, clinic staff, or providers, even if the study assessed REMS ETASUs. These surveys or qualitative studies did not include objective safety data related to outcomes of medical abortion.

- Opinions, commentaries, or policy/advocacy statements. These publications did not include objective safety data related to outcomes of medical abortion.

- Safety data related to mifepristone use for second trimester medical abortion. These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.

- Safety data related to mifepristone use for spontaneous first trimester abortion (i.e., miscarriages). These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.

- Safety data that pertained only to surgical abortion or did not separate out medical abortion from surgical abortion.

- Other safety information unrelated to the REMS elements (e.g., articles limited to case reports or those discussing unrelated gynecologic or medical issues)

- Publications for which it was not possible to conduct a full review of the methods or results, i.e., the references were limited to an abstract of the study methods and results.

- Publications that provided only general statistics on abortion care in the United States.

- Information pertinent to molecular or other basic science aspects of mifepristone.

- Data on the logistics of accessing abortion care in general, such as time to appointment or the distance traveled to obtain care.

- Publications that provided data not related specifically to abortion care or the REMS (e.g., references focused on federal poverty guidelines, poverty data, or the financial impact of the COVID-19 pandemic).

One exception to the above literature search criteria was the inclusion in Section 3.2.2 of this review, which discusses the *Patient Agreement Form*, of publications that discussed changes in provider volume. The data discussed in relation to provider volume was obtained from surveys. This data was included because changes in provider volume could only be obtained from well-conducted survey studies.

Regarding medical/scientific references submitted with letters from the plaintiffs in the *Chelius* litigation, we applied the same criteria as for the literature search, as described above.

Letters from the plaintiffs in the *Chelius* litigation included several references that preceded our 2016 review of the REMS. Two of those pre-2016 studies were not captured in our 2016 literature search. These two studies were assessed as part of our current review; their results are consistent with the existing safety profile of the approved medical abortion regimen, and therefore, support our current conclusions regarding the REMS. See Appendix A.

3.2.1. Evaluation of the requirement for healthcare providers who prescribe the drug to be specially certified (ETASU A)

In order to become specially certified, prescribers must: 1) review the prescribing information for mifepristone and 2) complete the *Prescriber Agreement Form*. In signing the *Prescriber Agreement Form*, prescribers agree they meet the qualifications listed below:

- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to

ensure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of mifepristone (which the provider can access by phone or online).

In addition to meeting these qualifications, as a condition of certification the healthcare provider also agrees to follow the guidelines for use below:

- Review the *Patient Agreement Form* with the patient and fully explain the risks of the mifepristone treatment regimen. Answer any questions the patient may have prior to receiving mifepristone.
- Sign and obtain the patient's signature on the *Patient Agreement Form*.
- Provide the patient with a copy of the *Patient Agreement Form* and the Medication Guide.
- Place the signed *Patient Agreement Form* in the patient's medical record.
- Record the serial number from each package of mifepristone in each patient's record.
- Report deaths to the Applicant, identifying the patient by a non-identifiable patient reference and the serial number from each package of mifepristone.

The literature review was the primary source of information that contributed to our reassessment of ETASU A.

We continue to be concerned that absent these provider qualifications, serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed. Our review of the literature did not identify any studies comparing providers who met these qualifications with providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention or arrange for such care through others if needed, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol. Therefore, our review continues to support the conclusion that a healthcare provider who prescribes mifepristone should meet the above qualifications. We conclude it is reasonable to maintain the requirement for a one-time prescriber certification where prescribers attest to having the ability to diagnose an intrauterine

pregnancy, to diagnose an ectopic pregnancy,[e] and to either manage serious complications themselves or arrange for other providers to provide the needed care in a timely manner.

In addition, in signing the *Prescriber Agreement Form* and placing it in the patient's medical record, the prescribers acknowledge the requirement to report patient deaths associated with mifepristone to the manufacturer. Such a requirement ensures that the manufacturer receives all reports of patient deaths and, in turn, fulfills its regulatory obligations to report those deaths to the FDA.

As discussed in Section 3.2.2 below, there is a potential for doubling of the number of prescribers of mifepristone if the in-person dispensing requirement in ETASU C is removed from the Mifepristone REMS Program. Given the potential addition of new prescribers, in addition to the considerations described above, we conclude that we should maintain the requirement for prescriber certification, to ensure that providers meet the necessary qualifications and adhere to the guidelines for use. Our literature review supports that these requirements are still necessary, and the potential increase in new prescribers under the REMS is a further reason to maintain prescriber certification. Healthcare provider certification continues to be a necessary component of the REMS to ensure the benefits of mifepristone for medical abortion outweigh the risks. The burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one time for each applicant.

3.2.2. Evaluation of the requirement for the drug to be dispensed with evidence or other documentation of safe-use conditions (ETASU D)

In order to receive mifepristone for medical termination of pregnancy through 70 days gestation, the patient must sign a *Patient Agreement Form* indicating that the patient has received, read, and been provided a copy of the *Patient Agreement Form* and received counseling from the prescriber regarding the risk of serious complications associated with mifepristone for this indication. The *Patient Agreement Form* ensures that patients are informed of the risks of serious complications associated with mifepristone for this indication.

[e] American College of Obstetricians and Gynecologists (ACOG) Practice Bulleting Number 191, February 2018. Tubal Ectopic Pregnancy. https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/03/tubal-ectopic-pregnancy. Mifepristone is not effective for terminating ectopic pregnancy. Some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. A missed ectopic pregnancy that ruptures is a medical emergency that requires immediate surgical intervention.

In a number of approved REMS, *Patient Agreement Forms* or *Patient Enrollment Forms* ensure that patients are counseled about the risks of the product and/or informed of appropriate safe use conditions.[f]

As a condition of certification under the Mifepristone REMS Program, healthcare providers must follow the guidelines for use of mifepristone, including reviewing the *Patient Agreement Form* with the patient, fully explaining the risks of the treatment regimen, and answering any questions the patient may have before receiving the medication. With this form, the patient acknowledges that they have received and read the form, and that they have received the counseling regarding when to take mifepristone, the risk of serious complications associated with mifepristone and what to do if they experience adverse events (e.g., fever, heavy bleeding). Both the healthcare provider and patient must sign the document and the patient must receive a copy of the signed form. In addition to the counseling described in the *Patient Agreement Form*, patients also receive a copy of the Medication Guide for mifepristone. Ultimately, the *Patient Agreement Form* serves as an important counseling component, and documentation that the safe use conditions of the Mifepristone REMS Program have been satisfied, as the prescriber is required to place the signed *Patient Agreement Form* in the patient's medical record.

Prior to the March 29, 2016 approval of the S-020 efficacy supplement for Mifeprex, FDA undertook a review of all elements of the REMS. At that time, the (b) (6) ((b) (6)), along with the (b) (6) ((b) (6)), recommended removal of the *Patient Agreement Form* (ETASU D). This recommendation received concurrence from the (b) (6) on February 23, 2016. The rationale for this recommendation in the 2016 review[g] is summarized here as follows:

- The safety profile of Mifeprex is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance.
- Established clinical practice includes patient counseling and documentation of informed consent and evidence shows that practitioners are providing appropriate patient

[f] REMS@FDA, https://www.accessdata fda.gov/scripts/cder/rems/index.cfm, Accessed November 15, 2021.
[g] (b) (6) Clinical Review, NDA 020687/S20, dated March 29, 2016. https://darrts fda.gov/darrts/faces/ViewDocument?documentId=090140af803dc7bd&_afrRedirect=386175573203745

counseling and education; the *Patient Agreement Form* is duplicative of these established practices.

- Medical abortion with Mifeprex is provided by a small group of organizations and their associated providers. Their documents and guidelines are duplicated in the *Patient Agreement Form*.
- ETASUs A and C remain in place: The *Prescriber Agreement Form* and the requirement that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals under the supervision of a certified prescriber, remain in place.

In light of a memorandum from the Director of the Center for Drug Evaluation and Research, an addendum to the (b) (6) March 29, 2016 review and a memorandum from the signatory authority in (b) (6) indicated that the *Patient Agreement Form* would be retained in the REMS.[h,i]

The current review of literature from March 29, 2016 to July 26, 2021, is relevant to our assessment of the necessity of the *Patient Agreement Form* as part of the REMS. While our literature search yielded no publications which directly addressed this element of the REMS, we identified the following literature that focused on the informed consent process. These studies were reviewed for their potential relevance on this topic, though the articles do not directly assess the need for the *Patient Agreement Form* as a condition necessary to assure safe use of Mifepristone under ETASU D.

- Two studies[1,2] (both authored by Dr. Grossman in 2021) used the *Patient Agreement Form* and additional clinic-specific written informed consent forms as part of the study methodology. One study evaluated medical abortion with pharmacist dispensing of mifepristone and another evaluated mail-order pharmacy dispensing. Safety and efficacy outcomes were not assessed regarding the element of consent in isolation or the *Patient Agreement Form*.
- Several studies included use of electronic or verbal consent. Two studies were conducted using signed electronic consent (Chong[3], Kerestes[4]). Aiken[5] reported that patients had the option of providing consent verbally and the discussion had to be recorded in the notes. Rocca[6] described obtaining verbal informed consent from patients seeking medical abortion provided in pharmacies or government-certified

h (b) (6) Review of proposed REMS modifications to Mifeprex. March 29, 2106.
i (b) (6) Summary of Regulatory Action for Mifeprex. March 29, 2016.

public health facilities by auxiliary nurse midwives (ANMs) in Nepal. Outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

- A retrospective chart review (Wiebe[7]) was conducted in Canada. This study included telemedicine abortions between January 31, 2017 and January 31, 2019 and a similar group of controls seen in the clinic during the same time frame, matched by date of initial appointment. As part of the telemedicine process, patients read a consent form (not specified whether they could view an electronic version) and gave verbal consent "witnessed by the counselor". Again, outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

After review, we conclude that there are no outcome data from these studies that address the need for the *Patient Agreement Form* as a condition necessary to assure safe use of mifepristone. Nor do any of these studies provide evidence of whether the patient's informed consent has been adequately documented under the process set out in the study protocol. Therefore, these studies do not provide evidence that would support removing ETASU D.

Although (b) (6) agrees that informed consent in medicine is an established practice, the National Abortion Federation's 2020 Clinical Policy Guidelines for Abortion Care[8] continue to include a detailed section on patient education, counseling, and informed consent. The guidelines state that these steps are essential parts of the abortion process; that they should be conducted by appropriate personnel, with accurate information, including about alternatives and potential risks and benefits; and that the patients must have an opportunity to have any questions answered to their satisfaction prior to any intervention. Under these guidelines, documentation must show that the patient affirms that they understand all the information provided and that the decision to undergo an abortion is voluntary. The guidelines specifically list the risks that must be addressed at a minimum, including those pertinent to medical abortion: hemorrhage, infection, continuing pregnancy, and death. Additionally, Practice Bulletins from ACOG[9] and the Society of Family Planning also support detailed patient counseling.

In addition, trends in US clinical practice are developing which could negatively impact adequate patient counseling about the risks of medical abortion. One survey by Jones 2017[10] of abortion providers in the United States and Canada prior to the COVID-19 pandemic did reveal strong adherence to evidence-based guidelines. However, this same survey noted continued increasing uptake of medical abortion by US providers. Grossman[11] conducted a US survey in

2019 which suggested that the number of obstetrician/gynecologists providing medical abortion care may be increasing and that uptake might increase if mifepristone were dispensed by pharmacies instead of being dispensed in-person. A subsequent survey of US obstetricians/ gynecologists by Daniel in 2021[12] evaluated a subsample (n = 868) from a prior national survey of providers and found that 164 (19%) reported providing medical abortion in the previous year. Of those obstetrician/gynecologists not providing medical abortion, 171 (24%) said they would offer the method to their patients if the in-person dispensing requirement for mifepristone were removed. This indicates a potential doubling of providers (+ 104%, 95% confidence interval (CI): 97% −112%). There were geographical variations, with the largest potential increases being in the Midwest (+ 189%, 95% CI: 172% −207%) and the South (+ 118%, 95% CI: 103% −134%).

Based on the articles discussed above, removal of the in-person dispensing requirement from the Mifepristone REMS Program (as discussed below in section 3.2.3) could significantly increase the number of providers to a larger group of practitioners. The *Patient Agreement Form* is an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients, and also provides the information in a brief and understandable format for patients. The requirement to counsel the patient, to provide the patient with the *Patient Agreement Form*, and to have the healthcare provider and patient sign the *Patient Agreement Form*, ensures that each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care. The single-page *Patient Agreement Form* is in line with other elements of this REMS, in that it supports the requirement that certified prescribers be able to accurately assess a patient, counsel a patient appropriately and recognize and manage potential complications. The form is placed in the patient's medical record to document the patient's acknowledgment of receiving the information from the prescriber and a copy is provided to the patient. We determined, consistent with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients, and that the *Patient Agreement Form* remains necessary to assure the safe use of Mifepristone.

After considering potential burden on healthcare providers and patients and considering the available data discussed above, including the potential for increased prescribing of mifepristone if in-patient dispensing is removed from the REMS, we conclude that the *Patient Agreement Form* should remain a safe use condition in the REMS.

3.2.3. Evaluation of the requirement for drug to be dispensed only in certain healthcare settings (ETASU C)

Mifepristone applicants must ensure that mifepristone is available to be dispensed to patients only in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber. This creates what we refer to in this document as an in-person dispensing requirement under the REMS; i.e., the patient must be present in person in the clinic, medical office or hospital when the drug is dispensed. The mifepristone REMS document states that mifepristone may not be distributed to or dispensed through retail pharmacies or settings other than these.

The following information contributed to our analysis of this requirement: Mifepristone REMS Program year-one assessment data, postmarketing safety information and literature review.

REMS Assessment Data

Reporting period for the Mifepristone REMS Program - April 11, 2019 through February 29, 2020

We evaluated information included in the one-year (1st)[j] REMS assessment reports for the Mifepristone REMS Program, which included healthcare provider certification data, program utilization data, compliance data, audit results and patient exposure data.[13] The assessment reports were submitted on April 10, 2020 by the NDA Applicant and April 15, 2020 by the ANDA Applicant and cover a reporting period from April 11, 2019 through February 29, 2020. During this reporting period, the NDA Applicant reported (b) (4) newly certified healthcare providers, and the ANDA Applicant reported (b) (4) newly certified healthcare providers in the Mifepristone REMS Program. The NDA Applicant reported a total of (b) (4) certified healthcare providers (includes new and previously certified) ordered mifepristone during the assessment reporting period, and the ANDA Applicant reported a total of (b) (4) certified healthcare providers ordered mifepristone during the assessment reporting period. The NDA Applicant estimated that a total of (b) (4) patients were exposed to mifepristone during the assessment reporting period. The ANDA Applicant reported an estimated total of (b) (4) patients were exposed to mifepristone during the reporting period.

During the reporting period, a small number of non-compliance events were reported. The authorized distributor for the NDA applicant reported to the NDA Applicant that they experienced deviations with scanning of the product serial numbers which were confirmed during the February 2020 audit. The authorized distributor conducted a root cause analysis and developed a corrective and preventive action (CAPA) on February 12, 2020. The CAPA was

[j] This REMS assessment report was the first to be submitted following the approval of the single, shared system REMS for mifepristone.

validated and deployed with monitoring of the system through April 10, 2020. The corrective action will prevent similar events from occurring in the future.

January 27, 2020 through September 30, 2021

During the timeframe from January 27, 2020 through September 30, 2021, there were periods when the in-person dispensing requirement was not being enforced.

- On July 13, 2020, the United States District Court for the District of Maryland granted a preliminary injunction in the *ACOG* case to temporarily bar enforcement of the in-person dispensing requirement during the COVID-19 PHE.
- On January 12, 2021, the United States Supreme Court issued a stay of the injunction.
- On April 12, 2021, the FDA issued a General Advice Letter informing the applicants of the Agency's intent to exercise enforcement discretion during the COVID-19 public health emergency regarding the in-person dispensing requirement in the Mifepristone REMS Program.[k,l]

To better understand whether there was any impact on safety or noncompliance during the periods when the in-person dispensing requirement was not being enforced, we requested additional information from the Applicants to provide for more comprehensive assessment of the REMS for the time period from January 27, 2020 (the effective date of the COVID-19 PHE) to September 30, 2021. We requested the Applicants provide a summary and analysis of any program deviation or noncompliance events from the REMS requirements and any adverse events that occurred during this time period that had not already been submitted to FDA. As part of an additional request for information for the REMS assessment report, the Applicants were also asked to submit the adverse events to FAERS and to notify FDA that the reports were submitted.

Between January 27, 2020 and September 30, 2021, the NDA Applicant distributed (b) (4) shipments representing (b) (4) tablets. The NDA Applicant reported that there were (b) (4) shipments representing a total of (b) (4) tablets sent to (b) (4) non-certified healthcare providers.[m,n] (b) (4) of these healthcare providers subsequently became certified while (b) (4) did not. Of the (b) (4) healthcare providers who were not subsequently certified, (b) (4) returned a total of 12 of the 13

[k] FDA General Advice Letter for NDA 20687, April 12, 2021.
[l] FDA General Advice Letter for ANDA 091178, April 12, 2021.

[m] NDA 020687 September 9, 2021 response to the FDA's September 2, 2021 Information Request.
[n] NDA 020687 October 8, 2021 response to the FDA's June 30, 2021 Information Request.

Mifeprex tablets to the distributor. (b) (4) non-certified healthcare provider dispensed one tablet to a patient; no adverse events were reported. The NDA Applicant attributed the non-compliance observed to the authorized distributor's transition to a new platform. The NDA Applicant implemented a corrective and preventative action to address this issue, which we found to be acceptable.

The ANDA Applicant distributed (b) (4) shipments representing (b) (4) tablets of mifepristone from January 27, 2020 to September 30, 2021 and reported no instances of shipments to non-certified healthcare providers during this timeframe.

The NDA and the ANDA applicants reported a total of eight cases reporting adverse events between January 27, 2020 and September 30, 2021. These eight cases were also identified in the FAERS database and are described in the section below.

The number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use for medical termination of pregnancy is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these reported adverse events. Further analysis of the adverse events is included below in the section on Pharmacovigilance Data.

Pharmacovigilance Data

The (b) (6) ((b) (6) conducted a search of the FAERS database and the published medical literature to identify U.S. postmarketing adverse events that reportedly occurred from January 27, 2020 through September 30, 2021 with mifepristone use for medical termination of pregnancy.[o,p]

The data for this time period were then further divided into date ranges when the in-person dispensing requirement was being enforced per the REMS (January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021) versus when the in-person dispensing requirement was not being enforced (July 13, 2020 - January 12, 2021 (in-person dispensing requirement was temporarily enjoined) & April 13, 2021 - September 30, 2021 (in-person dispensing requirement was not being enforced because of the COVID-19 PHE)).

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[o] (b) (6). Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. (b) (6) # 2007-525. Finalized April 12, 2021.

[p] (b) (6) Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. (b) (6) # 2007-525. Finalized December 16, 2021.

A total of eight cases that met the search criteria were identified in FAERS and no additional case reports were identified in the medical literature. Two of the eight cases reported adverse events that occurred when the in-person dispensing requirement in the REMS was being enforced (i.e., January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021). These two cases reported the occurrence of uterine/vaginal bleeding (case 1) and uterine/vaginal bleeding and sepsis (case 2). Of note, uterine/vaginal bleeding and sepsis are labeled adverse events. Five of the eight cases reported adverse events that occurred when the in-person dispensing requirement was not being enforced (i.e., July 13, 2020 - January 12, 2021 & April 13, 2021 - September 30, 2021). These five cases reported the occurrence of ongoing pregnancy (case 3), drug intoxication and death approximately 5 months after ingestion of mifepristone (case 4), death [cause of death is currently unknown] (case 5), sepsis and death (case 6), and pulmonary embolism (case 7). Although these adverse events occurred during the period when the in-person dispensing requirement was not being enforced, the narratives provided in the FAERS reports for cases 5, 6, and 7 explicitly stated that mifepristone was dispensed in-person. Of note, ongoing pregnancy, and sepsis, including the possibility of fatal septic shock, are labeled adverse events. The remaining case from July 2021 reported the occurrence of oral pain/soreness (case 8) but did not provide sufficient information to determine the exact date of the adverse event. Based upon the U.S. postmarketing data reviewed, no new safety concerns were identified by (b) (6)

In addition to the FAERS data provided above, (b) (6) routinely monitors adverse events reported to FAERS and published in the medical literature for mifepristone for medical termination of pregnancy. (b) (6) has not identified any new safety concerns with the use of mifepristone for medical termination of pregnancy.

To enable additional review of adverse events, the Applicants were requested[q] to provide a summary and analysis of adverse events reported with incomplete medical abortion requiring surgical intervention to complete abortion, blood transfusion following heavy bleeding or hemorrhage, ectopic pregnancies, sepsis, infection without sepsis, hospitalization related to medical abortion, and emergency department (ED)/urgent care encounter related to medical abortion. The Applicant for Mifeprex provided a summary of postmarketing safety information from March 29, 2016, when S-020 was approved, through September 30, 2021, on August 27 and October 8, 2021. During the time period in question, (b) (4) tablets were shipped, and

[q] On August 5, 2021, an IR was sent to the Applicants requesting a summary and analysis of adverse events from March 29, 2016 through June 30, 2021 and from July 1, 2021 through September 30, 2021.

48 adverse events were received. The 48 adverse events included 4 deaths (one of which occurred in 2010 but was reported in 2017), 25 incomplete abortions requiring surgical intervention, 17 blood transfusions following heavy vaginal bleeding, 2 ectopic pregnancies, 7 infections (1 sepsis and 6 infection without sepsis), 13 hospitalizations, and 43 ED or urgent care visits related to medical abortion. For the period between January 27, 2020 and September 30, 2021, a time frame that includes the entire period when the COVID-19 public health emergency (PHE) has been in effect, there were three adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 1 (uterine/vaginal bleeding), case 2 (uterine/vaginal bleeding and sepsis), and case 4 (drug intoxication and death).

The ANDA Applicant provided a summary of postmarketing safety information from April 11, 2019 (date of ANDA approval) through September 30, 2021. On August 26, 2021, the Applicant provided distribution and adverse event information from April 11, 2019 through June 30, 2021. During this time period, a total of (b) (4) tablets were shipped. There were 7 adverse events including 3 deaths (1 from sepsis, 1 from bilateral pulmonary artery thromboemboli, 1 in a patient who complained of not being able to breathe), 1 ongoing pregnancy treated with uterine aspiration, 2 blood transfusions, 1 sepsis (with death), 1 hospitalization, and 3 ED or urgent care visits related to medical abortion. On October 12, 2021 the Applicant provided information from July 1, 2021 to September 30, 2021; there were no additional adverse events. For the period between January 27, 2020 and September 30, 2021, there were four adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 3 (ongoing pregnancy), case 5 (death unknown cause), case 6 (sepsis and death), and case 7 (pulmonary embolism).[r]

The postmarketing data from FAERS were analyzed by (b) (6) to determine if there was a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. Based on this review, we conclude that there does not appear to be a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. This suggests that mifepristone may be safely used without an in-person dispensing requirement.

[r] The eighth FAERS case, oral pain/soreness, was not within the scope of the August 5, 2021 IR and was not considered for this review of postmarketing safety information submitted by the Applicants in response to the IRs.

(b) (6) review of the Applicants' IR responses, which included the same cases identified by (b) (6) from FAERS, did not change our conclusion.[s]

Literature Review

Published studies have described alternatives in location and method for dispensing mifepristone by a certified prescriber (or an equivalent healthcare provider in countries other than the US). Some studies have examined replacing in-person dispensing in certain health care settings with dispensing at retail pharmacies (Grossman[2], Wiebe[7], Rocca[6]) and dispensing mifepristone from pharmacies by mail (Grossman[1], Upadhyay[14], Hyland[15]). Other studies have evaluated two modes of dispensing by prescribers: (1) prescribers mailing the medications to women (Gynuity study [Raymond[16], Chong[3], Anger[17]], Kerestes[4], Aiken[5] (2021)) and (2) prescribers using couriered delivery of medications (Reynolds-Wright[18]). Other studies have evaluated dispensing mifepristone by mail by an entity described as "a partner organization" (Aiken[19] (2017), Norton[20], Endler[21]). For ease of review, in the sections below that describe these studies, we have separated relevant references by the methodology used to dispense mifepristone.

Retail pharmacy dispensing

Three studies report medical abortion outcomes for retail pharmacy dispensing of mifepristone after clinical evaluation. Grossman[2] conducted a US-based study in which mifepristone and misoprostol were dispensed from a pharmacy partnered with the clinic where the participant had an evaluation by ultrasound and counseling. Of the 266 participants enrolled, 260 had known abortion outcomes. Complete abortion without additional procedure occurred in 243 participants (93.5% of those with known outcomes). Seventeen participants (6.5% of those with known outcomes) were diagnosed with incomplete abortion and underwent uterine aspiration. The reported proportion of complete abortion is within the range described in the approved mifepristone labeling. However, the finding represents a lower-than-expected efficacy based on the cohort's GA (84% of participants were at ≤ 56 days GA, a cohort for which the labeled success rate is 96.8%). No participants experienced a serious adverse event, were hospitalized, or required transfusion. Three participants had ED visits with treatment (intravenous hydration, pain medication, pelvic infection after uterine aspiration for incomplete abortion). The study's

[s] The reporting period of (b) (6) assessment of the adverse events in FAERS is not identical to the time period for summaries of adverse events in the IRs to the Applicants. Therefore, the numbers of cases and adverse events summarized in (b) (6) assessment may differ from the numbers of cases and adverse events summarized by the Applicants in their responses to IRs (note that each case report may include more than one adverse event).

safety and efficacy outcomes are consistent with labeled frequencies. The majority of participants (65%) were very satisfied with the experience. There were some complaints from participants about not receiving all prescribed medications at the initial pharmacy visit, privacy not being adequately maintained, and perceived negative pharmacist attitude.

Overall, we conclude that this study has limited generalizability because it was conducted in two US states and involved partnered pharmacies, some of which were in the same building as the clinic. Additionally, all participating pharmacies in this study were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. The study conditions may not be generalizable to US retail pharmacies; there is insufficient information to assess this. Rocca[6] conducted an observational study evaluating 605 participants at ≤63 days GA who obtained medical abortions in Nepal by comparing the provision of medical abortion service by newly trained nurse midwives in pharmacies to medical abortion provided in government-certified clinics. Participants who presented to pharmacy study sites underwent clinical screening including a pelvic exam by trained nurse midwives at the pharmacy (which was equipped with an examination room) and if eligible for medical abortion, were dispensed mifepristone and misoprostol in the pharmacy at the time of their visit. Participants who presented to public health facilities underwent clinical screening including pelvic examination by abortion providers including trained nurse midwives and if eligible for medical abortion were dispensed mifepristone and misoprostol in the clinic at the time of their visit. The authors reported that, with respect to complete abortion (>97%) and complications (no hospitalizations or transfusions), evaluation and dispensing in pharmacy was non-inferior to in-clinic evaluation and dispensing.

Wiebe,[7] in a retrospective, chart review study conducted in Canada, compared abortion outcomes of 182 women at ≤ 70 days GA who underwent medical abortion with telemedicine consult, and either received medications by courier or picked them up at a local pharmacy, with outcomes of a matched control cohort of 199 women who received the medications at a pharmacy after an in-clinic visit. The groups had similar documented complete medical abortion outcomes (90%, calculated maintaining subjects with unknown outcomes in the denominator; ≥ 95% calculated with known outcomes only). The telemedicine group had one case of hemorrhage (0.5%) and one case of infection requiring antibiotics (0.5%) compared with no cases of hemorrhage or infection requiring antibiotics in the in-clinic cohort. The telemedicine group had more ED visits (3.3% compared to 1.5% in-clinic cohort). Both models of dispensing mifepristone resulted in efficacy and safety outcomes within labeled frequency.

None of the three studies described above allow a determination regarding differences in safety between in-person dispensing by a certified prescriber in a health care setting and dispensing through a retail pharmacy, due to limitations on the generalizability of the studies to the current retail pharmacy environment in the US. The outcome findings from the one US study (Grossman[2]), in which the pharmacies were partnered with prescribers, may not be generalizable to much of the US as they do not reflect typical prescription medication availability with use of retail pharmacy dispensing. Although retail pharmacy dispensing of mifepristone and misoprostol in Canada has been described in the literature, there are important differences in healthcare systems between Canada and the US that render the findings from studies in Canada (Wiebe[7]) not generalizable to the US. In the Wiebe study, timely provision of medication from the retail pharmacy was accomplished by either courier to the woman or faxed prescription to the woman's pharmacy. It is unknown whether conditions that allow timely access to medications for medical abortion would occur in retail pharmacies throughout the US. Canada's federal government has reaffirmed that abortion is an essential health service[t] which may have implications affecting access to medical abortion from retail pharmacies in Canada. The Rocca[6] study evaluated medical abortion provided in Nepali pharmacies and essentially moved the abortion provider and clinical examination into the pharmacy, a scenario that is not, at this time, applicable to the US retail setting.

Mail order pharmacy

Grossman[1] published an interim analysis of an ongoing prospective cohort study evaluating medical abortion with mifepristone and misoprostol dispensed by mail-order pharmacy after in-person clinical assessment. All participants were evaluated for eligibility during a clinic visit with GA up to 63 days confirmed with either an ultrasound or examination; instead of receiving medication at the clinic visit, participants received medications from a mail-order pharmacy. A total of 240 participants have been enrolled; three participants did not take either medication. A total of 227 (94.6%) provided some outcome information, of whom 224 provided abortion outcome information. Complete abortion without additional procedures occurred in 217 participants (96.9% of those with known outcomes). Two (0.9%) participants experienced serious adverse events (SAE); one received a blood transfusion, and one was hospitalized overnight. Nine (4%) participants attended 10 ED visits. In this interim analysis, the outcomes are consistent with labeled frequencies. With respect to the time interval between a

[t] As noted in Mark[23] and Martin[24], most provincial and federal health insurance programs in Canada cover medical abortion, and covered services are free at the point of care.

participant's clinic visit and receipt of medications, of the 224 participants with known abortion outcomes, 184 (82.1%) received medication within 3 days. However, 17% received between 4-7 days and one participant waited over 7 days for receipt. Seven of 216 (3.2%) participants who completed the day-3 survey reported compromised confidentiality (e.g., someone found their medication, privacy concerns).

Upadhyay[14] reports findings from a retrospective cohort study of 141 women undergoing medical abortion in the US without a consultation or visit. Eligibility was assessed based on a participant-completed online form collecting pregnancy and medical history. Participants who were considered eligible received medication delivered by a mail-order pharmacy. Three interactions via text, messaging or telephone occurred to confirm medication administration, assessment of expulsion and pregnancy symptoms, and results of a 4-week home pregnancy test. Abortion outcome was determined by either the day 3 assessment or the 4-week pregnancy test. The investigators reported a complete abortion rate without additional procedures of 95% (105 participants out of 110 for whom outcomes were known) and stated that no participants had any major adverse events. The proportion of abortion outcomes assessed at 3 days versus 4 weeks is not reported. Regardless, determining outcomes at 3 days is insufficient to determine outcome rates or safety findings because a 3-day follow-up period is too short. Additionally, a substantial number of participants (31) provided no outcomes information. Among the 141 participants enrolled, 128 had any follow-up contact with the study staff, and 110 provided outcomes information. Excluding outcomes of 22% of the cohort is a limitation of this study. This study used a model with numerous deviations from standard provision of medical abortion in the US, such as no synchronous interaction with the prescriber during informed consent or prior to prescribing medication, no confirmation of self-reported medical, surgical, and menstrual history. Further, follow-up information based on a 3-day period is insufficient to determine outcome rates or safety findings. These deviations, limited follow-up information, and small sample size limit the usefulness of this study.

Hyland[15] describes findings from a cohort study in Australia evaluating medical abortion outcomes utilizing telemedicine and a central mail order pharmacy. All participants obtained screening tests including ultrasound confirmation of GA. A total of 1010 participants completed the screening process and were provided mifepristone and misoprostol. Abortion outcomes were determined for 754 (75%) of the 1010. Outcomes for the remaining 256 participants (25%) were not included because 31 provided no relevant information after shipment, 14 reported not taking misoprostol, and 211 did not have "full follow up" (i.e., known outcome of either complete medical abortion, uterine evacuation, or ongoing pregnancy with plan to continue).

Complete abortions without additional procedures occurred in 727 participants (96% of those with definitively documented outcomes) and is consistent with labeled efficacy. Of the 754 participants included in the analysis 717 (95%) had no face-to-face clinical encounters after medications were mailed while 21 (3%) were admitted to the hospital and 16 (2%) had an outpatient encounter. One participant who was hospitalized and underwent a surgical uterine evacuation received a transfusion. Not included in the findings are 7 hospitalizations occurring in 7 participants who did not have "full follow up". The authors do not report any other adverse events and conclude use of the telemedicine medical abortion service is safe. The reasons for hospitalization are not discussed by the authors; therefore, it is unknown why the patients were hospitalized. Although the reported number of hospitalizations (3%) is higher than the less than 1% in the FDA-approved mifepristone labeling, conclusions regarding the safety findings in this study cannot be made in the absence of information about the reasons for hospitalization. Other limitations of this study include incomplete information about outcomes with face-to-face encounters, and not reporting outcomes of 25% of the enrolled cohort.

Overall, the three studies evaluating mail order pharmacy dispensing suggest that the efficacy of medical abortion is maintained with mail order pharmacy dispensing. In the Grossman[1] study, the interim analysis, although small, does not raise serious safety concerns. We note that 18% of participants did not receive medications within 3 days; the potential for delay in receiving medication by mail could limit the GA eligible for medical abortion through mail order pharmacy dispensing, because women at GA closer to 70 days might not receive medication in time. A small proportion (3%) of participants raised concerns regarding the issues of confidentiality and privacy. Safety findings from the Hyland[15] study are difficult to interpret. Although only one transfusion is reported, and the authors state the findings demonstrate safety, the higher hospitalization rates, and lack of information on the reasons for hospitalization do not allow any conclusions about safety findings. Lastly, the Upadhyay[14] study had no reported adverse events, but the findings are less useful because of the limited follow-up, and because medical abortions were provided using a model with numerous deviations from standard provision of medical abortion in the US.

Clinic dispensing by mail

A total of five studies evaluated clinic dispensing by mail.[3,4,5,16,17] Gynuity Health Projects conducted a prospective cohort study (the "TelAbortion" study) evaluating use of telemedicine for remote visits and mifepristone being dispensed from clinics via overnight or regular tracked mail. Three publications reviewed have reported outcomes for the Gynuity population

exclusively: Raymond[16] from May 2016 to December 2018, Chong[3] from May 2016 to September 2020 and Anger[17] from March 2020 to September 2020. Due to the pandemic, the Gynuity study deviated from the protocol requirement of confirmation of GA by examination or ultrasound for many participants treated from March 2020 onward (although none of the three publications reported on the single element of dispensing mifepristone from the healthcare setting by mail). A fourth study, Kerestes,[4] reports outcomes of medical abortion at the University of Hawai'i from April 2020 to November 2020: seventy-five (of whom 71 were enrolled in the Gynuity study) of the 334 participants in Kerestes were dispensed mifepristone by mail after a telemedicine consult. The section below discusses these four studies from the US as well as a large UK study by Aiken[5] (2021).

Raymond [16] (2019) reported outcomes from the Gynuity study prior to the pandemic. In the TelAbortion study, participants were not required to have an in-person clinic visit; rather, they obtained screening tests at laboratories and radiology offices and then communicated with the abortion provider by videoconference. If the participant was eligible for treatment, the provider dispensed the medications by mail. Of 433 women screened, 165 (38%) either declined to schedule the videoconference or did not keep the videoconference appointment. Among the 268 participants evaluated via videoconference, medication packages were sent to 248. Abortion outcomes were determined for 190 (77%) of the 248; outcomes for 58 (23%) participants were unknown. Complete abortion without additional procedures occurred in 177 participants (93% of those with known outcomes). The investigators obtained follow-up information from 217 participants after package shipment; there were two hospitalizations (one received a transfusion for severe anemia despite having had a complete abortion), and 16 other participants (7%) had clinical encounters in ED and urgent care centers. The reported outcomes in Raymond[16] (2019) are similar to outcomes described in approved labeling except the combined ED/urgent care center encounters (7%) exceeded the ED visits in approved labeling (2.9-4.6%). The authors note that half of the ED/urgent care visits did not entail any medical treatment and opine that the increased number of visits may have been due to the study participants living farther from the abortion providers.[16] All participants received medications within 8 days.

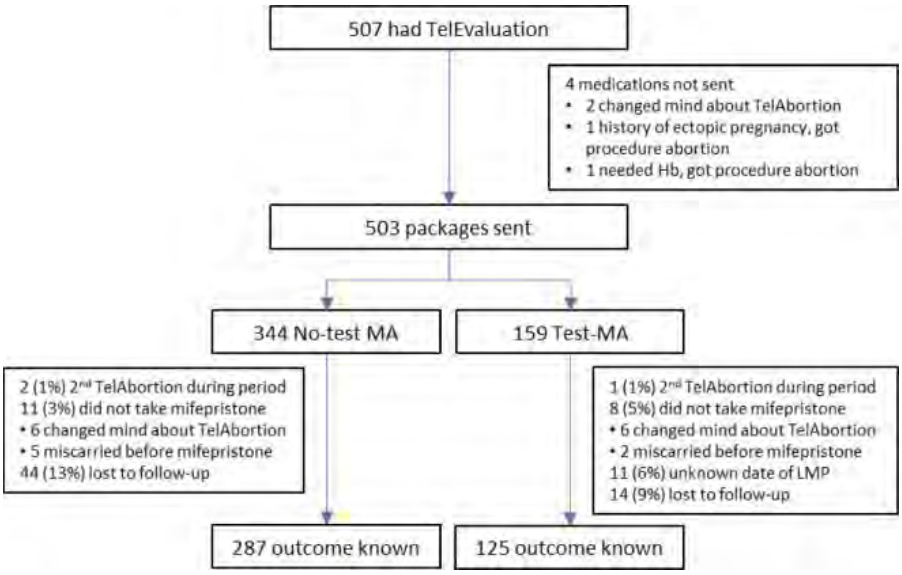
Chong[3] updated the findings from the Gynuity study described in Raymond[16] and reported on 1157 medical abortion outcomes, of which approximately 50% occurred during the period of the COVID-19 PHE. Although a screening ultrasound was required per the protocol, sites determined in 52% (346/669) of abortions that occurred during the period of the COVID-19 PHE that, in order to avoid potential exposure to COVID-19 at a health care facility, those

Reference ID: 4905882

participants were not required to obtain a screening ultrasound. Use of urine pregnancy test to confirm abortion completion also increased from 67% (144/214) in the 6 months prior to the pandemic to 90% (602/669) in the 6 months during the pandemic. Of the 1390 participants to whom medicine packages (containing both mifepristone and misoprostol) were mailed, 1157 (83.2%) had known abortion outcomes. Complete abortion without a procedure occurred in 1103 participants (95% of the those with a known outcome). Ten women experienced an SAE (5 transfusions (0.4%) and 7 hospitalizations (0.7%)) and 70 (6%) participants had unplanned clinical encounters in ED/urgent care. Surgical interventions were required in 47 participants (4.1% of 1390) to complete abortion. The reported outcomes in this study are similar to outcomes described in approved labeling, except that the combined ED/urgent care center encounters (6%) exceeded the ED visits in approved labeling (2.9-4.6%).

Anger[17] compared outcomes among participants enrolled in the Gynuity study who did versus did not have confirmation of GA/intrauterine location with an examination or ultrasound from 10 jurisdictions across the US. These participants were screened for enrollment from March 25 through September 15, 2020. All participants had a telemedicine consultation and received mifepristone and misoprostol by mail from the healthcare facility. Determination of which participants did not require confirmation of GA by examination or ultrasound to be eligible depended on the study clinician's assessment of eligibility for "no-test medication abortion"[u] based on a sample protocol published by Raymond[22] (2020). There were two key differences between the two groups. Participants for whom the study clinician determined a pre-abortion ultrasound was required were more likely than the participants who had no ultrasound or examination to live further than 150 miles from the clinic (51.2% vs. 31.7%) and were more likely to have a GA above 63 days (12.0% vs. 1.7%). The study sites shipped 503 medication packages during the analysis period; 344 packages went to the "no test" group while 159 went to the "test" medical abortion cohort (see figure below). However, because the two cohorts were not randomized in this study, they had different baseline characteristics. Consequently, findings based on the comparisons between the two cohorts should be interpreted carefully.

[u] "No-test medication abortion" refers to medical abortion provided without a pretreatment ultrasound, pelvic examination, or laboratory tests when, in the judgment of the provider, doing so is medically appropriate (appropriateness based on history and symptoms); "no-test medication abortion" does include post-abortion follow up. A sample protocol is described by Raymond et al.[22]



Source: Figure 1 in this publication. MA= medical abortion.

The investigators' analyses excluded 91 (18% of 503; 57 in the no-test group and 34 in the test group) participants because they did not provide a date of the last menstrual period (LMP), did not take mifepristone, or did not have a recorded abortion outcome. Overall, 410 participants (81.5% of 503) provided outcomes data. There were no reported ectopic pregnancies in either group. The number of ED/urgent care visits and the proportion of unplanned clinical encounters that led to medical treatment were not reported. In the no-test group, complete medical abortion was confirmed in 271 participants who took medications (94% among those with known outcome). In the no-test cohort, two participants were "hospitalized and/or blood transfusion," and 36 (12.5%) had an unplanned clinical encounter (participant sought in-person medical care related to abortion and the visit was not planned prior to abortion).

In the test medical abortion group, complete abortion was confirmed in 123 participants (of 125 with known outcomes); the completion rate was 98% among those with known outcomes. In the test medical abortion group, one participant was "hospitalized and/or blood transfusion," and 10 (8.0%) had an unplanned clinical encounter. The authors concluded that, compared to participants who had an ultrasound prior to medical abortion, those without an examination prior to medical abortion were more likely to require procedural interventions and had more unplanned clinical encounters.

Kerestes[4] was the only publication that linked outcomes of medical abortion with different delivery models. Participants included in the report had GA up to 77 days and received

medications in Hawaii between April 2020 and January 2020. A total of 334 medication packages (to 330 unique participants) were dispensed containing mifepristone and misoprostol; three different delivery models were used concurrently: 110 (32.9%) had traditional in-person visits, 149 (44.6%) had telemedicine consultation with in-person pick-up of medications, and 75 (22.5%) were sent medications by mail (71 of these were enrolled through Gynuity's TelAbortion study). Seven participants of the 330 participants who received 334 medication packages reported that they did not take them and were excluded from analysis of the outcomes. Among participants with follow-up data, the rates of successful medical abortion without surgery were 93.6%, 96.8%, and 97.1% in the in-clinic group, telemedicine + in-person pickup group, and telemedicine + mail group, respectively; these were consistent with outcomes in approved labeling. Blood transfusion was given to two participants (both in the telemedicine + in-person pickup group). Eleven participants went to an ED. Although ED visits occurred the most frequently in the telemedicine + mail group (four participants or 5.8%) and the least in the in-person group (two participants or 2.1%), the study reported no increases in other serious adverse events.

Taken together, the three Gynuity study reports[3,16,17] and Kerestes[4] support dispensing mifepristone and misoprostol by mail after a telemedicine visit. Efficacy was maintained in all four studies. All of the studies reported SAEs frequencies comparable to labeled rates, except two of the Gynuity study reports (Raymond[16], Chong[3]) and Kerestes[4] report a higher frequency of ED/urgent care visits than the labeled frequency of ED visits. We do not know whether the reporting of combined ED and urgent care visits represents an increased rate of ED visits compared to the labeled rate of ED visits (2.9-4.6%). Other labeled SAEs (e.g., transfusion) occur infrequently (< 1%).

Aiken[5] (2021) reports outcomes of medical abortion up to 70 days GA in the UK before and during the pandemic in a retrospective cohort study. In the UK, prior to the COVID-19 pandemic, all patients attended an in-clinic visit where they received an ultrasound, were administered mifepristone in the clinic, and given misoprostol in-clinic for use at home (traditional model). During the pandemic, medical abortion consultations were performed remotely by telephone or video. Based on the consultation and questionnaire (including date of last menstrual period; menstrual, contraceptive and medical history; symptoms; risk for ectopic pregnancy), an assessment of eligibility for treatment via telemedicine was made. If eligible, medications were delivered to participants via mail or were made available for collection from the clinic for use at home. If the participant was assessed to be ineligible for treatment via

telemedicine, an in-person assessment with ultrasound was performed and medications were provided from the clinic for home use (hybrid model).

The study compared the two cohorts: 22,158 obtained medical abortion before the pandemic and had in-person visits and dispensing (traditional model) and 29,984 obtained medical abortion during the pandemic with either in-person visit and in-person dispensing, or a telemedicine visit and dispensing by mail or picked up from the clinic (hybrid model). Outcomes were obtained from electronic records and incident databases. Outcomes of all hospitalizations related to abortion, ED visits, infection without sepsis, and hemorrhage without transfusion were not reported. The investigators' analysis for non-inferiority determined the efficacy and safety were comparable between both cohorts. Complete abortion occurred in > 98% in both cohorts. Hemorrhage requiring transfusion was reported in 0.04% and 0.02% of the traditional and hybrid cohorts, respectively; this is lower than the labeled 0.5% transfusion rate. There were no severe infections requiring hospitalization, major surgery or deaths reported.

A secondary analysis of the hybrid cohort was reported. Within the 29,984-person hybrid model cohort, 11,549 (39%) abortions were conducted in-person (in-person assessment with ultrasound was performed and medications provided from the clinic for home use) and 18,435 (61%) abortions were provided by telemedicine visit, without tests or confirmation of GA/intrauterine position by ultrasound, and medications either mailed or picked up from the clinic. Outcomes stratified by type of mifepristone dispensing were not reported. The rate of complete abortion was slightly higher in the telemedicine group (99.2%) than that in the in-person group (98.1%). There were no significant differences in the rates of reported SAEs. Adjustments for clinical and demographic characteristics were made because the two groups differed in baseline characteristics, including a higher proportion of pregnancies with GA over 6 weeks in the in-person group (68.2% compared with 55.1%). The authors conclude a hybrid model for medical abortion that includes no-test medical abortion[u] (no ultrasound, no pelvic exam, no pregnancy test) is effective and safe.

We conclude that although the Aiken[5] (2021) study has a large sample size and includes 85% of all medical abortions performed in England and Wales during the study period, the study has limitations. The authors acknowledge the main limitation of their study was that analysis was based on deidentified information in the NHS database and the investigators were unable to verify the outcomes extracted. Other limitations included that their search only captured

outcomes in electronic records and incident databases that met the authors' defined threshold for SAE reporting, and that the labeled abortion outcomes considered serious, such as hospitalizations related to abortion, infection without sepsis, hemorrhage without transfusion, or ED/urgent care visits, were not all included in the authors' definition of serious adverse event.

Data from the mail order dispensing studies with telemedicine visits from Gynuity (Raymond, Chong and Anger),[3,16,17] Kerestes[4], and Aiken[5] (2021) support that efficacy of medical abortion was maintained. The Aiken[5] study appears to be of sufficient sample size to determine whether safety outcomes with mail dispensing differ from in-person dispensing; however, the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings. Study reports of Raymond[16] Chong[3], and Kerestes[4] all suggest there may be an increase in ED/urgent care visits with telemedicine visits and dispensing by mail without increases in other adverse events. Anger's[17] comparative analysis suggests a pre-abortion examination may decrease the occurrence of procedural intervention and decrease the number of unplanned visits for postabortion care. Overall, despite the limitations noted, these studies support that dispensing by mail is safe and effective. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other SAEs related to mifepristone use. One reason for the increase in frequent ED/urgent care visits in the Raymond[16] publication, according to its authors, may have been that a substantial proportion of participants lived significant distances from their providers and increased distances have been associated with higher use of ED following treatment. Raymond[16] reported that half of the participants who had an ED/urgent care visit did not require medical treatment.

Clinic dispensing by courier

Reynolds-Wright[18] reported findings from a prospective cohort study of 663 women at less than 12 weeks' GA in Scotland undergoing medical abortion at home with use of telemedicine during the pandemic (from April 1 to July 9, 2020). The majority of medical abortions (78.7%) used telemedicine visits, eliminated pre-abortion ultrasound, and provided mifepristone for pick up at the service or by couriered delivery to woman's home. The number of couriered deliveries was not reported; thus, this study does not provide abortion outcomes separately for couriered delivery of mifepristone and misoprostol. With access to NHS regional hospital databases, the investigators were able to verify pregnancy outcomes and complications. Of the 663 participants, 642 (98.2%) were under 10 weeks GA, 21 (1.8%) were between 10 and 12 weeks

GA, and one participant was never pregnant. A total of 650 participants had complete abortion without requiring surgical intervention (98%), 5 (0.8%) an ongoing pregnancy and 4 (0.6%) an incomplete abortion. The outcomes from this study in Scotland are consistent with labeled mifepristone outcomes. The study shares the same limitations as the Aiken[5] (2021) study.

Partner organization dispensing by mail

Women on Web (WoW), an internet group, connects patients and providers outside of the US and provides medical abortion globally, dispensing mifepristone through "a partner organization" by mail.[v] Medical abortion eligibility is determined using an online questionnaire with asynchronous physician review. If eligible, medications are mailed to the women. WoW provides help and support by email or instant messaging.

Aiken[19] (2017) conducted a population-based study analyzing findings from 1,636 women in the Republic of Ireland and Northern Ireland who were sent medications between 2010 and 2012. Receipt of medications was confirmed for 1,181 women, among whom 1,023 confirmed use of mifepristone and misoprostol; outcome information was available for 1,000 (61% of women sent medications). Of the 1,000 women, the majority (781, 78%) were less than 7 weeks GA and 219 (22%) were at 7-9 weeks. Complete abortion without surgical intervention occurred in 947 (94.7% of 1,000 with known outcome); 7 (0.7%) women received a blood transfusion, 26 (2.6%) received antibiotics (route of administration undetermined) and 87 (8.7%) sought medical care at a hospital or clinic for symptoms related to medical abortion. Hospitalizations related to abortion were not reported. The reported proportion of complete abortion is within the range labeled for medical abortion up to 70 days (92.7-98.1%). However, the finding of 94.7% complete abortion represents a lower-than-expected efficacy based on the cohort's GA (almost 80% less than 7 weeks, labeled success for medical abortion ≤ 49 days is 98.1%). This study has limitations, including outcomes based on self-report without validation of completed abortion by examination or laboratory testing, and no known outcomes for 39% of study cohort. Additionally, the authors noted medical abortion was provided in a legally-restrictive setting, where the law provided a maximum penalty of life imprisonment for the woman undergoing the abortion, which may affect participants' self-reporting.

[v] In March 2019, FDA sent a WL to Aidaccess.org, a group affiliated with WoW. Aidaccess.org received this WL because it was introducing misbranded and unapproved new drugs into the U.S. In the context of this REMS review, studies involving WoW are included solely for purposes of evaluating of data regarding the methods of dispensing mifepristone.

Endler[21] and Norten[20] have reported outcomes from WoW cohorts but do not provide relevant information on mifepristone dispensing by mail, because neither provide meaningful outcomes data for consideration. Endler[21] compared the outcomes of self-reported heavy bleeding and clinical visits occurring during the "first or second day of abortion" that occurred in women undergoing medical abortion at 9 weeks GA or less, with outcomes from women at more than 9 weeks GA. Outcome data from day 1 or 2 is of limited usefulness. Norten[20] describes findings from a survey of women who were sent medical abortion medication through WoW and provided self-reported outcomes. Results were based on surveys returned from only 37% of participants, a return rate that is too low for the study to be considered valid.

WoW uses a model with numerous deviations from the standard provision of medical abortion in the US. For example, this model has no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history or confirmed pregnancy testing. Further, although Aiken[19] (2017) is a large cohort study, the outcomes are self-reported with no verification of complete abortion by laboratory or clinical evaluation and 39% of outcomes are unaccounted for. These limitations in the Aiken study result in the data being insufficient to determine the safety of dispensing mifepristone by mail through a partner organization.

4. Discussion

After review of the published literature, safety information collected during the COVID-19 PHE, postmarketing data, information from the first Mifepristone REMS Program assessment report, responses to information requests to the Applicants, and information provided by advocacy groups, individuals and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that the REMS can be modified to reduce burden without compromising patient safety.

Prescriber Certification

None of the publications we reviewed would support a conclusion that a healthcare provider who prescribes mifepristone does not need to meet the qualifications included in the Mifepristone REMS Program as described above in section 3.2.1. Absent these provider qualifications, serious complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed.

We conclude that prescriber certification (ETASU A) should be maintained. The current process requires the prescriber to agree to the requirements of the Mifepristone REMS Program and to attest that they meet the qualifications described in section 3.2.1 above. The REMS has been structured to minimize burden to prescribers by requiring only a one-time certification by the prescriber for each Applicant. We have determined that healthcare provider certification continues to be necessary to ensure the benefits outweigh the risks, especially considering that, if the in-person dispensing requirement is removed from the Mifepristone REMS Program, the number of new providers may increase (see discussion in section 3.2.2 above).

Drug to be dispensed with evidence or other documentation of safe use conditions

The requirement to counsel the patient and provide them with the *Patient Agreement Form* ensures that each patient is informed of the appropriate use of mifepristone, the risks associated with treatment, and what to do if they experience symptoms that may require emergency care.

In 2016, we initially recommended eliminating the *Patient Agreement Form* (see section 3.2.2), though the form was ultimately maintained as part of the REMS. As discussed above, our current literature review has indicated that there is no basis to remove the *Patient Agreement Form* from the REMS. In addition, surveys we reviewed suggest that if the in-person dispensing requirement for mifepristone is removed, there could be a potential doubling of medical abortion providers. This potential doubling of medical abortion providers supports the continued need to ensure that patients are consistently provided patient education under the Mifepristone REMS Program regarding the use and risks of mifepristone. The *Patient Agreement Form* is an important part of standardizing the medication information that prescribers communicate to their patients, including new prescribers, and also provides the information in a brief and understandable format to patients. We determined, in accordance with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients.[w]

Given the likelihood of a potential increase in new prescribers if the in-person dispensing requirement is removed from the Mifepristone REMS Program, we conclude that maintaining the *Patient Agreement Form* remains necessary to assure safe use at this time.

[w] *The Patient Agreement Form* can be signed in person or through other means.

Drug to be dispensed only in certain healthcare settings

As discussed above in section 3.2.3, our evaluation of information submitted by the applicants in the one-year (1st) REMS assessment report for the Mifepristone REMS Program and in response to follow-up requests from the Agency indicates that the number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these adverse events. We further conclude, based our review of the postmarketing safety data from FAERS during the COVID-19 PHE and information submitted by the applicants for the timeframe of January 27, 2020 through September 30, 2021, that there does not appear to be a difference in adverse events between periods during the COVID-19 PHE when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced; nor have we identified any new safety concerns with the use of mifepristone for medical termination of early pregnancy.

Alternatives to in-person dispensing of mifepristone have been investigated in several studies and countries. The literature review identified 15 publications[x] that assessed safety outcomes from various medication delivery models (US, UK, Canada, Ireland, Australia, Nepal), including dispensing by retail and mail order pharmacies, prescribers mailing medications or using couriered service to deliver medications, and dispensing by "partner organizations". The ability to generalize the results of these studies to the US population is hampered by differences in pre-abortion care (e.g., telemedicine versus in-person, testing), and the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy.

In addition, there are factors which complicate the analysis of the dispensing element alone. Some of these factors are: (1) only a few studies have evaluated alternatives for in-person dispensing of mifepristone in isolation; for example, most studies on mail dispensing of mifepristone also include telemedicine consultation, and (2) because most SAEs with medical abortion are infrequent, though they can be life threatening, further evaluation of changes in dispensing would require studies with larger numbers of participants. We did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the US.

[x] The 15 publications correspond to endnote numbers: 1-7, 14-21.

Based on the literature identified by our review, dispensing mifepristone by mail from the clinic or from a mail order pharmacy does not appear to jeopardize the efficacy of medical abortion. The studies we reviewed are not adequate on their own to establish the safety of the model of dispensing mifepristone by mail, although the safety and efficacy outcomes reported in these studies remain within the ranges described in mifepristone labeling except for increased numbers of ED/urgent care visits and hospitalizations.

Four publications (Raymond[16], Chong[3], Anger[17] and Kerestes[4]), describe a relevant US cohort where dispensing mifepristone from the clinic by mail was paired with telemedicine visits. These studies showed that efficacy was maintained and there was no increased frequency of SAEs except for higher ED/urgent care visits. The increased ED/urgent care visits were not associated with increases of other SAEs, and in the view of one study's authors (Raymond[16]), may be associated with participants being located significant distances from their providers. The Aiken[5] (2021) study of a large UK cohort where the clinics mailed mifepristone report small (lower than labeled) occurrences of transfusion and no significant infections requiring hospitalization. In Grossman[1] and Hyland[15], where the pharmacies mailed mifepristone after prescribers confirmed GA, efficacy is maintained. Grossman's[1] interim analysis found no increases in SAEs. Hyland[15] reported higher numbers of hospitalizations but did not report increases of other SAEs. Overall, while the studies assessing mifepristone dispensing by mail suggest more frequent encounters with healthcare providers, they generally support a conclusion that dispensing by mail is safe. Despite the limitations of the studies we reviewed, we conclude that overall, the outcomes of these studies are not inconsistent with our conclusion that, based on the 1st year REMS assessment report and postmarketing safety data, mifepristone will remain safe, and efficacy will be maintained if the in-person dispensing requirement is removed from the Mifepristone REMS Program.

Based on the REMS assessment data, FAERS data from the time period when the in-person dispensing requirement was not being enforced, our review of the literature, and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that mifepristone will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met, and pharmacy certification is added as described below.

Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to

ensure that the benefits of mifepristone for medical abortion outweigh the risks. Therefore, to reduce the burden imposed by the REMS, the Mifepristone REMS Program should be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies, in addition to in-person dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C.

New requirement to be added for pharmacy certification

The current distribution model requires the certified prescriber to dispense mifepristone directly to the patient in a clinic, medical office, or hospital. During the periods when the in-person dispensing requirement was not being enforced, both applicants used mail order pharmacies to receive and hold mifepristone on behalf of the certified healthcare providers who had purchased the product.[j,y,z] Pursuant to a prescription for mifepristone, the mail order pharmacy would ship the product to a named patient.

The Mifepristone REMS Program continues to require that mifepristone be prescribed only by certified prescribers. With the removal of the in-person dispensing requirement, however, the drug is no longer required to be dispensed only in a clinic, medical office or hospital. Under the REMS as modified, mifepristone can be dispensed through a pharmacy, provided the product is prescribed by a certified prescriber and all other requirements of the REMS are met. Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies under ETASU B. Adding the pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Without pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber. Adding pharmacy certification ensures that ETASU A is met prior to dispensing the product to a patient; certified prescribers, in turn, have agreed to meet all the conditions of the REMS, including ensuring that the *Patient Agreement Form* (ETASU D) is completed. In addition, wholesalers and distributors can only ship to certified pharmacies. Based on our review of the safety data and our consideration of the distribution model implemented by the Applicants during the periods

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y ANDA 091178: September 23, 2021 response to the September 15, 2021 information request; October 11 and 16, 2021 responses to the June 30, 2021 and July 15, 2021 information requests; October 26, 2021 response to the October 22, 2021 information request; October 29, 2021 response to the October 27 information request.
z NDA 020687: September 20, 2021 response to the September 15, 2021 information request; October 26, 2021 response to the October 22 information request.

when the in-person dispensing requirement was not being enforced, as well as REMS assessment data and published literature, we conclude that provided all other requirements of the REMS are met, the REMS program, with the removal of the in-person dispensing requirement and the addition of a requirement for pharmacy certification, will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients. As modified, the REMS would allow, for example, dispensing by mail order or specialty pharmacies, similar to the distribution model used by applicants during the periods when the in-person dispensing requirement was not being enforced.[aa]

The above recommendations were discussed with the (b) (6) ((b) (6) and senior leadership from CDER on November 2, 2021. The (b) (6) (b) (6) along with senior CDER leadership, concurred with removing the in-person dispensing requirement provided that all of the remaining REMS requirements are met, including but not limited to prescriber certification where prescribers need to attest to having certain qualifications, and maintaining the *Patient Agreement Form*. The (b) (6) (b) (6) and senior leadership from CDER were also in favor of adding pharmacy certification to assure the safe use of mifepristone.

5. Conclusions and Recommendations

Based on the results of REMS assessments; our review of safety data collected during the PHE as well as data from FAERS; our literature search; and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, (b) (6) and (b) (6) have concluded that a REMS modification is necessary and should include the following changes:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified.

[aa] Our current conclusion that the REMS would allow dispensing by mail order or specialty pharmacies is based on data received from Applicants relating to the periods when the in-person dispensing requirement was not enforced and mail-order pharmacies were used to dispense the product, as well as our analysis of postmarketing safety data and available literature. At this time we do not have data (from the Applicants or from other sources) to assess the certification of retail pharmacies under the REMS. We have not yet determined the details of pharmacy certification requirements, including whether any limitations on the types of pharmacies that may dispense the product are necessary.

(b) (6) and (b) (6) recommend the Applicants be issued a REMS Modification Notification Letter that requests submission within 120 days from the date of the letter.

6. References

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7. Appendix A

References Cited in Letters from Plaintiffs

References cited in letter from *Chelius v. Becerra* Plaintiffs (September 29, 2021)	
References included in the REMS review	
Aiken A et al. BJOG 2021: 128 (9): 1464-1474	
Chong, et al. Contraception 2021; 104(1) 43-48	
Daniel S. et al. Contraception 2021; 104(1): 73-76	
References excluded from the REMS review	**Rationale for Exclusion**
Am. Coll. of Obstetricians & Gynecologists, *Position Statement: Improving Access to Mifepristone for Reproductive Health Indications* (June 2018), https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications	Policy/advocacy statement
House of Delegates, Am. Med. Ass'n., *Memorial Resolutions Adopted Unanimously No. 504 (2018)* https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/hod/a18-resolutions.pdf	Policy/advocacy statement
Cong. Of Delegates, Am. Acad. Of Fam. Physicians, *Resolution No. 506 (CoSponsored C) Removing Risk Evaluation and Mitigation Strategy (REMS) Categorization of Mifepristone* (May 24, 2018) https://www.reproductiveaccess.org/wp-content/uploads/2019/02/Resolution-No.-506-REMS.pdf	Policy/advocacy statement
Schummers L et al, Contraception 2020; 102(4): 273	Abstract
Upadhyay UD et al.) Obstet & Gynecol 2015; 125: 175	Published prior to March 29, 2016-July 26, 2021 timeframe for current literature review. We note that the extensive literature review conducted as part of the 2016 review, which was consistent with the division's standard approach for reviewing an efficacy supplement

Reference ID: 4905882

	and encompassed 90 references, did not capture this publication. However, the authors' conclusion in this publication is consistent with our review of the safety data in 2016.
Kapp N et al. Best Pract Clin Obstet Gynaecol. 2020;63:37-44	Abstract. Also outside the scope of first trimester medical abortion.
Fuentes L et al. J Women's Health 2019; 28 (12): 1623, 1625 Bearak JM, Lancet Pub Health 2017 Nov;2(11): e493, e495-96 Cartwright A et al 20 J Med Internet Res 2018 20(5):e10235 Barr-Walker J, et al PLoS One 2019;14(4): e0209991 Grossman et al JAMA Network 2017;317(4):437, 437-438 Dobie S et al 31 Fam Plan Persp 1999; 31(5): 241-244 Shelton JD 8 Fam Plan Persp 1976; 8(6):260, 260-262 Norris AH et al Am J Pub Health 2020; 110 (8): 1228,1232 Upadhyay UD et al Am J Pub Health 2014; 104(9):1687, 1689	Focused on the logistics of accessing abortion care.
CDC MMWR Abortion Surveillance – United States, 2018 https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T5_down	Contains primarily general statistics on abortion care by state.

References cited in appendix from *Chelius v. Becerra* Plaintiffs (September 29, 2021)
References included in the REMS review
None

References excluded from the REMS review	Rationale for Exclusion
Jones RK et al Guttmacher Institute Abortion Incidence and Service Availability in the United States, 2017 (2019) Guttmacher Inst, Induced Abortion in the United States (2019)	Contains primarily general statistics on abortion care and logistics of accessing abortion care.
University of Minnesota Healthy Youth Dev. Prevention Rsch Ctr, 2019 Minnesota Adolescent Sexual Health Report 3 (2019)	Not related specifically to abortion care.
Jerman J et al Guttmacher Inst, Characteristics of U.S. Abortion Patients in 2014 and Changes since 2008 (2016)	Contains figures on patient characteristics from 2008-2014.
Roberts CM et al Women's Health Issues 2014; 24:e211, e215	Focused on cost of abortion.
CDC MMWR Abortion Surveillance 2018 https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T7 down (last updated Nov. 7, 2020)	Contains primarily statistics on number of abortions in the US.
Jones RK Persp on Sexual & Reprod Health 2017; 49:17, 20	Focused on abortion incidence and service availability.
Fuentes L et al (as above) Bearak JM et al (as above) Cartwright A et al (as above) Johns NE et al. BMC Health Serv Res 2017; 17: 287, 294	Focused on logistics of accessing abortion care.

References cited in letter from Society of Family Planning (August 11, 2021)
References included in the REMS review
Grossman D. Obstet Gynecol 2019;133 (3): 477-483

Grossman D et al. Obstet Gynecol 2021; 137 (4): 613-622.	
Winikoff B et al. Obstet Gynecol 2012; 120: 1070-1076 reviewed in 2016 clinical memo	
Chen MJ et al. Obstet Gynecol 2015;126(1):12-21 reviewed in 2016 memo	
Chong et al. Contraception 2021;104(1): 43-48	
Aiken A et al. BJOG 2021; 128 (9): 1464 -1474	
Hyland 2018 et al. Aust New Zeal J Obstet Gynaecol 2018; 58 (3): 335-340	
References excluded from the REMS review	**Rationale for Exclusion**
Schummers L et al. BMJ Sex Reprod Heal 2021;47(e1)	Abstract
Kapp et al. 2020 (as above)	Abstract
Upadhyay et al. 2015 (as above)	(See rationale above)
Srinivasulu et al. Contraception 2021; 104(1):92-97	Survey on clinician perspectives on access to mifepristone.
Calloway D et al. Contraception 2021; 104(1): 24-28	Primarily addresses provider stigma around abortion care.
Rasmussen et al. Contraception; 104(1): 98-103	Opinion/commentary
Cleland et al. Obstet Gynecol 2013;121(1):166-171	Published prior to March 29, 2016 - July 26, 2021 timeframe for current literature review. We note that the extensive literature search conducted as part of the 2016 clinical review, which was consistent with the division's standard approach for reviewing an efficacy supplement and encompassed 90 references, did not capture this publication. However, the authors' conclusion in this publication is consistent with our review of the safety data in 2016.
National Academy of Sciences, Engineering, and Medicine. Safety and Quality of Abortion Care in the US 2018	General information about abortion care in the US. Did not provide safety data relevant to the elements of the REMS
Raymond EG. Obstet Gynecol 2012: 119(2): 215-219	Does not separate out medical and surgical abortion.

Bartlett LA et al. Obstet Gynecol 2004; 103(4): 729-737	Focused on surgical abortion.
Jones RK, Jerman J. Time to appointment and delays in accessing care among U.S. abortion patients, Guttmacher 2016	Focused on logistics of accessing abortion care.
Foster DG et al. Perspect Sex Reprod Health 2013; 45(4):210-218	Focused on second trimester abortion.
Ely G et al. Heal Soc Work 2019;44(1):13-21	Focused on logistics of accessing abortion care.
Munro S et al. Ann Fam Med 2020; 18(5):413-421.	Survey on physician perspectives on implementing medical abortion with mifepristone.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s025

OTHER REVIEW(S)

Review of Labeling

(b) (6)

NDA Number/Supplement	**020687/025**
Applicant	**Danco Laboratories, LLC**
Product Name	**Mifeprex (mifepristone) tablets**
Therapeutic Class	**Progestin antagonist**
Indication	**For the medical termination of intrauterine pregnancy through 70 days gestation, in a regimen with misoprostol**
Material Reviewed	**Prescribing Information and Medication Guide received December 16, 2022**
Date of Review	**January 3, 2023**
Reviewer	(b) (6)

This memorandum is the (b) (6) (Division's) review of the proposed revisions to the labeling and Medication Guide for Mifeprex submitted by Danco Laboratories (Applicant) on December 16, 2022. These revisions are to align the language in the Prescribing Information and the Medication Guide with the proposed modification to the Mifepristone single, shared system Risk Evaluation and Mitigation Strategy (REMS) (referred to as the Mifepristone REMS Program) submitted under NDA 020687/Supplement-025, as amended.

1. Background

Mifeprex (mifepristone), in a regimen with misoprostol, is indicated for the medical termination of intrauterine pregnancy through 70 days gestation. Mifeprex and its approved generic are subject to the Mifepristone REMS Program to mitigate the risk of serious complications associated with mifepristone. The Mifepristone REMS Program consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

The goal of the Mifepristone REMS Program is to mitigate the risk of serious complications associated with mifepristone by:

- Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program (ETASU A).
- Ensuring that mifepristone is only dispensed in certain healthcare settings by or under the supervision of certified prescribers (ETASU C).
- Informing patients about the risk of serious complications associated with mifepristone (ETASU D).

On December 16, 2021, FDA sent REMS Modification Notification letters to the Applicants for Mifeprex and the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg (Danco

Laboratories and GenBioPro, respectively). The letters informed the Applicants of the FDA's determination that the approved Mifepristone REMS Program must be modified to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks by: (1) removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement") (ETASU C) and (2) to add the requirement for certification of pharmacies that dispense the drug (ETASU B).[1] For a detailed discussion of the modification recommendations refer to the REMS Modification Rationale Review, jointly completed by the (b) (6) and the (b) (6) on December 16, 2021.[2]

As proposed by the Applicants in their December 16, 2022, amendments to their pending supplements, the modified goal of the Mifepristone REMS Program would read as follows:

> The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:
>
> a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
>
> b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
>
> c) Informing patients about the risk of serious complications associated with mifepristone.

The Division reviewed the Applicant's proposed revisions to the approved Mifeprex labeling under NDA 020687 Supplement 025, as amended, which provides REMS document and materials to align with the changes described in the REMS Modification Notification letters. Specifically, the requirement that mifepristone must be dispensed to patients in certain healthcare settings (ETASU C) was removed and the dispensing of mifepristone through specially certified pharmacies (ETASU B) was added. This REMS modification ensures that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. There were no changes to ETASU A and ETASU D (prescribers must be specially certified and mifepristone must be dispensed to patients with evidence of safe use conditions, respectively).

On December 16, 2022, final labeling for the Mifeprex Prescribing Information (PI) and Medication Guide (MG) were received to align with the Mifepristone REMS Program modification. This submission is reviewed below. Review of the labeling changes made in the PI

[1] REMS Modification Notification letter dated December 16, 2021.
https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80633e9f
[2] REMS memorandum dated December 16, 2021.
https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80633d74

and in the MG for the approved generic (ANDA 091178) will be completed by the (b) (6) .

2. **Review of Labeling Changes**

Prescribing Information and Medication Guide

The following two changes were made in both the PI and MG for Mifeprex:

1. Gender neutral edits were made throughout the PI and MG.

   Reviewer comment: The Division agrees to the use of gender-neutral language to align with such changes previously approved for documents associated with this REMS.

2. Removal of instructions for patients to take the MG when they visit an emergency room or another healthcare provider who did not prescribe Mifeprex, so the provider knows that the patient is undergoing a medical abortion.

   Reviewer comment: The Applicant requested this change. Removal of the instructions in the PI and MG aligns with the updated Patient Agreement Form submitted in Supplement S-025, which removes instructions for patients to take the MG to healthcare visits with providers who did not provide Mifeprex. Although these instructions were added to the MG a number of years ago, upon further consideration the Division agrees with removing them because patients seeking emergency medical care are not likely to carry a MG with them, the MG is readily available online, and information about medical conditions and previous treatments can be obtained at the point of care.

Prescribing Information

Additional changes were made in the PI to include pharmacy dispensing in Section 5.3 Mifepristone REMS Program and Section 17 Patient Counseling Information. Typographical errors were corrected in Sections 16 and 17.

1. Section 5.3 Mifepristone REMS Program

   The Applicant proposed changes to one of the three bulleted ETASU requirements, to state "MIFEPREX must only be dispensed to patients by or under the supervision of a certified prescriber, or by certified pharmacies on prescriptions issued by certified prescribers."

   Reviewer comment: The revised language is consistent with the REMS modification to include certified pharmacy dispensing. The Division agrees with the proposed language.

2. Section 17 Patient Counseling Information

The Applicant proposed changes to one of the two bulleted ETASU requirements, to state "MIFEPREX is only dispensed by or under the supervision of certified prescribers or by certified pharmacies on prescriptions issued by certified prescribers."

Reviewer comment: As above, the revised language for the PI for the approved MIFEPREX product is consistent with the REMS modification to include certified pharmacies and the Division agrees with the proposed language.

3. Section 16 How Supplied/Storage and Handling and Section 17 Patient Counseling Information
    a. Both Sections 16 and 17 refer to the "mifepristone REMS Program" which was edited to "Mifepristone REMS Program".
    b. In Section 17, reinstatement was made of "a" before Patient Agreement Form in the bullet "Patients must sign a Patient Agreement Form".

Reviewer comment: The Applicant will be informed of these minor edits.

Medication Guide

Additional changes were made in the MG within the section titled "How should I take Mifeprex?", as follows:

1. Addition of obtaining Mifeprex at a pharmacy: "Mifeprex will be given to you by a healthcare provider or pharmacy."
2. Removal of statement "Your healthcare provider will either give you or prescribe for you 4 misoprostol tablets to take 24 to 48 hours later."

Reviewer comment: The proposed MG changes for Mifeprex are acceptable to (b) (6). The addition of Mifeprex to be dispensed at a pharmacy reflects the REMS modification change. The statement on misoprostol dispensing is removed because it is not necessary to specify in the Mifeprex labeling how misoprostol is dispensed. The directions to take misoprostol tablets 24 to 48 hours after taking mifepristone are maintained in the Mifeprex patient instructions.

3. Conclusion

We received the final proposed labeling revisions to the Prescribing Information and Medication Guide from the Applicant on December 16, 2022. The Prescribing Information and Medication Guide for Mifeprex were revised to align with the Mifepristone REMS Program modification, which include removing the requirement that Mifeprex be dispensed only in certain healthcare settings and adding the requirement for pharmacy certification. The proposed labeling revisions were reviewed and found to be acceptable with minor edits.

All labeling changes outlined above will be applied to the approved generic mifepristone (ANDA 091178). The (b) (6) will review labeling for the approved generic and ensure it mirrors the updated approved labeling for the Mifeprex product.

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

TO: FILE

FROM: [redacted] (b) (6) [redacted] (b) (6) Digitally signed by [redacted] (b) (6) Date: 2022.12.23 13:11:43 -05'00'

DATE: December 23, 2022

SUBJECT: Review of Supplemental Drug Applications Proposing Modifications to the Mifepristone REMS Program

FDA is currently reviewing a supplemental new drug application from Danco Laboratories, LLC (Danco) and a supplemental abbreviated new drug application from GenBioPro, Inc. (GBP) that propose to modify the Mifepristone Risk Evaluation and Mitigation Strategy (REMS) Program as approved under Danco's new drug application for Mifeprex (mifepristone) (NDA 020867) and GBP's abbreviated new drug application for Mifepristone Tablets 200 mg (ANDA 091178). Citing the Comstock Act, 18 U.S.C. §§ 1461, 1462, Plaintiffs in *Alliance for Hippocratic Medicine v. U.S. Food and Drug Administration*, No. 2:22-cv-00223-Z (N.D. Tex.), have alleged that FDA's actions regarding mifepristone do not comply with "federal laws that expressly prohibit the mailing or delivery by any letter carrier, express company, or other common carrier of any substance or drug intended for producing abortion" and also that FDA "failed to acknowledge and address" those laws. Complaint ¶¶ 22, 392 (Nov. 18, 2022). This memorandum notes that the Office of Legal Counsel of the United States Department of Justice, which provides controlling advice to Executive Branch officials on questions of law, has concluded that the Comstock Act provisions cited by Plaintiffs "[do] not prohibit the mailing of mifepristone or misoprostol where the sender lacks the intent that the recipient will use them unlawfully. And in light of the many lawful uses of mifepristone and misoprostol, the fact that these drugs are being mailed to a jurisdiction that significantly restricts abortion is not a sufficient basis for concluding that the mailing violates [these provisions]." Memorandum for Thomas J. Marshall, General Counsel, United States Postal Service, from Christopher H. Schroeder, Assistant Attorney General, Office of Legal Counsel, *Re: Application of the Comstock Act to the Mailing of Prescription Drugs That Can Be Used for Abortions*, at 15 (December 23, 2022).[1] Thus, even if the Comstock Act provisions bear on FDA's analysis of the pending supplemental drug applications, in light of the conclusions set forth by the Office of Legal Counsel, they pose no issue for FDA's approval of the applications.

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[1] The Office of Legal Counsel's analysis applies to 18 U.S.C. § 1461 and § 1462. *See id.* at 1 n.3.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s025

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum
REMS Modification: Removal of a Requirement and Addition of a Requirement
U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

(b) (6)

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NDA/ANDA #s:	NDA 20687, ANDA 91178
Products:	Mifeprex, mifepristone, 200 mg tablets
APPLICANTS:	Danco, GenBioPro
FROM:	(b) (6) (b) (6)
DATE:	December 16, 2021

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifeprex was approved on September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (subpart H) and subsequently was deemed to have a REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007. The Mifeprex REMS with elements to assure safe use (ETASU) was approved on June 8, 2011 and a supplemental efficacy application and REMS modification was approved on March 29, 2016. The Mifepristone REMS Program (a single, shared system REMS that currently includes NDA 020687 and ANDA 91178) was approved on April 11, 2019.

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone. The current Mifepristone REMS Program includes elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. Elements to assure safe use include requirements for prescriber certification (ETASU A), that mifepristone be dispensed only in certain healthcare settings by or under the supervision of a certified prescriber (ETASU C), and that mifepristone be dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions consists of a Patient Agreement Form between the prescriber and the patient, indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with mifepristone.

The requirement under ETASU C that mifepristone be dispensed only in certain health care settings, specifically clinics, medical offices, and hospitals, is referred to as the "in-person dispensing requirement."

On January 31, 2020 the Secretary of Health and Human Services (HHS) declared COVID-19 a public health emergency (PHE) as of January 27, 2020. During the COVID-19 pandemic, there have been periods when the in-person dispensing requirement has not been enforced. From July

13, 2020 until January 12, 2021, enforcement was barred by an injunction issued in the *ACOG v. FDA* litigation. More recently, on April 12, 2021, the Agency stated its intent to exercise enforcement discretion with respect to the in-person dispensing requirement during the COVID-19 PHE, which is still ongoing as of the date of this review. These circumstances have provided additional information regarding the in-person dispensing requirement as there have been periods when the in-person dispensing requirement was not enforced.

As part of the May 7, 2021, joint motion to stay the *Chelius v. Becerra* litigation, the Agency agreed to undertake a full review the Mifepristone REMS Program, in accordance with the REMS assessment provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[1]

After consultations between the (b) (6) , analyzing several different sources of information, including published literature, safety information collected during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, REMS assessment reports, and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius* litigation, we determined that the approved REMS for mifepristone could be modified without adversely impacting patient safety. Importantly, our review did not identify any differences in adverse events between periods when the in-person dispensing requirement was being enforced and periods when that requirement was not being enforced. The data suggested that the requirements for prescriber certification (ETASU A) and the Patient Agreement Form (ETASU D) should be maintained, while the in-person dispensing requirement (under ETASU C) could be removed, to reduce the burden imposed by the REMS. In determining that the in-person dispensing requirement could be removed, we concluded that a new requirement for pharmacy certification (ETASU B) is necessary to ensure the benefits of the product outweigh the risks.

(b) (6) and (b) (6) assessment and recommendations were (b) (6) (b) (6) on November 2, 2021. The (b) (6) unanimously agreed with our recommendations.

For more detailed information on the review and assessments of the information, refer to the REMS Modification Rationale Review, jointly completed by (b) (6) and (b) (6) on December 16, 2021.

In conclusion, provided all other conditions of the Mifepristone REMS Program are met and that the other elements of the REMS are maintained (ETASU A and D), the following are required:

1. Modification of the Mifepristone REMS Program to remove the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals. This would allow, for example, dispensing of mifepristone by mail, via certified prescribers or pharmacies, in addition to in-person

[1] Section 505-1(g)(2) of the FD&C Act (21 U.S.C. § 355-1(g)(2)).

dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C . We find that this provision is no longer necessary to ensure that the benefits of the drug outweigh the risks and that removing it will help minimize the burden of complying with the REMS on the healthcare delivery system.

2. Modification of the Mifepristone REMS Program to add a requirement under ETASU B that pharmacies that dispense the drug be specially certified.

Based on the (b) (6) and (b) (6) determination that a modified REMS with the components described above is necessary to reduce the burden imposed by the REMS and ensure the benefits of mifepristone outweigh the risks, FDA is requiring submission of the proposed REMS modification within 120 days of the date of the notification letter.

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Center for Drug Evaluation and Research (CDER)

Application Type	NDA and ANDA
Application Number	NDA 020687 and ANDA 91178
Supplement Number, Date Received	NDA Supplement-025 and ANDA Supplement-004 received June 22, 2022 (sequence 18 and 87 respectively) and amended October 19, 2022 (sequences 22 and 91 respectively), November 30, 2022, and December 9, 2022 (sequences 25 and 93 respectively)
Targeted Action Date	December 19, 2022
(b) (6) **#**	2022-1169
Reviewer Names	(b) (6)
(b) (6)	(b) (6)
(b) (6)	(b) (6)
Review Completion Date	December 14, 2022
Subject	Review of proposed Major REMS Modification
Established Name	Mifepristone REMS Program
Name of Applicant	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablet

1. Introduction

Refer to the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178.

The Applicants submitted proposed modifications to the Mifepristone REMS Program on June 22, 2022 in response to REMS Modification Notification letters issued on December 16, 2021 to Danco and GBP, requiring the following modifications to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks:

- removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement")
- addition of certification of pharmacies that dispense the drug

The comments in this review focus on the Applicants' amendments that were received on December 9, 2022, which included updates to the REMS Document and materials that were discussed and edited during a teleconference between the Agency and Applicants on December 8, 2022.

2. Comments to the Sponsor

General Comments

The documents have been revised for you per the comments below.

REMS Document

We have revisions in the REMS document in the following sections:

II. A.2.a.iv.2) l, the language must be updated to replace "provider" with "prescriber," and to remove the phrase that (b) (4) .

II.A.2.c.ii A requirement was added to ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form* (b) (4) .

II. A.3, we have the following edits to align with the statue. Mifepristone must be (b) (4) dispensed (b) (4) to patients with evidence or other documentation of safe use conditions as ensured by the certified prescriber in signing the *Prescriber Agreement Form*.

II.B.5 must be updated to include: Mifepristone Sponsors must audit their certified pharmacies within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter audit certified pharmacies that have ordered mifepristone in the previous 12 months to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their pharmacy compliance if noncompliance is identified.

REMS Supporting Document

We require clarification and revisions in several sections. A red-lined Supporting Document has been attached for reference.

The wording in the Supporting Document was not consistent with the REMS document and REMS materials. Throughout the Supporting Document, the document was revised to align with the wording in the REMS Document, *Prescriber Agreement Form, Patient Agreement Form*, and *Pharmacy Agreement Form*.

The Supporting Document is inconsistent with respect to grammar and punctuation, as well as with respect to capitalization, italicization, and terminology. Review and revise the Supporting Document for grammar and punctuation, and for consistency in capitalization, italicization, and terminology.

The term "(b) (4)" was replaced with "supervised healthcare providers" where applicable.

There was minimal information about account set up processes for the certified prescribers and pharmacies. Include explanation of how accounts will be set up and maintained and what information from the account set up process will be used for REMS assessments.

There was also minimal information about how Sponsors will communicate with each other when stakeholders report information that the other needs to know such as when stakeholders report patient deaths to the wrong Sponsor or when decertifications of pharmacies or prescribers take place. Clarify what actions require timely communication between Sponsors and the timeline in which these actions should be reported to the other Sponsor.

Prescriber Agreement Forms for Danco Laboratories, LLC and GenBioPro, Inc.

(b) (4). This data will be available through the account set up process.

Pharmacy Agreement Forms for Danco Laboratories, LLC and GenBioPro, Inc.

(b) (4) must be removed as it is redundant to the language later in the form. The confidentiality requirement later in the form, under the requirements that certified pharmacies must put processes and procedures in place to accomplish, must be further aligned with the confidentiality requirement added to the REMS Document (discussed above).

Patient Agreement Form

The Patient Agreement Form is acceptable.

Resubmission Instructions

Accept all track changes and submit the following revised REMS materials by 12/16/22. The next submission to the Gateway should include Clean Word, Tracked Word, and pdf formatted versions of the following documents and one clean compiled PDF file that includes the REMS Document and all REMS materials in their final format:

REMS Document
Prescriber Agreement Form for Danco Laboratories, LLC
Prescriber Agreement Form for GenBioPro, Inc.
Pharmacy Agreement Form for Danco Laboratories, LLC
Pharmacy Agreement Form for GenBioPro, Inc
Patient Agreement Form
REMS Supporting Document with the Assessment Plan

Appendix
REMS Document
Prescriber Agreement Form for Danco Laboratories, LLC
Prescriber Agreement Form for GenBioPro, Inc.

Pharmacy Agreement Form for Danco Laboratories, LLC
Pharmacy Agreement Form for GenBioPro, Inc
REMS Supporting Document

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Center for Drug Evaluation and Research (CDER)

Application Type	NDA and ANDA
Application Number	NDA 020687 and ANDA 91178
Supplement Number, Date Received	NDA Supplement-025 and ANDA Supplement-004 received June 22, 2022 (sequence 18 and 87 respectively) and amended October 19, 2022 (sequences 22 and 91 respectively), November 30, 2022
[redacted] #	2022-1169
[redacted]	[redacted]
[redacted]	[redacted]
Review Completion Date	December 8, 2022
Subject	Review of Proposed Major REMS Modification: Draft REMS Assessment Plan Comments
Established Name	Mifepristone REMS Program
Name of Applicant	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablet

1. Introduction

Refer to the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and from GenBioPro Inc. (GBP) for abbreviated new drug application (ANDA) 091178.

The Applicants submitted proposed modifications to the Mifepristone REMS Program on June 22, 2022 in response to a REMS Modification Notification letter issued on December 16, 2021 to Danco and GBP, requiring the following modifications to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks:

- removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement")
- addition of certification of pharmacies that dispense the drug

The comments in this review focus on revisions to the REMS Assessment Plan.

2. Comments to the Applicant

We have provided a draft REMS Assessment Plan as discussed on the December 7, 2022 teleconference. The proposed Agency edits have been marked in tracked changes from the Mifepristone REMS Assessment Plan in the April 11, 2019, Supplement Approval Letter. Refer to the attached Draft REMS Assessment Plan with tracked changes. Review of the REMS proposal is ongoing; these comments should not be considered final.

We have the following comments:

1. Provide each assessment plan metric for the two previous, current, and cumulative reporting periods (if applicable) for both the NDA and ANDA unless otherwise noted.
2. The Assessment Plan Categories of 1) Program Implementation and Operations and 2) Overall Assessment of REMS Effectiveness were added.
3. A REMS Certification Statistics metric was added to capture the following:
    a. Total number of certified, newly certified, and active prescribers along with a summary of the practice setting of the certified prescribers and the method in which they became certified.
    b. Total number of certified, newly certified, and active certified pharmacies.
    c. Total number of authorized, newly authorized, and active wholesaler/distributors.
4. A Utilization Data metric was added to capture wholesaler/distributor shipment and pharmacy data.
5. A REMS Compliance Data metric was added to capture stakeholder audit results and a summary of instances of non-compliance and actions taken to address non-compliance.

Resubmission Instructions

Submit the revised REMS Assessment Plan in the REMS Supporting Document with your 12/9/22 submission. Accept the tracked changes in the draft REMS Assessment Plan with which you agree and only indicate any new changes you propose as tracked changes in your next submission. The submission should include clean Word, tracked changes Word, and pdf formatted versions of the following document.

Appendix

REMS Assessment Plan

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Center for Drug Evaluation and Research (CDER)

Application Type	NDA and ANDA
Application Number	NDA 020687 and ANDA 91178
Supplement Number, Date Received	NDA Supplement-025 and ANDA Supplement-004 received June 22, 2022 (sequence 18 and 87 respectively) and amended October 19, 2022 (sequences 22 and 91 respectively), November 30, 2022
PDUFA Date	December 19, 2022
(b) (6) **#**	2022-1169
Reviewer Names	(b) (6)
(b) (6)	(b) (6)
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Review Completion Date	December 5, 2022
Subject	Review of proposed Major REMS Modification
Established Name	Mifepristone REMS Program
Name of Applicant	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablet

1. Introduction

Refer to the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178.

The Applicants submitted proposed modifications to the Mifepristone REMS Program on June 22, 2022 in response to REMS Modification Notification letters issued on December 16, 2021 to Danco and GBP, requiring the following modifications to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks:

- removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement")
- addition of certification of pharmacies that dispense the drug

The comments in this review focus on the Applicants' amendments that were received on October 19 and 20, 2022 and November 30, 2022 (REMS Document). The comments also reflect the REMS Document that was further discussed and edited during a teleconference between the Agency and Applicants on December 1, 2022.

2. Comments to the Sponsor

General Comments

We have updated the REMS Document as discussed during the December 1, 2022 teleconference and aligned the REMS materials. Your edits, where the Agency agrees, have been accepted and Agency edits have been marked in tracked changes. Refer to the attached, red-lined REMS Document and REMS Materials. Review of the REMS proposal is ongoing; these comments should not be considered final.

- The Agency has determined that further clarification that certified prescribers are responsible for overseeing implementation and compliance with the REMS Program is appropriate in the *Prescriber Agreement Form* and has been added. This clarification provides flexibility for certified prescribers in overseeing REMS implementation and compliance. The certified prescriber may do so in a manner that may include the use of a larger healthcare team and delegation of tasks. We have determined that to make additional changes to the prescriber certification requirements would constitute a substantive modification to the REMS that would go beyond the required REMS modifications set forth in the December 16, 2021 REMS Modification Notification letters. Adequate rationale is required to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FD&C Act. Your application does not include such adequate rationale.
- We agree that healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone is dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification and have added this clarification to the *Prescriber Agreement Forms* and *Pharmacy Agreement Forms*. These clarifications negate the need for further clarification in the REMS Document as you proposed in the footnote to section II.A.2.
- Moving forward, italicize all proper names of forms e.g. *Prescriber Agreement Form* in the REMS.

Prescriber Agreement Forms for Danco Laboratories, LLC and GenBioPro, Inc.

The instructions on the *Prescriber Agreement Forms* were revised for clarity. Prescriber information collected on the forms was updated to capture practice setting (b) (4) address, and an additional line for medical license state was added. Duplicative or unnecessary instructions have been removed.

Pharmacy Agreement Forms for Danco Laboratories, LLC and GenBioPro, Inc.

The titles of the *Pharmacy Agreement Forms* were edited to remove "(b) (4)." The REMS pharmacy requirements will dictate whether a pharmacy can participate in the Mifepristone REMS Program and therefore (b) (4). Additional information fields regarding authorized representatives and pharmacies were added and the term "(b) (4)" was replaced with "pharmacy." Duplicative or unnecessary instructions have been removed.

Patient Agreement Form

The first paragraph of the form has been aligned with the currently approved Mifepristone REMS Program and clarification that signatures on the document can be written or electronic was added. Risk information regarding ectopic pregnancy has been reorganized. (b) (4) .

Resubmission Instructions

Accept all track changes and submit the following revised REMS materials by 12/08/22. The next submission to the Gateway should include Clean Word, Tracked Word, and pdf formatted versions of the following documents and one clean compiled PDF file that includes the REMS Document and all REMS materials in their final format:

REMS Document
Prescriber Agreement Form for Danco Laboratories, LLC
Prescriber Agreement Form for GenBioPro, Inc.
Pharmacy Agreement Form for Danco Laboratories, LLC
Pharmacy Agreement Form for GenBioPro, Inc
Patient Agreement Form
REMS Supporting Document with the Assessment Plan
Updated prescription label and Medication Guide

Appendix

REMS Document
Prescriber Agreement Form for Danco Laboratories, LLC
Prescriber Agreement Form for GenBioPro, Inc.
Pharmacy Agreement Form for Danco Laboratories, LLC
Pharmacy Agreement Form for GenBioPro, Inc
Patient Agreement Form

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Center for Drug Evaluation and Research (CDER)

Application Type	NDA and ANDA
Application Number	NDA 020687 and ANDA 91178
Supplement Number, Date Received	NDA Supplement-025 and ANDA Supplement-004 received June 22, 2022 (sequence 18 and 87 respectively) and amended October 19, 2022 (sequences 22 and 91 respectively)
Action Date	December 19, 2022
[redacted] **#**	2022-1169
Reviewer Names	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Review Completion Date	November 23, 2022
Subject	Review of proposed Major REMS Modification
Established Name	Mifepristone REMS Program
Name of Applicant	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablet

1. Introduction

Refer to the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and from GenBioPro Inc. (GBP) for abbreviated new drug application (ANDA) 091178.

The Applicants submitted proposed modifications to the Mifepristone REMS Program on June 22, 2022 in response to a REMS Modification Notification letter issued on December 16, 2021 to Danco and GBP, requiring the following modifications to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks:

- removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement")
- addition of certification of pharmacies that dispense the drug

Danco amended their submission on October 19, 2022 and GBP amended their submission on October 20, 2022.

2. Comments to the Sponsor

General Comments

For clarity, we have used the approved REMS Document to provide edits. Your proposed edits and Agency edits have been marked in tracked changes. Refer to the attached, red-lined REMS Document. Review of the REMS proposal is ongoing; these comments should not be considered final.

We have additional questions that must be addressed. Refer to the red-lined REMS Document attached. You must address the following question with your next submission:

1. Refer to the distributor requirement on page five (in all markup), "Put processes and procedures in place to maintain a distribution system that is secure, confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, proof of delivery and controlled returns of mifepristone" (underline added for emphasis)

Clarify whether the packages that are tracked by the distributors will still be done by serial numbers or if tracking will only use the NDC and lot numbers.

REMS Goal

(b) (4)

We have revised the goal to the following:

"The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.

b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers or by certified pharmacies.

c) Informing patients about the risk of serious complications associated with mifepristone."

REMS Document

We have provided edits to the REMS Document to reflect the requirements communicated in the December 16, 2021 letter and to incorporate additional requirements. We have determined that for this modification we will not be using the format for the REMS that is in the 2017 draft Guidance for Industry - Format and Content of a REMS Document, as not all requirements are easily transferred to the newer format and may result in creating unnecessary confusion to stakeholders. Note that all REMS Materials and the REMS Supporting Document must align with the REMS Document.

Prescriber requirements were edited for clarity, brevity and to align with certified prescriber qualifications in the currently approved REMS. Additional requirements were needed to address situations that may arise if a certified prescriber opts to dispense through a certified pharmacy.

Pharmacy requirements were revised: to ensure pharmacies are able to ship mifepristone using a shipping service that provides tracking information, to include the use of an authorized representative to coordinate REMS implementation on behalf of the pharmacy, to dispense mifepristone such that it is delivered to the patient within four calendar days of the date the pharmacy receives the prescription, and to confirm with the prescriber and document the appropriateness of dispensing mifepristone for patients who will not receive the drug within four calendar days of the date the pharmacy receives the prescription. Additional record-keeping and reporting requirements were also added.

Additional Sponsor requirements were added to support prescriber, pharmacy, and distributor REMS stakeholder requirements, and to ensure the REMS operates as intended.

REMS Supporting Document

The REMS Supporting Document must be included in your next submission and is necessary to help us understand how these changes will be implemented before we can take an action.

Resubmission Instructions

Submit the following revised REMS materials by 11/30/22. Accept the track changes in the REMS Document with which you agree in the Word newly redlined documents and only indicate any new changes you propose as redlined changes in your next submission. The next submission to the Gateway should include Clean Word, Tracked Word, and pdf formatted versions of the following documents:

REMS Document
REMS Supporting Document

Appendix

REMS Document

5 Pages of Draft REMS Documents Have Been Withheld in Full as B4 (CCI/TS) Immediately Following This Page

Reference ID: 5083134

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (6)

11/23/2022 11:42:12 AM

(b) (6)

11/23/2022 11:48:25 AM

(b) (6)

11/23/2022 11:51:57 AM

(b) (6)

11/23/2022 11:53:43 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s025

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

U.S. FOOD & DRUG ADMINISTRATION

NDA 020687

REMS MODIFICATION NOTIFICATION

Danco Laboratories, LLC
(b) (4), (b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6):

We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for mifepristone was originally approved on June 8, 2011, and your single shared system REMS (SSS REMS) was approved on April 11, 2019. Your last SSS REMS modification was approved May 14, 2021. The SSS REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In accordance with section 505-1(g)(4)(B) of the Federal Food, Drug, and Cosmetic Act (FDCA), we have determined that your approved REMS for mifepristone must be modified to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks.

This determination is based on a review of published literature, safety information collected during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, REMS assessment reports, and information provided by advocacy groups, individuals, the Applicants, and plaintiffs in ongoing litigation.

Your approved REMS must be modified as follows:

Elements to Assure Safe Use: We have determined that the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement") is no longer necessary to ensure the benefits of mifepristone outweigh the risks of serious complications associated with mifepristone that are listed in the labeling of the drug. Removal of the requirement for in-person dispensing will also minimize the burden on the healthcare delivery system of complying with the REMS.

Elements to Assure Safe Use: Pursuant to 505-1(f)(1), we have also determined that an additional element to assure safe use is necessary to mitigate the risk of serious

complications associated with mifepristone listed in the labeling of the drug. Modification of the Mifepristone REMS to allow dispensing of mifepristone by pharmacies requires the addition of certification of pharmacies that dispense the drug.

Your REMS must include elements to mitigate this risk, including at least the following:

- Healthcare providers have particular experience or training, or are specially certified

- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified

- The drug is dispensed to patients with evidence or other documentation of safe use conditions.

  The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above). Include an intervention plan to address any findings of non-compliance with the ETASU.

The proposed REMS must include a timetable for submission of assessments.
The proposed REMS modification submission should include a new proposed REMS document and appended REMS materials, as appropriate, that show the complete previously approved REMS with all proposed modifications highlighted and revised REMS materials.

In addition, the submission should also include an update to the REMS supporting document that includes a description of all proposed modifications and their potential impact on other REMS elements. Revisions to the REMS supporting document should be submitted with all changes marked and highlighted.

Because we have determined that a REMS modification as described above is necessary to minimize the burden on the health care delivery system of complying with the REMS, and to ensure that the benefits of the drug outweigh the risks, you must submit a proposed REMS modification within 120 days of the date of this letter.

Submit the proposed modified REMS as a Prior Approval supplement (PAS) to your NDA.

Because FDA is requiring the REMS modifications in accordance with section 505-1(g)(4)(B), you are not required to submit an adequate rationale to support the proposed modifications, as long as the proposals are consistent with the modifications described in this letter. If the proposed REMS modification supplement includes changes that differ from the modifications described in this letter, an adequate rationale is required for those additional proposed changes in accordance with section 505-1(g)(4)(A).

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687/S-000
PROPOSED REMS MODIFICATION-AMENDMENT

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

In addition to submitting the proposed modified REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS modification submission.

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

If you have any questions, call (b) (6), at (b) (6).

Sincerely,

{See appended electronic signature page}

(b) (6)
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (6)

12/16/2021 03:09:07 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-687

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 20-687

MIFEPRISTONE TABLETS

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS (HFD-580)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-687

Mifepristone Tablets

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research (CDER) has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **Mifepristone Tablets, The Population Council** has prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Mifepristone is a synthetic drug which will be administered orally to provide a medical approach to the termination of early pregnancy. Mifepristone may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites.

The projected environmental introduction concentration from use is less than 1 ppb. CDER has routinely found that concentrations less than 1 ppb have no effect on relevant standard test organism, therefore the applicant has submitted a Tier 0 EA in accordance with CDER guidance.

Disposal may result from production waste such as out of specification lots, returned goods and user disposal of empty or partly used product and packaging. Pharmaceutical waste will be disposed of by the manufacturer and The Population Council at licensed disposal facilities. At U.S. hospitals, pharmacies or clinics, empty or partially empty packages will be disposed of according to standard procedures.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

7/9/96 /S/
DATE PREPARED BY

7/11/96 /S/
DATE CONCURRED

Center for Drug Evaluation and Research

Attachment: Environmental Assessment

APPEARS THIS WAY
ON ORIGINAL

1. DATE

March 1, 1996

2. NAME of APPLICANT

The Population Council

3. ADDRESS

1230 York Avenue
New York, NY 10021

4. DESCRIPTION OF PROPOSED ACTION

a. Requested Approval

Applicant seeks approval for mifepristone tablets, (200 mg/tablet), packaged in a 200 µm white opaque poly (vinyl chloride-aceto chloride) blister with a 20 um aluminum foil with heat sealable varnish.

b. Need for Action

Mifepristone is a synthetic norsteroid which has demonstrated activity as a potent antagonist for progestins and glucocorticoids, due to its high relative binding to the progestorone and glucocorticoid receptor.
Progesterone is a critical hormone in mammalian reproduction and is essential for the maintenance of pregnancy. Withdrawl of the influence of progesterone in the uterus due to its competitive inhibition by mifepristone at the receptor site results in uterine bleeding, disruption of the placental function and disruption of the inhibitory effects of progesterone on the myometrial stimulatory actions of prostaglandins. These antiprogestational activities of the compound serve to provide a medical approach to the termination of early pregnancy.

c. Production Location

To perserve confidentiality of proprietary information, the name and location of the third-party manufacturer of

mifepristone drug substance and drug product is contained in confidential Appendix A.

d. Locations of Use

The drug product will be used by women in the United States. It will be administered in hospitals, health clinics and private physicians' offices.

e. Disposal Sites

Rejected, expired, returned or waste drug products are expected to be disposed of in accordance with the Center for Disease Control Guidelines for the handling of hazardous waste in the clinic or healthcare provider's office.

Rejected, expired or waste drug products will be collected and sent to a licensed facility to be processed and incinerated or for grinding and landfill. The facility and the permit/license under which it operates is identified in confidential Appendix B.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

a. Nomenclature

i. Established Name

Mifepristone

ii. Brand/Proprietary Names

Tradename in US not established
Mifegyne® (tradename used in European countries)
Xi Bai Lu (tradename used in China)

iii. Chemical Names

Chemical Abstracts:
(11beta,17beta)-11-[(4-dimethylamino)phenyl]-17-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one

IUPAC:
11beta-(4-Dimethylaminophenyl)-17beta-hydroxy-17α-(1-propynyl)-estra-4,9-dien-3-one

02

iv. Laboratory Code Designations

RU 38 486
RU 486

b. Chemical Abstracts Service (CAS) Registration Number

84371-65-3

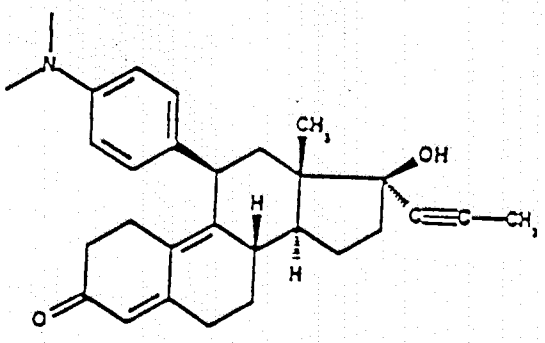
c. Molecular Formula

$C_{29}H_{35}NO_2$

d. Molecular Weight

429.58

e. Structural Formula



f. Physical Description

Mifepristone is a light yellow to yellow crystalline powder. The melting point is 191 - 196° C.

g. Additives

The dosage form is a pale yellow, cylindrical biconvex tablet, 11 ml in diameter. Each 350 mg tablet contains:

mifepristone: 200 mg
colloidal silica anhydrous: 3 mg
maize starch: 102 mg
povidone: 12 mg
cellulose microcrystalline: 30 mg
magnesium stearate: 3 mg

h. Impurities

The drug substance specifications, including impurities is included in confidential Appendix C.
No impurities are greater than 1%.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

Items a - d are covered in the information included in confidential Appendix A.

The Material Safety Data Sheet (MSDS) is included in nonconfidential Appendix D.

e. Expected Introduction Concentrations

i. Expected Introduction Concentration from Use

The expected environmental concentration was calculated using the following equation:

EIC-Aquatic (ppm) = A x B x C x D

where A = kg/year production
B = 1/liters per day entering POTW's*
C = year/365 days
D = 10^6 mg/kg (conversion factor)

* 1.115 x 10^{11} liters per day entering publicly owned treatment works (POTW's), Source: 1992 Needs Survey, Report to Congress, September 1993, EPA 832-R-93-002

The actual calculations are considered confidential business information and are provided in confidential Appendix E.

The expected concentration is less than 1 ppb, which normally relieves the applicant from providing information in format items 7 - 11 and 15 in accordance with the Tier 0 approach described in the FDA's *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Appliations and Supplements* (November 1995).

7 - 11. Not provided, based on the Tier 0 approach described in FDA's *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Appliations and Supplements* (November 1995).

12. LIST OF PREPARERS

Ann Robbins, Ph.D
Scientist

The names of prepares from the third party manufacturer are contained in confidential Appendix A.

13. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of the Population Council.

The undersigned official certifies that the EA summary document and Appendix E contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CRF 1506.6

Date Mar 1 1996

Signature Ann Robbins

Ann Robbins, Ph.D
Scientist
The Population Council
Center for Biomedical Research

The certification from the third-party manufacturer is included in confidential Appendix A.

14. REFERENCES

Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Appliations and Supplements, Center for Drug Evaluation and Research (CDER), FDA, November 1995.

APPENDICES

Appendix A: (CONFIDENTIAL) Information on third party manufacturer
Appendix B: (CONFIDENTIAL) Name and location of licensed disposal site
Appendix C: (CONFIDENTIAL) Drug substance specifications
Appendix D: Material Safety Data Sheet (MSDS)
Appendix E: (CONFIDENTIAL) Expected introduction concentration calculations

APPENDIX D

APPEARS THIS WAY
ON ORIGINAL

MATERIAL SAFETY DATA SHEET

1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION

IDENTIFICATION OF THE SUBSTANCE OR PREPARATION

TRADE NAME	: MIFEPRISTONE
CHEMICAL FAMILY	: Hormone
FORMULA	: C29H35NO2
MOLECULAR MASS	: 429
KIND OF USE	: Medical use

2. COMPOSITION/INFORMATION ON INGREDIENTS

SUBSTANCE

CAS NUMBER	: 84371-65-3
CHEMICAL NAME	: 17beta-hydroxy-11beta-(4-dimethylaminophenyl)17-alpha-(pro 1-ynyl)estra 4,9-dien 3-one.

3. HAZARDS IDENTIFICATION

MAIN HAZARDS : TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

4. FIRST-AID MEASURES IN CASE OF EXPOSURE

INHALATION	: Make the victim blow his nose Make victim breathe fresh air
SKIN CONTACT	: Rinse with plenty of water
EYES CONTACT	: Rinse immediately with plenty of water for at least 15 minutes
INGESTION	: Alert a physician

5. FIRE-FIGHTING MEASURES

SUITABLE EXTINGUISHING MEDIA	: Usual means .
UNSUITABLE EXTINGUISHING MEDIA	: None.

FIRE AND EXPLOSION HAZARDS	: In case of fire, the product emits toxic and irritating fumes .
SPECIAL PROTECTIVE EQUIPMENT	: Wear a self-contained respiratory apparatus.
OTHER RECOMMENDATIONS	: None.

6. ACCIDENTAL RELEASE MEASURES

MEASURES AFTER LEAKING OR SPIL	: Collect thouroughly into plastic bag. Avoid dust emissions. Rinse the polluted area with plenty of water.

7. HANDLING AND STORAGE

HANDLING

TECHNICAL MEASURES	: Mechanical sucking ventilation at source of formation of dust.
SPECIAL PROTECTION MEASURES	: Have a shower after handling.

STORAGE

SENSITIVITY TO DAMP	: Not observed.
SENSITIVITY TO LIGHT	: Not observed.
SENSITIVITY TO OXIDATION	: Sensitive to air
SPECIAL STORAGE REQUIREMENTS	: Room temperature (<86 F)
STORAGE CONDITIONS	: Usual conditions (T <= 86 F, away from light)
SHELF LIFE	: 5 years.
STORAGE FACILITIES	: Toxic products.
INCOMPATIBLE SUBSTANCES	: None.
RECOMMENDED PACKAGING MATERIAL	: Glass, polythene.
SUPPLIER PACKAGING	: polythene bag.
PACKAGING MATERIAL TO BE AVOIDED	: Unknown.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

CONTROL OF EXPOSURE

TWA	: ND
STEL	: ND
IDLH	: ND
OLFACTORY THRESHOLD	: ND

PERSONAL PROTECTION/WORKSHOP

RESPIRATORY TRACT PROTECTION	: Wear a dust respirator.
PROTECTIVE GLOVES	: Wear suitable gloves
EYES PROTECTION	: Wear glasses
OTHER EQUIPMENT PROTECTION	: Complete overall, skullcap

PERSONAL PROTECTION/LABORATORY

RESPIRATORY TRACT PROTECTION	: Wear a dust respirator.
PROTECTIVE GLOVES	: Wear suitable gloves
EYES PROTECTION	: Wear glasses

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE	: Crystallized solid,(yellow)

pH	: Not applicable.
CHARACTERISTIC TEMPERATURES	: Melting point : 192-196°C
FLASH POINT	: Not applicable.
AUTOINFLAMMABILITY	: Not determined.
EXPLOSIVITY CHARACTERISTICS	: NA
COMMENTS ON FLAMMABILITY	: Not concerned.
VAPOUR PRESSURE	: Not determined.
VOLUMIC MASS	: Not determined.
SOLUBILITY	: Insoluble in water Soluble in : alcohol,ether,chloroform.
OTHER DATA	: alpha D : + 143° (1%,chloroform). alpha D : + 125°(0.5%, methylene chloride)

10. STABILITY AND REACTIVITY

HAZARDOUS REACTIONS	: Unknown.
HAZARDOUS DECOMPOSITION PRODUCTS	: Unknown.

11. TOXICOLOGICAL INFORMATION

ACUTE TOXICITY	: LD 50 oral route/rat : > 5000 mg/kg. LD50 oral/route in dogs : > 5000 mg/kg.
PHYSIOLOGICAL ACTIVITY	: Substance physiologically very active., : anti-progestative, abortive.
SPECIFIC EFFECTS	: Teratogenicity : embryolethal in rat, mice, rabbit per oral route. Not teratogenic in surviving rat and mice foetuses. Teratogenic effects have been seen in rabbit foetuse (undirect action, at low frequency). Mutagenicity : not mutagenic.
COMMENTS/SYMPTOMS	: TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.
OTHER RECOMMENDATIONS	: Handling inadvisable for pregnant women Possibly, seek medical advice

12. ECOLOGICAL INFORMATION

ENVIRONMENT	: Biodegradable in natural media

13. DISPOSAL CONSIDERATIONS

NEUTRALIZATION OF THE PRODUCT	: Set in specialized and approved recuperator service
DESTRUCTION SOILED PACKAGING	: Empty and rinse well.

14. TRANSPORT INFORMATION

INTERNATIONAL REGULATIONS

LAND WAYS	: 6.1,90°b,6.1
MARITIME WAYS	: 6.1,gr II,p6236.6 poison
AERIAL WAYS	: 6.1,gr II,,6 poison
CARGO	: 615 (100 kg)
PASSENGERS	: 613 (25 kg)
ONU	: 2811

OTHER REGULATIONS

LAND WAYS - FRANCE : 6.1,90°b,6.1

SPECIAL PRECAUTIONS

15. REGULATORY INFORMATION

COMMUNITY REGULATIONS

LABELLING (EEC NUMBER)	: Labelling according to EEC regulations
SYMBOLS	: T
PHRASES	: (B) R23/24/25 S36/37/39-S15
SPECIAL RISKS	: TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.
SAFETY ADVICES	: Wear suitable protective clothing, gloves and eye/ face protection. Keep away from heat.
ADDITIONAL LABELLING	: Room temperature (<86 F)

16. OTHER INFORMATION

FURTHER INFORMATIONS : None.

All the regulatory instructions mentioned are intended to help the addressee to comply with his obligations when using the product.This list cannot be considered as exhaustive and does not discharge the addressee from his duty to enquire about all other regulatory provisions which may apply to the posession and handling of the product for which he bears sole liability.

The information given in this data sheet has been introduced in accordance with the guidelines established by article 10 of EEC directive, dated March 5, 1991.
This data sheet complements the user's instructions, but does not replace them.
The information it contains is based on the knowledge available about the product concerned at the time it was compiled. Users are further reminded of the possible risks of using a product for purposes other than those for which it was intended.
The required information complies with current EEC legislation; addressees are requested to apply any additional national requirements.

/S/

JUL 22 1996

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-687

MIFEPRISTONE

TABLETS

DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS (HFD-580)

CENTER FOR DRUG EVALUATION AND RESEARCH

DATE COMPLETED: July 9, 1996

SUMMARY

A FONSI is recommended.

Precautions taken at the sites of manufacture and the disposal methods are expected to minimize occupational exposures and environmental release.

A Tier 0 EA was submitted in accordance with the Industry Guidance. The production estimate is [redacted] kg which is equivalent to an EIC of [redacted] ppb. There is no information that indicates extraordinary circumstances exist that would warrant the submission of additional environmental information.

APPEARS THIS WAY
ON ORIGINAL

ENVIRONMENTAL ASSESSMENT

1. Date:

EA dated: 03/01/1996
Consult #1: 03/20/1996

2. Name of applicant/petitioner:

The Population Council

ADEQUATE

3. Address:

1230 York Avenue
New York, NY 10021

ADEQUATE

4. Description of the proposed action:

a. Requested Approval:

The applicant is requesting approval of the product--200 mg mifepristone tablets. A brief description of the product packaging is provided. The product will be in packaging that is commonly used.

ADEQUATE

b. Need for Action:

Used in the termination of early pregnancy.

ADEQUATE

c. Production Locations:

i. Proprietary Intermediate(s):

The chemist confirmed that there are no proprietary intermediates manufactured elsewhere.

ADEQUATE

ii. **Drug Substance:**

ROUSSEL UCLAF
Vertolaye Plant
63480 Vertolaye
France

ADEQUATE

iii. **Finished Dosage Form:**

ROUSSEL UCLAF
USIPHAR Plant
Route de Choisy-au-Bac
60205 Compiegne
France

ADEQUATE

Facility Description & Adjacent Environment:
A brief description has been provided for each of the facilities. **ADEQUATE**

Note: The information for both of these production facilities is classified as confidential. [redacted] the review chemist, was consulted as to what companies were identified on the labeling. The labeling only identifies The Population Council as the distributor, therefore these facilities can be confidential.

d. **Expected Locations of Use (Drug Product):**

The drug will be used by women in the United States. It will be administered in hospitals, health clinics and physicians' offices. **ADEQUATE**

e. **Disposal Locations:**

Disposition of rejected, expired, returned or waste drug products are expected to disposed of:

1. "In accordance with the Center for Disease Control [sic] Guidelines for handling of hazardous waste in the clinic or healthcare provider's office";

2. The applicant will use a licensed incineration or grinding and landfill facility to dispose of this type of material.

The applicant is in the process of identifying a licensed disposal site to dispose of this product. In the past FONSI's have been written for EAs with identification of the disposal facility as long as it was indicated that a licensed facility would be used. Lack of this information is not considered sufficient to delay issuance of a FONSI. **ADEQUATE**

5. **Identification of chemical substances that are the subject of the proposed action:**

Drug Substance: Mifepristone

Chemical Name: Chemical Abstracts
(11beta, 17beta)-11-[(4-dimethylamino) phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-diene-3-one

IUPAC
11-beta-4-dimethylaminophenyl-17beta-17α-(1-propynyl-estra-4,9-diene-3-one

CAS #: 84371-65-3

Molecular Weight: 429.58

Molecular Formula: $C_{29}H_{35}NO_2$

Structural Formula: Provided on page 3.

Physical Descrip.: Light yellow to yellow crystalline powder

Additives: The excipients used in the drug product are provided.

Impurities: They state that there are no impurities greater than [redacted]. The Industry Guidance indicates that identification is not necessary in this case.

ADEQUATE

6. **Introduction of substances into the environment: For the site(s) of production:**

a. **Substances Expected to be emitted:**

The chemicals expected to be emitted from drug substance manufacture are include on pages 75-78. The composition of the drug product is included in the non-confidential EA. **ADEQUATE**

b. Controls (Air, Liquid Effluent, Solid):

Drug substance:
In the table listing the emitted substances there is a discussion of the depollution treatment for each waste stream. In general, air emissions are filtered, pre-treated aqueous waste streams are subjected to biological treatment, some solvents are incinerated or recovered and solid waste is sent to off-site disposal facilities in accordance with French regulations.

Drug product:
In general, air emissions are filtered, pre-treated aqueous waste streams are subjected to biological treatment, solvents are incinerated and solid waste is either incinerated or in the case of packaging material recycled.

ADEQUATE

c. Compliance with Federal, State and Local Emission Requirements:

Although there is no specific statement regarding compliance, the manufacturer states that their facilities "operate with all technical means required to protect, preserve and enhance the quality of the environment as specified by French Law in the fields of environmental protection and occupational hygiene." Various French laws and requirements are cited throughout the document. English translations of French government reports are also included as supporting information (originals not provided).
ADEQUATE

d. Effect of Approval on Compliance with Current Emissions Requirements:

It is stated that approval will have no adverse effect upon compliance with current emission requirements.
ADEQUATE

e. Estimated Expected Emitted Concentration/Quantities:

The production estimate is [redacted] kg which is equivalent to an EIC of [redacted] ppm ([redacted] ppb, [redacted] pptr). These calculations do not consider metabolism.
ADEQUATE

7. **Fate of emitted substances in the environment:**
8. **Environmental effects of released substances:**
9. **Use of resources and energy:**
10. **Mitigation measures:**
11. **Alternatives to the proposed action:**

Format items 7-11 are not normally necessary if the EIC is < ppb (See "Tier 0" Industry Guidance). The EIC is much less than ppb even without consideration of metabolism. There are no extraordinary circumstances that indicate additional environmental information is warranted. **ADEQUATE**

12. **List of preparers, & their qualifications (expertise, experience, professional disciplines) and consultants:**

The preparers are identified along with their titles/experience. **ADEQUATE**

13. **Certification:**

The certification is acceptable except Appendix E is listed as non-confidential which contradicts the listing in format item 15. I spoke to Ann Robbins of The Population Council on 7/9/96 and she confirmed that Appendix D is the non-confidential appendix. This will be corrected by hand. **ADEQUATE**

14. **References:**

References are provided. **ADEQUATE**

15. **Appendices:**

Five appendices are attached, four are designated as confidential. **ADEQUATE.**

The EA is formatted appropriately for public release.

APPEARS THIS WAY
ON ORIGINAL

Endorsements:

[redacted] /S/ 7/9/96
/S/ 7/11/96

CC: Original to NDA 20-687/through [redacted]
EA File 20687

[redacted]

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-687

MEDICAL REVIEW(S)

JAN 27 2000

MEDICAL OFFICER'S REVIEW OF AMENDMENTS 024 AND 033
FINAL REPORTS FOR THE U.S. CLINICAL TRIALS INDUCING ABORTION UP TO 63 DAYS GESTATIONAL AGE AND COMPLETE RESPONSES REGARDING DISTRIBUTION SYSTEM AND PHASE 4 COMMITMENTS

NDA Number: 20-687

Applicant: Population Council
One Dag Hammarskjold Plaza
New York, New York 10017

Dates of Submission: June 3, 1999 and August 18, 1999

Dates Submissions Received: June 4, 1999 and August 19,1999

Date Review Completed: October 28, 1999

Date Review Revised: November 19, 1999

Date Review Finalized: November 22,1999

I. General Information:

A. Name of Drug:
1. Established Name: Mifepristone
2. Trade Name: None designated as yet.

3. Laboratory Code Name: RU 38486 (RU-486).

B. Pharmacologic Category: Antiprogestational and antiglucocorticoid agent.

C. Proposed Indication: Medical termination of intrauterine pregnancy through 49 days' pregnancy.

D. Dosage Form and Route of Administration: Tablet for oral administration.

E. Strength: Each tablet contains 200 mg of mifepristone.

F. Dosage: Three 200 mg tablets (600 mg) of mifepristone are taken as a single oral dose. Unless abortion has occurred, the patient takes two 200 μg tablets (400 μg) of misoprostol orally two days after ingesting mifepristone.

G. Related Drugs: None marketed.

H. Table of Contents:

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II. Manufacturing Controls: Please refer to chemist's review for details.

III. Pharmacology and Pharmacodynamics: Please refer to pharmacologist's review for details.

IV. Clinical Background:

Mifepristone is a synthetic steroid that was approved for the termination of pregnancy in France in December 1988 (launched September 1989), in Sweden in 1992, in the United Kingdom in 1991, and in China in 1988. (It should be noted that mifepristone used in China is not manufactured by Roussel Uclaf but by domestic companies). When administered alone in total doses of 1400-1600 mg over 1-10 days, the success rate was 64-85%. Subsequent studies demonstrated that the administration of mifepristone followed by a synthetic prostaglandin analog increases the success rate to over 95%. In a preliminary study of 100 women, the success rate of 600 mg mifepristone and 0.2 mg misoprostol was 95% for pregnancies of no more than 49 days of amenorrhea. Misoprostol is a synthetic prostaglandin E_1 analog [redacted] In the [redacted] misoprostol [redacted]

Nine phase 2 clinical studies to determine the most effective dose and dosage regimen for mifepristone used alone for the interruption of pregnancy were conducted in France between 1983 and 1986. Patients in these studies were entered with a target gestational age of less than or equal to 41 days of amenorrhea. One thousand patients were exposed to doses ranging from 100 mg for one to four days to 800 mg for one day.

Following completion of the phase 2 studies, nine phase 3 clinical trials employing a single 600 mg dose of mifepristone were conducted to evaluate the efficacy and the

safety of this dose. The target population was patients with pregnancies having a gestational age ≤42 days of amenorrhea. A total of 2,459 patients were studied.

The advantage of combining mifepristone 600 mg with a prostaglandin (sulprostone 250μg I.M. 36-48 hours later) for pregnancy interruption was demonstrated in 1985. A series of ten clinical trials were conducted between 1987 and 1991 to confirm and extend these initial observations. In addition to sulprostone, other prostaglandins including gemeprost, 15MePGF 2a, and prostine E_2 were evaluated. During the ten studies, a total of 19,947 patients were exposed to mifepristone administered as a single 600 mg dose. One of these studies enrolled over 16,000 patients. Very rare cases of hypotension and one myocardial infarction were reported. Successful termination of early pregnancy was achieved in 82.6 to 100% of the patients enrolled in these studies and the safety of mifepristone was confirmed.

The efficacy and safety of mifepristone given as a single 600 mg oral dose in combination with misoprostol 0.4 mg orally administered approximately 36 to 48 hours after mifepristone for termination of pregnancy was evaluated in two historically controlled, pivotal clinical trials conducted in France. The first study included women with intrauterine pregnancies of ≤ 49 days and the second study included women with intrauterine pregnancies of ≤63 days. In the second study, a second dose of 200 μg of misoprostal was given 3 hours after the first dose if complete abortion had not occurred. In the first study of 1205 evaluable patients, the complete abortion rate was 95.4% and in the second study of 1104 evaluable patients, the complete abortion rate was 92.8%. These two studies were evaluated in the review of a new drug application that was submitted March 16, 1996.

V. Regulatory Background:

2 **Page(s) Redacted**

Deliberative Process

VI. Statistical Consultation: None required

VII. Clinical Studies:

The efficacy and safety of mifepristone was evaluated in two prospective, open-label, multicenter clinical trials in the United States according to two identical protocols (166A and 166B) at 17 centers (University hospitals, Planned Parenthood clinics, and free-standing clinics). The studies were conducted at centers that could perform abortions by either vacuum aspiration or dilatation and curettage and had access to facilities that provided blood transfusions and performed routine emergency resuscitation procedures. The studies included patients in three gestational age groups:

Group 1: amenorrhea of ≤49 days
Group 2: amenorrhea of 50-56 days
Group 3: amenorrhea of 57-63 days

Data from the two studies were combined in the following evaluation.

A. Investigators:

Dr. Paul Blumenthal	Baltimore, Maryland
Dr. Lynn Borgatta	White Plains, New York
Dr. Mitchell Crenin	Pittsburgh, Pennsylvania
Dr. Catherine Dean	St. Louis, Missouri
Dr. Susan Haskell	Des Moines, Iowa
Dr. Tyrone Mallory	Atlanta, Georgia
Dr. Daniel Mishell, Jr.	Los Angeles, California
Dr. Mark Nichols	Portland, Oregon
Dr. Alfred Poindexter	Houston, Texas
Dr. Suzanne Poppema	Seattle, Washington

Dr. Eugene Rothenberg	Shrewsbury, New Jersey
Dr. Katherine Sheehan	San Diego, California
Dr. Laszlo Sogor	Cleveland, Ohio
Dr. Judith Tyson	Burlington, Vermont
Dr. Peter Vargas	Aurora, Colorado
Dr. Carolyn Westhoff	New York, New York

B. Objectives of the Study:

The study was conducted to evaluate the effectiveness, safety, acceptability, and feasibility of using mifepristone and misoprotol in a variety of clinical settings within the United States health care system for the induction of abortion in women whose duration of amenorrhea was no more than 63 days.

C. Rationale for the Study:

Extensive experience has been gained outside the United States with the use of mifepristone and various prostaglandin analogs, including misoprostol, for the termination of pregnancies up to 63 days, with complete abortion rates ranging from 92.7% to 99%. The applicant wished to confirm the efficacy and safety of the regimen in the United States.

D. Method of Assignment to Treatment:

Eligible patients fulfilling all of the inclusion criteria and none of the exclusion criteria were assigned to one of the three treatment groups, based on gestational age.

E. Number of Subjects:

A total of 2,121 patients were enrolled including 859 patients in groups 1,722 patients in group 2, and 540 patients in group 3.

F. Duration of Clinical Trial:

Patients were to receive mifepristone on day 1 and misoprostol on day 3 and were to be observed in the clinical setting for at least 4 hours after misoprostol administration. Patients were to return for evaluation on day 15.

G. Inclusion Criteria:

1. Was at least 18 years of age and in good general health.

2. Requested a voluntary termination of pregnancy.

3. Had a positive urine pregnancy test.

4. Had an intrauterine pregnancy with a duration of amenorrhea of ≤63 days (from the first day of her last menstrual period) that was confirmed by uterine size on pelvic examination and by vaginal ultrasound evaluation.

5. Agreed to have a surgical termination of pregnancy if the study procedures failed to terminate her pregnancy.

6. Was a resident of the United States.

7. Gave written informed consent to participate in the study and was willing and able to participate.

H. Exclusion Criteria:

1. Had evidence of any disorder which represented a contraindication to the use of mifepristone (such as adrenal disease or a condition requiring chronic corticosteroid administration) or misoprostol (such as asthma, glaucoma, mitral stenosis, arterial hypotension, sickle cell anemia, or a known allergy to prostaglandins).

2. Had a history of severe liver, respiratory, or renal disease or thromboembolism.

3. Had a cardiovascular disease, e.g. angina, valve disease, arrhythmia, cardiac failure, or insulin dependent diabetes.

4. Had hypertension that was being treated on a chronic basis or had blood pressure of greater than 140/90mmHg.

5. Was anemic (hemoglobin < 10 g/dL or hematocrit < 30%).

6. Had a known clotting defect or was receiving anticoagulants.

7. Had an IUD *in situ*.

8. Was breastfeeding.

9. Had adnexal masses or tenderness on pelvic examination that suggested pelvic inflammatory disease.

10. Had an ectopic pregnancy or threatened abortion.

11. Was over 35 years of age and smoked more than 10 cigarettes per day, and

had another risk factor for cardiovascular disease such as diabetes mellitus, hyperlipidemia, hypertension, or a family history of ischemic heart disease.

12. Was unlikely to understand and comply with the requirements of the study.

13. Lived or worked more than one hour from the emergency care facility that served the abortion center.

I. Trial Period:

September 13, 1994 to September 12, 1995

J. Dosage and Mode of Administration:

Patients were not to eat during the one hour before and after the administration of mifepristone. In the presence of the investigator, each patient was administered three 200 mg mifepristone tablets by mouth with no more than 240 mL of water. Patients were informed that they should not smoke during the 48 hours following mifepristone administration and on the day misoprostol was to be administered. Unless the investigator could verify unequivocally that complete abortion had occurred, patients were administered two 200 μg misoprostol tablets by mouth with no more than 240 mL of water in the presence of the investigator 36 to 60 hours after the administration of mifepristone.

K. Efficacy Assessments:

Pelvic examinations were performed before mifepristone administration at visit 1, before misoprostol administration at visit 2, during the 4 hour observation period after misoprostol administration, and at the visit 3 evaluation. At visit 1, patients also had transvaginal ultrasound examinations and quantitative hCG β subunit pregnancy tests performed. At visits 2 and 3, ultrasound examinations were performed at the discretion of the investigator.

The outcome of treatment was classified as follows:

1. Complete abortion: pregnancy termination and complete expulsion of the products of conception without the need of surgical intervention.

2. Incomplete abortion: pregnancy termination with either partial expulsion or nonexpulsion of the products of conception diagnosed at visit 3 or at study end if later than visit 3 with surgery required.

3. Ongoing pregnancy: a viable pregnancy diagnosed at visit 3 based on fetal heartbeat and/or fetal growth indicating gestations that are

two weeks older than at visit 1; surgery required.

4. Medical intervention: before visit 3, the investigator judged that a surgical intervention was medically indicated.

5. Patient request: before visit 3, the patient chose not to proceed with the medical method of abortion and requested surgical intervention.

In the analyses of treatment outcome, complete abortion only was classified as a treatment success. All other categories resulted in a surgical procedure and , therefore, were classified as treatment failures.

L. Safety Assessments:

Adverse events were summarized and evaluated.

M. Disposition of Patients:

A total of 2121 patients were enrolled. Of these, 2015 (95.0%) were included in the efficacy analyses. There were 106 patients excluded from the efficacy analyses because of failure to show up for visit 3, thus preventing confirmation of a final outcome. For 92 of these patients, there was some information suggesting a successful outcome. For one excluded patient, there was evidence that suggested failure. The remaining 13 women were lost to followup; 5 had continuing pregnancies when last seen at visit 2. All 2121 patients were evaluable for safety. A total of 827 patients in Group 1, 678 patients in Group 2, and 510 patients in Group 3 were included in the efficacy evaluation.

N. Demographic Characteristics:

Most patients were Caucasian (71%), 20-29 years of age (61%; mean age of 26.9 years), of normal body mass index (71%), nulliparous (55%) and had a previous elective abortion (51%). The differences among the three gestational age groups in race distribution and mean age, weight, and body mass index were small and not of clinical significance.

O. Results:

1. Efficacy:

Success and failure rates are summarized in Table 1.

Table 1
(Sponsor's Table 4.1)
Treatment Outcomes by Gestational Age (Evaluable Patients)

Treatment Outcomes	Group 1 ≤ 49 days N = 827	Group 2 50-56 days N = 678	Group 3 57-63 days N = 510
Total Successes	762 (92%)	563 (83%)	395 (77%)
RU-486 alone	40 (5%)	12 (2%)	4 (< 1%)
Plus misoprostol	722 (87%)	551 (81%)	391 (77%)
Total Failures	65 (8%)	115 (17%)	115 (23%)
Med intervention	13 (2%)	26 (4%)	21 (4%)
Patient request	5 (< 1%)	13 (2%)	12 (2%)
Incomplete ab	39 (5%)	51 (8%)	36 (7%)
Ongoing preg	8 (< 1%)	25 (4%)	46 (9%)

Failures are discussed in this review in the "Safety" section of "Results."

Complete abortion rates according to time of occurrence are displayed in Table 2 as confirmed by the investigators.

Table 2
(Sponsor's Table 5.1)
Time to Occurrence of Complete Abortion

Occurrence Time	Group 1 ≤ 49 days N =827	Group 2 50-56 days N=678	Group 3 57-63 days N=510
Mifepristone alone	40 (4.8%)	12 (1.8%)	4 (0.8%)
≤ 4h after misoprostol	376 (45.5%)	312 (46.0%)	178 (34.9%)
> 4h & < end of day 4	178 (21.5%)	118 (17.4%)	118 (23.1%)
After day 4	168 (20.3%)	121 (17.8%)	95 (18.6%)
Surgical intervention	65 (7.9%)	115 (17.0%)	115 (22.5%)

2. Safety:

Adverse events, regardless of causality, were reported for at least 99% of the patients in each gestational age group. More than one adverse event was reported for most patients. The majority of adverse events were of mild or moderate severity. Approximately 23% of the adverse events in each gestational age group were judged to be severe. The most common adverse event was abdominal pain, including uterine cramping. This was to be expected since the treatment procedure is designed to induce the uterine cramping (and bleeding) necessary to produce an abortion.

Other commonly reported adverse events were nausea, vomiting, headache, diarrhea, and dizziness. No serious adverse events were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than threefold that recommended for termination of pregnancy. Table 3 shows that the rates of most, but not all, adverse events that occurred in patients whose gestational age was ≤ 49 days were not significantly different from the rates across all gestational age groups.

Table 3

Most Commonly Reported Adverse Events

Adverse Event	Group 1 ≤ 49 days N=859 Percentage	Groups 1, 2, and 3 ≤ 63 days N=2121 Percentage
Abdominal pain (cramping)	96	97
Nausea	61	67
Headache	31	32
Vomiting	26	34
Diarrhea	20	23
Dizziness	12	12
Fatigue	10	9
Back pain	9	9
Uterine hemorrhage	5	7
Fever	4	4
Viral infections	4	4
Vaginitis	3	4
Rigors (chills/shaking)	3	3
Dyspepsia	3	3
Insomnia	3	2
Asthenia	2	2
Leg pain	2	2
Anxiety	2	2
Anemia	2	2
Leukorrhea	2	2
Sinusitis	2	2
Syncope	1	2

Table 4 shows the rates of adverse events in any gestational age group which were significantly different across gestational age groups.

Table 4
Adverse Events Significantly Different Across Gestational Age Groups

Adverse Event	Group 1 ≤ 49 days Percentage	Group 2 50-56 days Percentage	Group 3 57-63 days Percentage
Nausea	61	71	72
Vomiting	26	38	41
Diarrhea	20	23	26
Uterine hemorrhage	5	8	10

No patient was discontinued from the study because of an adverse event and there were no deaths.

The median bleeding duration for group 1 was 14 days and 15 days for groups 2 and 3.

The proportions of patients who received any medications for bleeding increased with increasing gestational age form 5.7% in group 1 to 10.7% in group 3. A total of 146 patients (6.9%) received uterotonics (ergot-type medications or oxytocin) for bleeding.

Fourteen patients (0.7%) were hospitalized for an adverse event. Of these patients, 2 of 4 in the ≤ 49 days group, 3 of 5 in the 50-56 days group, and 3 of 5 in the 56-63 days group had adverse events (severe excessive bleeding) which were considered to be study drug related. The other patients were hospitalized for reasons unrelated to study treatment (pneumonia, meningitis, automobile accident, depression, shooting injury, endometritis).

Nineteen patients (0.9%) had emergency room visits that did not result in hospitalization. Sixteen of these 19 patients had excessive bleeding (2, ≤ 49 days; 7, 50-56 days; 7, 57-63 days). The other three visits were for chest pain, nausea and vomiting, and cramping.

Four patients received blood transfusions (1, ≤ 49 days; 2, 50-56 days; 1, 57-63 days). Three of these patients were hospitalized.

IV fluids were administered for various reasons to 9 (1.0%) patients in the ≤ 49 days group, 19 (2.6%) in the 50-56 days group, and 18 (3.3%) in the 57-63 days group.

The following five potentially serious adverse events occurred:

A 34 year old patient with a 20 year history of seizures and a pregnancy of

46 days gestational age had a mild seizure (convulsion) on the day of mifepristone administration and received 250 mg of dilantin. In the opinion of the investigator, the patient's seizure was not related to treatment with mifepristone and she received misoprostol 47 hours after the mifepristone.

A 28 year old of 54 days gestational age with a negative gastrointestinal history reported possible blood in her stool a month after misoprostol administration. In the opinion of the investigator, the patient's melena was not related to study treatment.

A 23 year old of 57 days gestational age developed moderate purpura (body bruises) that lasted for one day without treatment ten days after receiving misoprostol. In the opinion of the investigator, the patient's purpura was not related to study treatment.

A 21 year old of 57 days gestational age developed severe viral meningitis 6 days after receiving misoprostol and was hospitalized. In the opinion of the investigator, the patient's meningitis was not related to study treatment.

A 27 year old of 60 days gestational age with a negative gastrointestinal history reported blood in her stool 3 days after receiving misoprostol. At the time of last contact with the patient three weeks later, no further incidents of melena had been reported. In the opinion of the investigator, the patient's melena was not related to study treatment.

The proportions of patients with a decrease in hemoglobin or hematocrit of more than 20% from their pre-mifepristone administration levels increased significantly with increasing gestational age, from 3.1% in the ≤ 49 days group to 8.0% in the 57-63 days group.

Of the 1028 patients with hemoglobin measurements before and after misoprostol administration, 131 had a decrease of at least 2mg/dL (7.8%, ≤49 days; 15.0%, 50-60 days; 17.4% 57-63 days).

Hypotension after administration of misoprostol occurred in 0.3% - 1.4% of all treated patients.

Hypertension after administration of misoprostol occurred in 1.5% - 1.7% of all treated patients.

Decrease in heart rate by > 20% after administration of misoprostol occurred in 18.2% - 21.3% of all patients.

Increase in heart rate by >20% after administration of misoprostol occurred in 11.8% - 14.1% of all patients.

For the subgroup of patients with a full panel of laboratory tests, the median changes were small and not of clinical significance.

Failure of the mifepristone - misoprostol procedure required surgical intervention which is an additional safety concern, albeit small. A total of 295 patients were classified as having failed medical abortion. Of these patients, 79 (27%) had ongoing pregnancies, 126 (43%) had incomplete abortions, 30 (10%) requested and had surgical terminations, and the remaining 60 (20%) patients had surgical terminations performed because of medical indications directly related to the medical procedure. In group 1 (≤ 49 days gestation), of the 65 failures, 8 (12%) patients had ongoing pregnancies, 39 (60%) patients had incomplete abortions, 5 (8%) requested and had surgical terminations performed, and the remaining 13 (20%) patients had surgical terminations directly related to the medical procedure. The failure rates for medical intervention, patient request, incomplete abortion, and ongoing pregnancy were significantly higher in groups 2 and 3 than in group 1.

For each gestational age group, the adverse event rates were highest at Planned Parenthood clinics and lowest at Free-Standing clinics, with university hospital clinics in the middle.

VIII. Reviewer's Comments, Evaluation, and Conclusions:

Two studies were conducted according to two identical protocols at 17 centers to evaluate a mifepristone - misoprostol regimen for the termination of pregnancies in the United States health care system. The studies included patients in three gestational age groups:

Group 1: amenorrhea of ≤ 49 days
Group 2: amenorrhea of 50-56 days
Group 3: amenorrhea of 57-63 days

The studies included women who requested a voluntary termination of pregnancy, had a positive pregnancy test, and a documented intrauterine pregnancy. Women with liver, respiratory, renal, adrenal, or cardiovascular disease, thromboembolism, hypertension, anemia, insulin-dependent diabetes mellitus, coagulopathy, or allergy to prostaglandins were excluded, as were women less than 18 years of age or those more than 35 years of age who smoked more than ten cigarettes per day and had another cardiovascular risk factor. Women were also excluded if they had intrauterine devices, were breast-feeding, were receiving anticoagulation or long-term glucocorticoid therapy, had adrenal masses, had

ectopic pregnancies, or had signs or symptoms suggesting that they might abort spontaneously. All the women agreed to undergo surgical termination of pregnancy if the medical method failed. A total of 2,121 women were enrolled in the two studies including 859 women who were in the ≤ 49 days group, which is the gestational age which is the subject of this application.

Pregnancy was measured from the first day of the last menstrual period according to menstrual history, pelvic examination, and vaginal ultrasonography and women were assigned to the appropriate gestational age group.

Three clinic visits were scheduled. At visit 1 (day 1), the women were assessed clinically and took three 200 mg tablets of mifepristone orally in the presence of the investigator. Patients did not eat for one hour before and after the consumption of the mifepristone. At visit 2 (day 3), they took 400 μg of misoprostol orally unless a complete abortion had already occurred. Patients did not smoke during the 48 hours following mifepristone consumption and on the day misoprostol was administered. Patients then remained at the clinics under observation for at least four hours. Adverse events such as nausea, vomiting, diarrhea, abdominal pain, and vaginal bleeding were rated by the women and recorded. Blood pressure and heart rate were measured at least hourly. Vaginal bleeding was recorded on a diary card and rated by each woman on days 1 through 15 as "spotting", "normal", or "heavy." During this period, the women were also monitored for the expulsion of the conceptus. At visit 3 (day 15), the treatment outcome was assessed.

Efficacy was defined as the termination of pregnancy with complete expulsion of the conceptus without the need for a surgical procedure. The need for a vacuum aspiration or dilatation and curettage constituted a failure. A surgical procedure was performed at any time if the investigator believed there was a threat to a woman's health (medically indicated), at a woman's request, or at the end of the study for an ongoing pregnancy or incomplete abortion.

A total of 106 women were excluded from the efficacy analysis because they did not return for visit 3. Evidence suggesting a successful outcome was available for 92 of these women, and evidence of failure for 1. The remaining 13 women were lost to followup; 5 had continuing pregnancies when last seen at visit 2. The efficacy analysis, therefore, included 2015 women. No additional information is available on the outcomes of the 5 women with continuing pregnancies who were lost to followup. All other women with continuing pregnancies were aborted surgically.

Efficacy was 92% in the ≤ 49 days group with a lower 95% confidence interval of 90%. This is somewhat less than the 95.5% efficacy with a lower 95% C.I. of 94.2% reported in the pivotal French studies upon which approval of this application was recommended.

Efficacy was 83% in the 50-56 days group with a lower 95% confidence interval of 80%. Efficacy was 77% in the 57-63 days group with a lower 95% confidence interval of 74%.

The 92% success rate in the ≤ 49 days group is an acceptable one.

The median duration of bleeding in the ≤ 49 days group was 14 days. The average duration of bleeding was 16 days. This is considerably longer than the average duration of 9 days reported in the French studies upon which approval of this application was recommended, but is an acceptable duration.

Excessive bleeding necessitated blood transfusion in only 1 patient in the ≤ 49 days group and required hospitalization of only 2 patients in the ≤ 49 days group. An additional 2 patients in the ≤ 49 days group were treated in the emergency room for excessive bleeding. Thirteen (2%) patients in the ≤ 49 days group required surgical intervention because of excessive bleeding. Bleeding was managed by the administration of uterotonic agents such as oxytocin, methylergonovine or vasopressin in 5% of patients in the≤ 49 days group.

The adverse event rates were higher in these studies than those in the pivotal French studies upon which approval of this application was recommended. This is shown in Table 5.

Table 5

Frequent Adverse Events (≤ 49 days) in French and U.S. Trials

Adverse Event	French Trials	U.S. Trials
Abdominal pain (cramping)	83%	96%
Nausea	43%	61%
Headache	2%	31%
Vomiting	18%	26%
Diarrhea	12%	20%
Dizziness	1%	12%

The majority of adverse events were of mild or moderate severity. The difference in the frequency of common adverse events noted above is acceptable.

In the pivotal French trials, 5.5% of subjects had a decrease in hemoglobin of greater than 2g/dL while in the U.S. trials, 7.8 % of patients in the ≤ 49 days group had such a decrease. This difference is an acceptable one.

The U.S. clinical trials confirmed the findings of the pivotal French trials that mifepristone and misoprostol are safe and effective in terminating pregnancies of up to 49 days gestation even though the success rate in the U.S. trials was lower

than that of the French trials. This lower success rate might be related to the lack of experience of most of the U.S. investigators with medical abortion. The lower success rate might also be attributable somewhat to the fact that in the U.S. trials, a woman's request for a surgical termination any time after receiving mifepristone was honored and classified as a failure rather than being excluded form the efficacy analysis. However, in the ≤ 49 days group, less than 8% of the failures (5 patients) were because of patient requests.

The success of medical termination of pregnancy decreased with advancing gestational age and the incidence of adverse events increased with advancing gestational age. The majority of surgical interventions were for incomplete abortion and excessive bleeding.

This method of pregnancy termination is of limited value because of the relatively short window of opportunity, in which it can be employed. Its safety and effectiveness is based on its use during the seven weeks following the first day of the last menstrual period. This means that most women would not suspect that they are pregnant and have a confirmatory pregnancy test until at least four weeks after the beginning of their last menses. This, then, leaves only a three week period for the women to secure this method of abortion.

Another disadvantage of this method of pregnancy termination is the need for at least three visits to the medical facility including at least a four hours stay after the administration of the misoprostol.

In addition, medical follow-up is required to ensure that surgical termination is performed in case the medical termination attempt fails since misoprostol has been reported to be teratogenic in humans (limb defects and skull defects).

In the U.S. clinical trials, an increase in the incidence of some adverse events (vomiting, nausea, diarrhea, uterine hemorrhage) occurred in the 50-56 and 57-63 days gestational age groups compared to the ≤ 49 days group. The safety profile of the ≤ 49 days group in the U.S. study did not differ significantly from the pivotal French studies, even though the incidence of common adverse events in the U.S. clinical trials was higher than that of the French trials in the ≤ 49 days group. The percentage of patients in the U.S. studies and the French studies requiring hospitalization, requiring blood transfusion and experiencing heavy bleeding was about the same. However, about 1.6% of the patients in the ≤ 49 days group in the U.S. study had surgical intervention because of heavy bleeding compared to less than 1% of patients in the French studies. The average duration of bleeding was 16 days in the U.S. studies compared to 9 days in the French studies.

While the U.S. clinical trials confirm the safety and efficacy of mifepristone and misoprostol found in the pivotal French studies for women seeking medical

abortions with gestations of 49 days duration or less, they demonstrate that with longer durations of gestation (50-56 days and 57-63 days), the treatment regimen is less effective and the incidence of adverse events is higher.

A comparison of medical termination of pregnancy with surgical termination is of interest in a polulation of women who are given a choice to select between medical and surgical termination of early pregnancy. Such a comparative clinical trial was conducted according to a uniform protocol from 1991 to 1993 in urban clinics in China, Cuba, and India, three countries where abortion is legal and available. A total of 1373 women with amenorrhea ≤ 56 days were given a choice of surgical abortion or mifepristone and misoprostol in the same dosage regimen as used in the U.S. studies. The results of this study were published in 1997. The medical regimen had more adverse events, particularly bleeding, than did surgical abortion. Failure rates for medical abortion exceeded those for surgical abortion (8.6% versus 0.4% in China, 16.0% versus 4.0% in Cuba, and 5.2% versus 0% in India). In each site failure rates of medical abortion increased with gestational age. Specific symptoms and adverse events, including cramping, nausea, and vomiting, were far more frequent among the medical than the surgical abortion patients. The only serious complication was excessive bleeding in medical abortion patients, which is a reason for surgical intervention and for dissatisfaction among medical abortion patients. Three patients (all medical abortions) received blood transfusions. This is a serious potential disadvantage of the medical method. On the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients. Slightly higher proportions of medical than surgical patients were dissatisfied (8.8% versus 3.8%). Despite the bleeding pattern and the failure rate of the medical abortion method, particularly in China, medical abortion by the mifepristone and misoprostol regimen was said by the authors of this published study to be safe, efficacious, and highly desired by and acceptable to women in developing countries.

The results of a smaller study published in 1999 comparing mifepristone to surgical abortion in U.S. women are consistent with the findings of the larger comparative clinical trial done in China, Cuba, and India. The study was a nonconcurrent, prospective, cohort analysis of 178 mifepristone - misoprostol and 199 suction curettage abortion subjects with intrauterine pregnancies ≤ 63 days gestational age. The medical abortion cohort represents all of the subjects enrolled at one U.S. clinical site for the mifepristone clinical trial between December, 1994 and August, 1995. The surgical abortion cohort was enrolled prospectively at the same clinical site between November, 1995 and December, 1996. Overall, 18.3% of medical and 4.7% surgical patients failed their primary procedure and received an unanticipated suction curettage (R.R. 3.93; 95% CI 1.87,8.29). The risk of failure demonstrated a statistically significant upward trend from 3.3 to 4.4 with advancing gestational age. Four mifepristone patients required curettage for acute bleeding while no surgical patients did. Nine

mifepristone patients required curettage to manage ongoing pregnancy while no surgical patients did. Five mifepristone patients required suction curettage because of incomplete abortion while no surgical patients did. Fourteen mifepristone and eight surgical patients required suction curettage for persistent bleeding. The median time delay for therapeutic curettage was significantly longer in the mifepristone group than in the surgical group (35 days versus 8 days). Mifepristone patients experienced significantly longer postprocedure bleeding than did surgical patients. The mean difference in bleeding days between cohorts was 9.6 days (95% CI, 6.8, 12.4). Mifepristone patients reported significantly longer bleeding in all three gestational age groups. Overall, mifepristone abortion patients reported significantly higher levels of pain, nausea, vomiting, and diarrhea during the actual abortion than did surgical patients. The use of antiemetic agents during the abortion procedure was significantly more common in mifepristone patients than surgical patients (31.1% versus 1%). Mifepristone patients were routinely offered oral narcotics for expulsion-related pain, and 78.5% used them. Mifepristone patients reported more problems during the follow-up interval than did surgical patients. Post-abortion pain occurred in 77.1% of mifepristone patients compared with only 10.5% of surgical patients (RR 7.4, 95% CI 4.7, 11.5). Nausea or vomiting in the follow-up interval was common in the mifepristone group (68.6%), but rare among surgical patients (0.6%) (RR 117.9, 95% CI 16.7, 834.7).

Although the mifepristone and surgical abortion techniques are both safe and effective, the abortion and post-abortion experiences differ significantly as reported in the two published studies above that permit direct comparison of the two techniques in a prospective manner.

IX. Labeling Evaluation:

Comments regarding labeling revisions were transmitted to the sponsor in a letter dated September 18, 1996. Revised draft labeling was submitted by the sponsor June 25, 1999 and currently is under review.

X. Conclusion:

The results of the U.S. studies do not adversely differ significantly from the results of the two pivotal French clinical trials which were the basis for the approvable letter to the sponsor September 18, 1996.

XI. Recommended Phase 4 Studies:

The medical officer, in his revised original NDA review, recommended that phase 4 studies with the following objectives be conducted:

A. To monitor the adequacy of the distribution and credentialing

system.

B. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.

C. To assess the long-term effects of multiple use of the regimen.

D. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.

E. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke.

F. To ascertain the effect of the regimen on children born after treatment failure.

The phase 4 recommendations were included in the approvable letter to the sponsor dated September 18, 1999.

XII. Consideration of Advisory Committee Members' Comments:

Part of the review process for this application included seeking expert advice from members of the FDA Reproductive Health Drugs Advisory Committee at a public meeting July 19, 1996. The committee voted 6-0 (with two abstentions) that the pivotal studies (French studies) presented at that time showed that the benefits of a mifepristone and misoprostol regimen for terminating early pregnancies outweighed its risks. The studies presented to the committee involved women treated within 49 days of the beginning of their last menstrual period.

Preliminary safety data from recently completed U.S. trials were also presented.

The committee recommended some phase 4 studies and individual committee members offered some individual comments for consideration by the FDA staff, particularly comments regarding labeling and the drug distribution system. All comments were carefully and fully considered and, to the extent possible, implemented.

The applicant was asked September 18, 1996 to submit a comprehensive description of the proposed distribution system. The following complete response from the applicant was submitted to FDA August 18, 1999 regarding the distribution system:

"The details of the distribution system for the product are in the process of being worked out with the proposed distributor. However, the following key principles will be adhered to in the final distribution arrangements:

- Product will only be available from one or two distributors nationwide and not through retail pharmacies or direct to physicians from the manufacturer.

- Each physician interested in obtaining the product must request the product from the distributors, register with them and open an account.

- Access to the distributors will be through the distributors' general order system and through a specially established toll free telephone number with product ordering as an option.

- Aside from standard credit checks run by the distributors to open a new account, each requesting physician will be required to register by providing their BNDD # and their state Medical License #, and signing a letter that they have the following:

  - The ability to accurately confirm the duration of pregnancy

  - The ability to determine blood Rh factor

  - Access to medical facilities equipped to provide emergency care should that become necessary.

In this same letter they will also be asked to indicate their agreement to:

- Obtain signed acknowledgment from the patient that they have been provided with the product label, that they have read and understood the patient information, have had the procedure, its risks and benefits explained to them, and that they agree to follow the treatment procedure.

- Place the dose # on the acknowlegement and in the patient record.

- Maintain complete records for each patient including blood tests, ultrasound examinations and progress noted.

- Fill out and return AE (Adverse Event) cards to the distributor, identifying patient by dose # only.

- Use every effort to ensure patients return for their follow up visit 14-20 days after taking the product.

- Provide the distributor with as much information as possible if there is an ongoing pregnancy following completion of the treatment procedure and this pregnancy is not terminated.

In addition, the toll free telephone number will enable providers to request training materials and information, and speak to an experienced medical consultant about either a non-emergency patient issue or an urgent medical problem or possible complication. Through a separate routing on the toll free telephone number, patients will have access to general information about the product, a provider location near them and web page addresses for more information.

The final distribution system will be more fully developed in the next few months but will always attempt to insure that the drug is only supplied to qualified physician/hospitals who register with the distributor, that the patient is given access to the product label and that the product # is placed on the acknowledgment in the patient's file and that the anonymity of the patient is maintained.

Market launch will not occur until the distribution system is finalized and there are adequate systems in place to track shipment and use."

FDA requested six phase 4 studies of the applicant's August 22, 1996 (and reminded them of their commitment to perform them in the approvable letter dated September 18, 1996). The requested studies are listed below:

1. To monitor the adequacy of the distribution and credentialing system.

2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.

3. To assess the long-term effects of multiple use of the regimen.

4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.

5. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke.

6. To ascertain the effect of the regimen on children born after treatment failure.

The applicant's complete response was submitted to FDA August 18, 1999 regarding the requested phase 4 studies as follows:
"We are mindful of our Phase 4 commitments as outlined in the Population Council's letter to FDA dated September 16, 1996. We plan to discuss in more detail and develop a consensus with the FDA post-NDA approval.

1. The Council recognizes the need for additional information about our proposed distribution and credentialing system and the necessity for making certain that it is designed to result in safe and efficacious abortions for women and in properly controlled access to the product. We will provide the FDA with a detailed product distribution and provider credentialing plan that describes our own monitoring indicators, and we would welcome additional discussion with the Agency at that time. We intend to monitor the distribution and credentialing system but we do not believe that the frequency of post-surgical complications will necessarily be a meaningful indicator of its effectiveness.

2. Although the Council cannot commit to a study that follows all women who have surgical abortions following failed mifepristone abortion, we would propose to investigate treatment failures among a representative sample of providers for a mutually agreeable period of time, for instance six months or one year. In such an investigation, we would classify women undergoing medical abortion according to whether they 1) completed their abortions successfully; 2) had a failed medical abortion and required a surgical abortion; 3) required surgical intervention for other reasons; or 4) were lost to follow-up.

   We are not able to commit to tracking down those women who are lost to follow-up because this would be very difficult and extraordinarily expensive. We are also concerned about the ethics of doing this, as it could violate women's privacy.

3. A prospective study of the long-term effects of multiple use of the regimen in all American women would be unduly burdensome, might result in an invasion of women's privacy and would not likely produce a meaningful scientific result for decades. However, the Council has been informed that central registries of mifeprostone users exist in Europe. We will examine these data sources to determine what can be learned about multiple use. In addition, in future studies of the regimen carried out by the Council in the U.S., we will attempt to develop a cohort of women who report more than one use of the regimen and agree to be followed.

4. We are willing to supply treatment failure data from a sample of providers for a mutually agreeable period to time, for instance six months or one

year, bearing in mind that such data will not include women lost to follow-up.

5. The Council agrees that it is desirable to have additional information on users of the regimen who are under age 18, or over age 35 or who are smokers. From the French and United States clinical trials, we do have some data on women who were more than 35 years old and on women who smoked. The French trials also included some subjects who were under age 18 years of age. We will submit an analysis of our safety and efficacy data on these subgroups. In addition, data on women under 18 or over 35 years of age and those who smoke will be collected in the sample of women we have agreed to study, as described in item Number 2 and 4 above.

6. Since live births are extraordinarily rare as outcomes of treatment with mifepristone (e.g. approximately 19 out of more than 250,000 in the French database) this issue is best approached by reporting through providers who utilize the regimen. We will instruct our distributor to include materials for providers that ask them to report to the distributor any treatment failure in which the woman decides to continue her pregnancy. The provider will ascertain which of these women agree to be followed to document the health of any children born of such pregnancies. In addition, any spontaneous reports of live births of children exposed to mifepristone *in utero* will be investigated."

Other issues raised by individual advisory committee members are addressed below:

While the DOSAGE AND ADMINISTRATION section of the labeling states that mifepristone may be administered by or under the supervision of a physician trained in abortion, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies, and with access to emergency medical facilities, the applicant has not mentioned anything about conducting training seminars for use of mifepristone, without financial incentive to physicians, and distributing the drug only to those physicians who completed the training. Perhaps the applicant will address this point when the details of the distribution system are submitted to FDA.

The applicant should be able to assess compliance with return visits of patients in the phase 4 studies to be performed.

A surgical termination, if needed, should be provided at no additional cost to the patient. It should be part of the mifepristone-misoprostol method of abortion.

Reasonable attempts to contact patients who do not return to confirm the abortion should be made by the physician.

The applicant intends to monitor the distribution system to ensure that only qualified physicians are treating patients.

The applicant will monitor the number of failed medical terminations and any resulting surgical complication.

The applicant will examine central registries of mifepristone users in Europe to determine what can be learned about multiple use. In addition, the applicant proposes to attempt to develop a cohort of women in future studies in the United States who report more than one use of the regimen and agree to be followed.

The applicant has some data on women who were more than 35 years of age, on women who smoked, and on women under 18 years of age. They will submit an analysis of safety and efficacy data on these subgroups. In addition, data on these subgroups will be collected during the phase 4 studies.

The outcomes of pregnancies not terminated by medical or surgical abortion should be followed up and reported by the physician. This should be part of the credentialing and distribution system.

Conditions of exclusions in the clinical trials are in the labeling.

There is no age restriction in the labeling. Women under 18 years of age or over 35 years of age were arbitrarily excluded from the clinical trials, but there is no biologic reason to think that the efficacy and safety of drug administration to these age groups is any different from that of women 18-35 years of age.

The labeling states that misoprostol should be taken two days after ingesting mifepristone.

Women who smoked at least 10 cigarettes per day were excluded from the French studies. Women in the French studies were informed that they should neither smoke nor drink alcohol during the 48 hours following mifepristone administration and on the day misoprostol was to be administered.

Women in the U.S. studies were informed that they should not smoke during the 48 hours following mifepristone administration and on the day misoprostol was to be administered. Women were excluded from the U.S.

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studies if they were over 35 years of age, smoked more than 10 cigarettes per day, and had another risk factor for cardiovascular disease. The labeling contains a cautionary statement that women who are more than 35 years of age and who also smoke 10 or more cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone. The labeling does not contain a statement that alcohol and/or tobacco should be avoided during treatment. Myocardial infarction has been associated with the administration of an intramuscularly administered prostaglandin, sulprostone, but no such association has been reported with the administration of misoprostol. The labeling for misoprostol does not contain any statement regarding avoiding smoking.

Several comments regarding labeling were made by individual advisory committee members and have been throughly considered.

Overall, I do not think that the labeling imparts an impression to the physician or patient that the treatment regimen is "free of adverse effects and free of actually serious side effects."

The use of mifepristone and misoprostol extends the options available to women for the elective termination of early pregnancy, but it is inappropriate to directly compare this regimen with surgical termination in terms of adverse events. For example, bleeding and cramping are to be expected with mifepristone and misoprostol and not generally expected with surgical termination. The two methods are usually appropriate for abortion at different gestational ages. Medical abortions are done usually during the fifth to seventh weeks of gestation. Surgical terminations are usually not done before the sixth week of gestation.

Reference to drugs known to cause enzyme induction has been deleted.

The risk of malformation occurring if pregnancy is not terminated after drug administration appears in table 2 of the labeling.

The labeling states that a surgical termination must be recommended for patients who have an ongoing pregnancy because of the risk of fetal malformation resulting from the treatment procedure.

The physician labeling mentions that although specific drug interactions have not been studied, it is possible that interactions could occur with drugs like aspirin or other non-steroidal anti-inflammatory agents that modify or inhibit prostaglandin synthesis and metabolism. The only available study, however, found no evidence that non-steroidal antinflamatory drugs inhibit the ability of misoprostol to induce uterine

contractions and expulsions. In the patient labeling, the patient is instructed to advise her medical provider of all the medications she is taking and not to take any of them or any other medications during the treatment procedure without first telling her medical provider.

The mifepristone labeling states that since the effects of mifepristone on infants are unknown, and it is not known if misoprostol or its active metabolite is excreted in human milk, breast feeding women should consult with their medical provider to decide if they should discard their breastmilk for a few days following administration of the medications.

The labeling for misoprostol states that it is not known if the active metabolite (misoprostol acid) is excreted in human milk, and therefore, misoprostol should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause significant diarrhea in nursing infants.

Two days is the optimal time to administer misoprostol after the administration of mifepristone because mifepristone requires 36-48 hours to sensitize the uterine muscle to prostaglandins. This information could be added to the labeling.

We do not know if, or to what extent, effectiveness decreases if administration of misoprostol is delayed past two days after the administration of mifepristone. We do know that administration of misoprostol 36-48 hours after the administration of mifepristone is well founded, based on the mechanism of action. The labeling does state that misoprostol should be administered two days after administration of the mifepristone.

Most of the data available are from women 18 years of age or older. However, the drug regimen is expected to be as safe and effective for pregnant women under the age of 18 years as it is for those over the age of 18 years.

Consideration should be given to including a statement under PRECAUTIONS in the physician labeling that the regimen is less effective and the incidence of adverse events is higher in women seeking abortion with pregnancies of greater than 49 days.

Consideration should also be given to including a statement in the patient labeling under "Are there any reasons that I should not have the treatment procedure?" that the regimen is less effective and the incidence of adverse events is higher in women seeking abortion with pregnancies greater than 49 days. This could follow the statements in the patient labeling that state,

"You should not have the treatment procedure if your medical provider determines that the duration of your pregnancy is more than 49 days. For many women this means that the first day of your last period was more than 49 days ago."

The physician labeling contains a PATIENT INFORMATION section that includes the statement, "Before giving you any medication, your medical provider will ask you to sign a statement that you have decided to terminate your pregnancy, and that you have read and understood this information." An ACKNOWLEGEMENT is included in the PATIENT INFORMATION section for the patient and medical provider to sign. Consideration should be given to adding the statement, "My medical provider has confirmed that I am pregnant and that the pregnancy is not greater than 49 days" and a statement that, " My medical provider has discussed with me alternatives to medical abortion including surgical abortion and continuation of this pregnancy."

Everyone who was a member of the advisory committee when mifepristone was presented and who is still a special government employee was sent the results of the U.S. studies in the form of a copy of the article, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States" by members of the Population Council published in the April 30, 1998 issue of the New England Journal of Medicine. The article accurately and succinctly summarizes the results of the studies.

XIII. Recommendation:

Approval of this application is recommended provided that the labeling is satisfactorily revised and the complete details of the distribution system which are yet to be submitted are acceptable.

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ON ORIGINAL

SEP 13 2000

September 12, 2000

Mifepristone Tablets, 200mg
NDA 20-687

Population Council
Safety Update Report #3

Medical Officer's Review of Safety Update No. 3 Dated March 31, 2000

This NDA Safety Update Report summarizes the body of information which has been obtained by the Population Council since the cut-off date for the previous NDA Safety Update Report submitted August 3, 1999. The primary source of new information for this report is the Periodic Safety Update Report #9 prepared by the manufacturer of mifepristone, as well as from foreign clinical studies sponsored by the Population Council and from the literature. The cut-off date for this third report is February 29, 2000.

The report from presents information from investigational and marketing experience with the product received by that company from worldwide sources. As stated in that report, there have been no specific actions taken with respect to the product for safety reasons such as rejection, withdrawal or suspension of marketing authorization, restrictions to distribution, suspension of clinical trials, modifications of dosage formulation, or changes in target population or indications. It is stated that in connection with new product approvals by European Union member countries via the mutual recognition procedure, some new textual changes were made to product labeling to reflect common usage practice and for purposes of accuracy and explanation.

One new area of safety concern is apparent in the new information presented in this NDA Safety Update Report. Following queries concerning the use of mifepristone in patients with acute hereditary hepatic porphyrias, conducted an experiment at The chick embryo liver in ovo is a validated model system and currently used to identify "inducing" effects of drugs by measuring increases in hepatic delta amino levulinate synthetase, a rate controlling enzyme, resulting in overproduction of porphyrin and cytochrome P 450. Mifepristone crystalline powder was tested on that model and appeared to be highly toxic on the chick embryo liver. Therefore, concluded that the drug should be contraindicated in patients with inherited porphyrias. This contraindication has been added to the updated Master Data Sheet dated December 1999 by It should be considered for inclusion in the labeling for Mifeprex as a contraindication, but since the contraindication would be based upon the results of a single nonclinical safety study, I am of the opinion that it does not warrant being in the labeling unless further confirmatory data becomes available.

The known number of subjects exposed to mifepristone in clinical studies for various indications is 32,439. Over patients have received mifepristone in commercial distribution since its initial marketing in France in 1989. No clinical studies were conducted in the U.S. by the Population Council during the period covered by this NDA

Safety Update Report.

Protocol 171 (not conducted under an IND) has recently been completed in India for pregnancy termination in 900 women. There were no hospitalizations and no unexpected adverse events. Losses to follow-up were 3.5% and 4.4%.

Protocol [redacted] not conducted under an IND) is ongoing [redacted]

Records have been maintained by [redacted] of ongoing pregnancies following administration of mifepristone and a prostoglandin for medical termination of the pregnancies. There are now reports of 107 ongoing pregnancies. Nine cases of fetal abnormalities have been reported as having occurred in association with these pregnancies. Eight of these occurred with the use of mifepristone and gemeprost. One occurred with the use of mifepristone alone.

Mifepristone is now approved for marketing in 21 countries.

The information contained in this Safety Update Report is consistent with the cumulative experience gained to date on mifepristone and does not reveal any unexpected, unanticipated safety issues that would change the benefit to risk ratio.

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NDA 20-687
Population Council

Mifepristone 200 mg Oral Tablets
Review completed November 19, 1999

Medical Officer's Review of Safety Update Report No. 2 Dated August 3, 1999

This second NDA Safety Update Report includes accumulated information relative to the safety of mifepristone which has been obtained by the Population Council since Many 25, 1996, the cut-off date for the first Safety Update Report submitted on June 20, 1996. The cut-off for this second report is June 30, 1999.

Information in the report includes that obtained from recently completed and ongoing clinical trials with the product sponsored by the Population Council and by the manufacturers, Roussel Uclaf. Additionally, the report contains Periodic Safety Update Reports prepared by the French manufacturers to summarize the worldwide safety experience with the product, updated information on international regulatory approvals and new information obtained from the literature. The report also contains a Clinical Expert Report on mifepristone which was prepared by and which summarizes the accumulated clinical documentation on the efficacy and safety of the product.

Five periodic safety update reports are submitted covering the period December 1, 1995 - August 31, 1998. An estimated patients received mifepristone under marketing conditions during this period.

In addition to the periodic safety update reports, international reports of adverse reactions have been submitted in two other formats: 1) two quarterly safety line listings of safety reports from clinical trials and of the drug during the period of April 1, 1996 - September 30, 1996 when Roussel Uclaf was responsible for the drug and 2) five individual safety reports (and one follow-up report) received form Roussel Uclaf that were reported to IND.

The periodic safety update reports provide a comprehensive summary of the safety information received by Roussel Uclaf from worldwide sources during the covered time periods. Three of the five individual safety reports are also included in the periodic safety update reports. A total of 67 reports were received during a 32 month period when patients received mifepristone. This is one report per patients treated. A total of 28 of these adverse events were assessed as serious. This is one serious report per patients treated. Five of these adverse events were some sort of urticaria or allergic reaction. One instance of disseminated intravascular coagulation was reported from the United Kingdom. Five

of the reports were of fetal abnormalities. The other reports were diverse. No unexpected safety issues are raised by this safety update report. Overall safety results are similar to those seen in the pivotal French studies and in the U.S. studies.

In the period since 1987, Roussel Uclaf have received information on continuing pregnancies after administration of mifepristone or mifepristone and prostaglandins for medical termination of the pregnancies. A report, updated through June 1999, includes 87 reports of ongoing pregnancies, of which 26 followed the use of mifepristone alone and the remainder followed the use of mifepristone and a prostaglandin (or unknown). Nine reports of fetal anomalies have been received. Mifepristone alone was used in one report and mifepristone and gemeprost was used in eight reports. The one report of a fetal anomaly in a patient who received mifepristone alone resulted in a therapeutic termination of pregnancy with cleft palate and sirenomelia which was believed not to be drug related because of embryogenesis considerations. Of the nine reports of fetal anomalies, three occurred in babies at term. One had bilateral talipes (club foot), one had fingernail defect 3, and the third had a heart malformation. Fifteen of the 87 ongoing pregnancies were lost to followup.

A total of 33 normal babies have been born to women who received mifepristone alone (10), mifepristone plus misoprostol (11), or mifepristone plus some other prostaglandin (12). Data are too limited to determine whether mifepristone is a human teratogen.

Ninety articles published between 1996 and 1999 are submitted. These studies report the use of mifepristone in different clinical conditions, variable dosages, and for variable time durations. There is nothing reported in any of these articles that would change the safety profile of mifepristone for early abortion.

In the reports of early pregnancy termination, adverse events and efficacy reported are similar to that reported in the pivotal French studies and in the U.S. studies.

Unrelated to pregnancy termination, but of interest, are two reports where mild elevations in hepatic transaminases were noted in some subjects. Kettel reported 7 subjects with endometriosis treated with mifeprisone, 5 mg daily for six months. Subjects with liver function abnormalities were excluded from treatment. One of the 7 subjects experienced a mild increase in liver transaminases. Perrault reported 28 subjects with untreated metastatic breast carcinoma treated with mifepristone, 200 mg daily. Mild elevations of AST were reported in 6 of the 28 subjects. (Six subjects had metastatic liver disease. It is not known how many, if any, of these subjects with metastatic liver disease were among the six reports of elevated AST.) These mild elevations in hepatic transaminases are of interest because some such changes were noted very early in abortion dose finding studies. However, 248 subjects in the U.S. studies had a full panel of laboratory tests at baseline and at visit 3 including alkaline phosphatase, AST, ALT, and LDH. The median changes noted were small and not of clinical significance.

The Clinical Expert Report on Mifepristone in Termination of Pregnancy is a review of the clinical documentation forming the basis for approval, key results from the published trials, and post-marketing surveillance data. It contains no new information.

We are informed that mifepristone was approved in eight countries (including Germany) July 6, 1999 under the mutual recognition procedure of the European Union.

No new areas of safety concern are apparent. Information contained in this safety update report is consistent with the cumulative experience gained to date from the pivotal French studies and the U.S. studies. The risk-benefit assessment remains unchanged.

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NDA 20-687
Mifepristone

The Population Council
August 28, 1996

Medical Officer's Summary of Safety Update Dated
June 20, 1996

Included in the Safety Update Report received June 27, 1996 are two new clinical study reports as well as new information regarding study reports previously submitted.

The first new clinical study report is entitled, "The Efficacy and Safety of Mifepristone 600 mg in a Single Dose in Combination with Intravenously Administered Sulprostone (Nalador) in Therapeutic Termination of Second Trimester Pregnancy". The second new clinical report is entitled "Role of Cortisol in the Thermal Response to Alimentation: Effect of Mifepristone" and consisted of twelve healthy, male volunteers, six of whom received a single 600 mg tablet and six of whom received a placebo.

Neither of the two new clinical study reports reveal any additional safety concerns not identified in the two pivotal clinical studies.

Newly completed clinical trials include three studies of labor induction, two studies of breast cancer, and the United States clinical trials of early pregnancy termination. Laboratory data from these completed studies have not yet been analyzed and, therefore, no information on laboratory data are reported in this safety update. Final data analysis and study reports for these six studies have not been completed. The results for termination of pregnancy studies conducted in the United States are expected to be in full agreement with the two pivotal clinical studies. No unanticipated safety issues were raised in these studies. Preliminary examination of information from the United States studies as it was forwarded weekly from the clinics directly to the sponsor during the course of the trials indicates that the final, analyzed results will be similar to those obtained in similar clinical trials of the same medical regimen.

The literature update includes eleven articles published in 1995 and one article published in 1996. Three articles are of particular interest. One is the publication of one of the pivotal clinical studies (FF/92/486/24) by Aubeny et.al. The second is entitled "A Comparative Analysis of Fall in Hemoglobin Following Abortions Conducted By Mifepristone (600 mg) and Vacuum Aspiration" by Thonneau et. Al. The investigators found significant blood loss in the two weeks following abortions by the mifepristone/sulprostone protocol while hemoglobin concentrations remained stable in women who had vacuum aspiration. Women who took mifepristone experienced a mean fall of 0.7 g/dl in hemoglobin two weeks after the abortion. The third article entitled "Clinical, Hormonal, and Sonographic Predictors of Successful RU-486-Induced Abortions" was by Menashe et.al. A small hematoma, seen as a localized detachment of the gestational sac, was observed in the decidua capsularis in women who aborted successfully. A significant decrease in plasma levels of estradiol and progesterone and significantly increased cortisol levels in the plasma of the patients who aborted were observed by the seventh day following treatment.

Table four of the Safety Update Report contains adverse reactions from all sources reported to Roussel Uclaf which were summarized in the quarterly line listings covering July 1, 1995 to September 30, 1995; October 1, 1995 to December 31, 1995; January 1, 1996 to March 31, 1996 and reported in the Periodic Safety Update No. 3 dated January 1996 for the period June 1, 1995 to November 30, 1995.

Of a total of forty eight patient reports of adverse experiences listed in Table 4, twenty-eight were reported from patients enrolled in the United States studies (protocols 166A and B). Of these twenty-eight reports, nineteen were metrorrhagia, three were abdominal pain, two were dehydration, and there were one each of depression, viral meningitis, vomiting, and syncope. Vacuum aspiration or D&C was performed in twelve cases of metrorrhagia and a blood transfusion was given in one case of metrorrhagia. Concomitant hypotension was also reported in four patients with severe metrorrhagia. The patient with syncope presented with a marked vasovagal reaction fifteen minutes after misoprostol administration.

In the section of the Safety Update Report entitled "Tolerance of RU 486 During United States Studies" there is Table 1 which was submitted to the sponsor by Russell Uclaf June 7,1995 which indicates that there were forty-seven serious adverse events plus 8 non serious adverse events in the United States studies (protocols 166 A and B). Table 2 indicates that of the forty-seven serious adverse events forty-one were related to bleeding, two to hypotension, and one each to vomiting, chest pain, infection, and accidental injury.

[redacted]

Also included is a half page document entitled "Notifications Report to Roussel Uclaf from Study English PMS" which lists seven reactions occurring in five patients. There were three reports of uterine hemorrhage, one incomplete abortion with bleeding, one convulsion, one congenital nail disorder, and one report of lack of efficacy.

Also included is a section entitled "New Foreign Marketing Information" which consists only of a core product information document from the product manufacturer revised in March 1995.

Since the start of the use of mifepristone until November 30, 1995, Roussel Uclaf has recorded fifty-three cases of continued pregnancy after the intake of mifepristone for early pregnancy termination (alone or associated with a postaglandin analog).

Among these fifty-three cases:

Nineteen pregnancies were delivered at term (or close to it):
Fifteen were uneventful pregnancies with children normal at birth.
One was normal but born prematurely (33-34 weeks) from caesarean section
One was normal except for common slight bilateral talipes.
One case involves unilateral fingernail defects.
One child was reported as strictly normal at birth but it was known that when she was three months old, the infant was diagnosed as having an autoimmune disorder with chronic giant cell hepatitis and immunohemolytic anemia and later died of severe infectious pneumonia likely exacerbated by immuno-suppressive drugs. The reporting physician's opinion (an expert in teratogenicity) was that the onset of the autoimmune disorder was coincidental and that the role of mifepristone could be reasonably excluded.

In fifteen cases information on further condition of the fetus was made available, mainly in the cases where pregnancy is known to have been terminated later:

In nine cases, termination was performed voluntarily and information either from histologic examination or from ultrasound was that the fetus was normal.

In one case, at therapeutic termination the fetus was noted to have sirenomelia associated with other fetal malformations. The opinion of the consulting embryologists to whom the case was submitted by Roussel Uclaf was that the role of mifepristone was very unlikely. This case has been published (Pons J.C. and all : Lancet, 1991, 328: 763).

In five cases of ongoing pregnancy, the latest available information during second trimester examination indicated normal pregnancy and fetus development.

In six cases, no information on the fetus could be obtained but pregnancy was known to have been terminated later.

In thirteen cases, no further information was made available; in most cases patients were lost to follow-up, and in some cases pregnancy is still ongoing.

Comment: This Safety Update does not reveal any unexpected, unanticipated safety issues that were not made known in the original submission of the NDA.

/S/

Concur: /S/ 9/11/96

APPEARS THIS WAY
ON ORIGINAL

NDA 20-687
Mifepristone

The Population Council
August 29, 1996

Medical Officer's Review of Safety Update Including a Summary Of International Post-Marketing Surveillance Data Dated July 25, 1996.

Submission dated July 25, 1996 contains summaries of all the safety information available to the sponsor from Roussel Uclaf International (France, Sweden, United Kingdom) post-marketing surveillance reports, starting from 1989, the first year mifepristone was on the market in France.

Spontaneous notification of suspected adverse events reported in post-marketing surveillance of mifepristone from June 1989 to June 1995 are listed in Table 7 of the submission. Causality by mifepristone is judged to be "unlikely", "unrelated", "not assessable", "insufficient data", "misuse", or "rumor" in the vast majority of cases. Adverse events that were possibly or probably related to drug use were usually expected events such as metrorrhagia. The most commonly used prostaglandin analogue during this period was sulprostone, given by injection.

The Mifepristone Safety Report covering the period January 1, 1991 through December 31, 1992 covers the first eighteen months since the launching of mifepristone in the United Kingdom. It also includes the period of discontinuation of sulprostone and the introduction in France of misoprostol as a possible alternative prostaglandin analogue. The report also contains the entire safety information available since [redacted] early pregnancy termination. In July, 1992, two new indications of mifepristone were approved in France, "therapeutic termination of second trimester pregnancy" and "labor induction in utero fetal death". [redacted]

The International Safety Report Periodic Update from January 1, 1993 to May 31, 1995 contains no unexpected or unanticipated reports of adverse reactions that were not already known. There were no post-marketing phase IV or surveillance studies reported in final form during this period. There is mention of about three thousand four hundred and thirty-five patients enrolled in the post-marketing surveillance program conducted by Roussel Uclaf in the United Kingdom during the period of this report, but no additional information is available.

Periodic Safety Update Report No. 3 from June 1, 1995 to November 30, 1995 has been reviewed previously by the Food And Drug Administration Medical Officer and his comments are in his Safety Update Review dated August 28, 1996. No unexpected or unanticipated adverse reactions were found in this periodic report.

Comment: From the cumulative experience to date, no new special areas of concern have been identified. The assessment of the risk-benefit ratio of mifepristone is unaltered by the data included in this Safety Update Report.

/S/

Concur: /S/ 9/9/96

APPEARS THIS WAY
ON ORIGINAL

NDA 20-687
Mifepristone

The Population Council
August 29,1996

Medical Officer's Review of United States Safety Data Dated July 14, 1996

Submission dated July 14, 1996 is a summary report of the serious adverse events from Protocols 166 A and B during the United States clinical trials. All of these reports have been submitted previously in IND

A total of fifty-two subjects had at least one SAE. There was more than one adverse event reported for most subjects. The most frequently reported SAE was hemorrhage (41 reports). This was followed by fainting/dizziness (20 reports) which includes all of the following events: fainting, feeling faint or lightheaded, dizziness, syncope, vasovagal reaction and passing out. Other serious adverse events that were reported by at least four subjects are listed in the summary below.

Total No. of Patients	Total No. of Clinics	Total No. of Adverse Events	Total Number of Treatments				Total No. Hospitalized
			D&C/ Asp.	Meth./ oxy.	IV Fluids	Transfusion	
52	13	Hemorrhage 41 Faint/Dizziness 20 Cramping 14 Vomiting 06 Hypotension 05 Tachycardia 04	34	15	28	04	26

These serious adverse events resulted in the hospitalization of twenty-six subjects. Four subjects received transfusions. A total of twenty-eight subjects received IV fluids (including 3 of the subjects that also had transfusions). A total of thirty-four subjects received a D&C or aspiration. All but two of the subjects who had a D&C or aspiration reported hemorrhage. Fifteen subjects recieved methergine or oxytocin for treatment of bleeding, although eleven of these subjects eventually had a surgical procedure.

It is not possible to make a complete comparison of the serious adverse events reported in the United States trial and the pivotal French studies in the NDA, due to different definitions of SAEs and different adverse event reporting requirements in the two countries. Also, the safety analysis of the United States trials has not been conducted, since the good clinical practice audit of the clinics is currently being completed. Therefore, t this time comparisons between the United States and NDA pivotal studies can only be made with the serious adverse events

reported from these fifty-two United States subjects, rather than other less serious adverse events that will be uncovered during the safety analysis of the entire United States database. However, some general comparisons can be made. The total number of subjects enrolled in United States Protocol 166A/B was 2,121. This is slightly less than the number of subjects (2480) enrolled in the pivotal French trials in the NDA. The number of transfusions is identical (4) in both studies and the number of hospitalizations is similar (26 in the United States trials and 21 in the pivotal trials). The number of reported cases of hemorrhage, metrorrhagia or excessive bleeding was similar in the two studies. Hemorrhage was reported by forty-one subjects in the United States studies. In the NDA pivotal studies, fifty-two subjects reported metrorrhagia or excessive bleeding, which was categorized as severe in twenty-one subjects. However, the manner in which the bleeding was treated differed in the two studies. In the Unites States trials, thirty-two of the thirty-four surgical interventions (D&C or aspiration) were performed on subjects experiencing hemorrhage. In the NDA pivotal trials, a total of fifteen subjects received surgical interventions for bleeding. The greater number of surgical interventions by United States investigators is not unexpected, due to their initial lack of experience in the control of bleeding during medical abortion. This was the first clinical trial of medical abortion in the United States, but medical abortion had been available in France for several years prior to the conduct of the French studies of mifepristone and misoprostol. The United States investigators have noted that as they gained experience with the bleeding that occurs during medical abortion, they were less likely to surgically intervene.

There were five cases of hypotension, in the United States trials, although blood pressure readings were given for only two of these subjects. There were seven cases of clinically relevant hypotension, one rated as severe, in the NDA pivotal trials. There were also a similar number of reports of tachycardia for United States subjects and in the pivotal trials (4 and 5 reports, respectively).

The incidence of other adverse events reported in the United States subjects, such as cramping or vomiting, cannot at this time be fairly compared to the numbers of these adverse events reported from all subjects in the NDA pivotal studies. This comparison must await the safety analysis of the United states database.

Conclusion:

The SAEs reported during the United States trial do not appear to differ significantly from those reported in the pivotal NDA trails, although a full comparison is not possible at this time. The higher incidence of surgical intervention in the United States trials may be explained by the initial inexperience of United States clinicians in providing medical abortion. Investigators in the United States trials have indicated that there was a learning curve associated with the treatment of bleeding during the trial. The incidence of other events such as hemorrhage, transfusions, and hospitalizations were similar in the two studies.

In summary, the current comparison of SAEs between the United States trial and the NDA pivotal trials indicated that medical abortion can be safely delivered in a wide variety of United States settings.

/S/

Concur: /S/ 9/9/96

APPEARS THIS WAY
ON ORIGINAL

EXHIBIT B-7

APPENDIX TO PETITIONER GENBIOPRO, INC.'S CITIZEN PETITION DATED JULY 3, 2025[1]

Source	Appendix Starting Page
Appendix Volume I	
108 Cong. Rec. 17366 (Aug. 23, 1962)	GBP-PET00001
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[1] This Appendix includes all documents cited in the accompanying July 3, 2025 Citizen Petition with the exception of certain documents not required by 21 C.F.R. § 10.20(c). Volumes I, II, III, IV, V, and IX contain copyright restricted materials.

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SEP 28 2000

NDA 20-687

Population Council
Attention: Sandra P. Arnold
Vice President, Corporate Affairs
1230 York Avenue
New York, NY 10021

Dear Ms. Arnold:

Please refer to your new drug application (NDA) dated March 14, 1996, received March 18, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MIFEPREX™ (mifepristone) Tablets, 200 mg.

We acknowledge receipt of your submissions dated April 19, June 20, July 25, August 15 and September 16 and 26, 1996; January 30, March 31, July 28, August 5, September 24, November 26, 1997; January 30 (2), February 19, April 27, June 25, October 26, December 8, 1998; February 8 and 22, March 31, April 28, May 10 and 20, June 3 (2), 15, 23, 25, and 30, July 14 (2) and 22, August 3, 13, 18 and 30, September 3, 8, 13 and 30, October 5, 26 and 28, November 16 and 29 (2), December 6, 7 and 23, 1999; and January 11, 21 and 28 (2), February 16 and 24, March 3, 6, 9, 10, 30 and 31 (2), April 20, May 3, 11 and 17, June 22 and 23, July 11, 13, 25 and 27, August 18, 21 and 24, September 8, 12, 15 (2), 19 (2), 20, 21, 22, 26 (2), and 27 (2), 2000. Your submission of March 30, 2000 constituted a complete response to our February 18, 2000 action letter.

This new drug application provides for the use of Mifeprex™ for the medical termination of intrauterine pregnancy through 49 days' pregnancy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to approve Mifeprex™ (mifepristone) Tablets, 200 mg, for use as recommended in the agreed upon labeling text. The application is approved under 21 CFR 314 Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced regulations.

The final printed labeling (FPL) [including the professional labeling (Package Insert), the Medication Guide required for this product under 21 CFR Part 208, the Patient Agreement Form, and the Prescriber's Agreement Form] must be identical to the submitted draft labeling (Package Insert, Medication Guide, Patient Agreement Form, and the Prescriber's Agreement Form submitted September 27, 2000; and the immediate container and carton labels submitted July 25, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative

purposes, this submission should be designated "FPL for approved NDA 20-687." Approval of this submission by FDA is not required before the labeling is used.

Under 21 CFR 314.520, distribution of the drug is restricted as follows:

Mifeprex™ must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex™.
- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well.
- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate.
- Must record the Mifeprex™ package serial number in each patient's record.

With respect to the aspects of distribution other than physician qualifications described above, the following applies:

- Distribution will be in accordance with the system described in the March 30, 2000 submission. This plan assures the physical security of the drug product and provides specific requirements imposed by and on the distributor including procedures for storage, dosage tracking, damaged product returns, and other matters.

We also note the following Phase 4 commitments, specified in your submission dated September 15, 2000. These commitments replace all previous commitments cited in the September 18, 1996 and the February 18, 2000 approvable letters. These Phase 4 commitments are:

1. A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention. Previous study questions related to age, smoking, and follow-up on day 14 (compliance with return visit) will be incorporated into this cohort study, as well as an audit of signed Patient Agreement forms.

2. A surveillance study on outcomes of ongoing pregnancies.

You have agreed to provide the final Phase 4 protocols for these studies within six months.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call [redacted]

Sincerely,

/S/

Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

U.S. FOOD & DRUG ADMINISTRATION

ANDA 091178/S-004

PRIOR APPROVAL SUPPLEMENT APPROVAL

GenBioPro, Inc.
(b) (6), (b) (4)

Attention: (b) (6), (b) (4)

Dear Sir or Madam:

This is in reference to your supplemental abbreviated new drug application (sANDA) received for review on June 22, 2022, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Mifepristone Tablets, 200 mg.

Reference is also made to any amendments submitted prior to the issuance of this letter.

The sANDA, submitted as "Prior Approval Supplement," provides for modification to the approved single, shared system (SSS) risk evaluation and mitigation strategy (REMS) for mifepristone 200 mg tablets in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation, as well as corresponding labeling revisions to the prescribing information and the Medication Guide to align with the modification to the Mifepristone REMS Program. This SSS REMS is known as the Mifepristone REMS Program.

APPROVAL & LABELING

We have completed the review of this sANDA, as amended, and it is **approved**.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

In order to ensure the benefits of Mifepristone Tablets, 200 mg. outweigh its risks and to minimize burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the REMS modifications outlined in our REMS Modification Notification letter dated December 16, 2021. In addition the following modifications were communicated during the course of the review:

- Revisions to the REMS goal to align with the updated REMS requirements.

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10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov

- Replacing serial number with recording of NDC and lot number of mifepristone dispensed.

- Additional edits for clarification and consistency in the REMS Document and REMS materials (*Prescriber Agreement Forms, Patient Agreement Form,* and *Pharmacy Agreement Forms*).

Your proposed modified REMS, received on June 22, 2022, and amended is approved and will be posted on the FDA REMS website: http://www.fda.gov/rems.

The modified REMS consists of elements to assure safe use and an implementation system.

The modification of the approved REMS must be fully implemented within 120 calendar days of this letter.

Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

We remind you that you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FD&C Act.

We remind you that section 505-1(f)(8) of the FD&C Act prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j) of the FD&C Act. A violation of this provision in 505-1(f) of the FD&C Act could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

ANDA 091178 REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 091178/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

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NEW SUPPLEMENT FOR ANDA 091178/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 091178/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR ANDA 091178

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

In addition to submitting the proposed REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS submission.

For more information on submitting REMS in SPL format, please email REMSWebsite@fda.hhs.gov.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

If your product is a combination product as defined by 21 CFR 3.2(e) and is comprised of drug and device constituent parts, we remind you that you must comply with the postmarking safety reporting requirements for an approved combination product (21 CFR Part 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts.

All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

If you have any questions, call (b) (6)

Sincerely,

{See appended electronic signature page}

(b) (6)

Center for Drug Evaluation and Research

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (6)

01/03/2023 05:42:43 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020687/S-014

SUPPLEMENT APPROVAL

Danco Laboratories, LLC
(b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (6):

Please refer to your Supplemental New Drug Application (sNDA) dated September 16, 2008, received September 17, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for MIFEPREX® (mifepristone) Tablets. We note that NDA 020687 is approved under the provisions of 21 CFR 314.520 (Subpart H).

This supplemental application provides for a proposed risk evaluation and mitigation strategy (REMS) for MIFEPREX (mifepristone) and was submitted in accordance with section 909(b)(1) of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Under section 909(b)(1) of FDAAA, we identified MIFEPREX (mifepristone) as a product deemed to have in effect an approved REMS because there were in effect on the effective date of FDAAA, March 25, 2008, elements to assure safe use required under 21 CFR 314.520.

We acknowledge receipt of your amendments dated December 9, 2008, November 8, 2010, and May 19 and 27, 2011.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for MIFEPREX (mifepristone) to ensure the benefits of the drug outweigh the risks of serious complications by requiring prescribers to certify that they are qualified to prescribe MIFEPREX (mifepristone) and are able to assure patient access to appropriate medical facilities to manage any complications.

Your proposed REMS, as amended and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

The REMS assessment plan will include the information submitted to FDA on May 27, 2011, and should include the following information:

a. Per section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.
b. Per section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify future submissions containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 020687
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 020687
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

As part of the approval under Subpart H, as required by 21 CFR 314.550, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days

before the intended time of initial distribution of the labeling or initial publication of the advertisement. Send one copy to the (b) (6) and two copies of the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, (b) (6)

Sincerely,

{See appended electronic signature page}

(b) (6)

ENCLOSURES:
REMS Document
REMS Materials

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

06/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020687/S-020

SUPPLEMENT APPROVAL

Danco Laboratories, LLC
(b) (4), (b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6):

Please refer to your Supplemental New Drug Application (sNDA) dated May 28, 2015, received May 29, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated July 17, 2015.

This "Prior Approval" supplemental new drug application proposes to provide for use through 70 days gestation, revise the labeled dose and dosing regimen and modify the REMS.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for pre-menarcheal patients because the use of this product before menarche is not indicated, and we have determined that you have fulfilled the pediatric study requirement for post-menarcheal patients.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Mifeprex (mifepristone) Tablets was originally approved on June 8, 2011. The REMS consisted of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS included revisions to both the prescriber and patient agreement forms.

Other changes proposed in the efficacy supplement prompted additional revisions to the Mifeprex REMS materials. During review of this efficacy supplement, we also assessed the current REMS program to determine whether each Mifeprex REMS element remains necessary to ensure that the drug's benefits outweigh the risks.

After consultations between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE), we have determined that the approved REMS for Mifeprex should be modified to continue to ensure that the benefits of Mifeprex outweigh its risks and to minimize the burden on the healthcare delivery system of complying with the REMS. The REMS modifications submitted by you on March 29, 2016 are approved.

We have determined that it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Mifeprex outweigh its risks. The

Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Your proposed modified REMS, submitted on July 17, 2015, and appended to this letter, is approved as amended. The modified REMS consists of elements to assure safe use (A, C and D), an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on June 8, 2011.

The REMS assessment plan will include the information submitted to FDA on March 29, 2016.

The revised REMS assessment plan must include, but is not limited to, the following:

REMS Assessment Plan

1. Number of prescribers enrolled (cumulative)
2. Number of new prescribers enrolled during reporting period
3. Number of prescribers ordering Mifeprex during reporting period
4. Number of healthcare providers who attempted to order Mifeprex who were not enrolled; describe actions taken (during reporting period and cumulative).
5. Number of women exposed to Mifeprex (during reporting period and cumulative)
6. Summary and analysis of any program deviations and corrective action taken
7. Based on the information reported, an assessment and analysis of whether the REMS is meeting its goals and whether modifications to the REMS are needed

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support any proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit any future supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 020687 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 020687/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 020687/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 020687

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate: (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call (b) (6) .

Sincerely,

{See appended electronic signature page}

(b) (6)

Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

03/29/2016

U.S. FOOD & DRUG ADMINISTRATION

NDA 020687/S-025

SUPPLEMENT APPROVAL

Danco Laboratories, LLC
(b) (4), (b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6):

Please refer to your supplemental new drug application (sNDA) dated and received June 22, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets, 200 mg.

This Prior Approval sNDA provides for modification to the approved single, shared system (SSS) risk evaluation and mitigation strategy (REMS) for mifepristone 200 mg tablets, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation, as well as corresponding labeling revisions to the prescribing information and the Medication Guide to align with the modification to the Mifepristone REMS Program. This SSS REMS is known as the Mifepristone REMS Program.

APPROVAL & LABELING

We have completed our review of the supplemental application, as amended. It is approved effective the date of this letter.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The Mifepristone REMS Program, of which Mifeprex is a member, was originally approved on April 11, 2019, and the most recent REMS modification was approved on May 14, 2021. The Mifepristone REMS Program consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In order to ensure the benefits of Mifeprex outweigh its risks and to minimize burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the REMS modifications outlined in our REMS Modification

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Notification letter dated December 16, 2021. In addition the following modifications were communicated during the course of the review:

- Revisions to the REMS goal to align with the updated REMS requirements.
- Replacing serial number with recording of NDC and lot number of mifepristone dispensed.
- Additional edits for clarification and consistency in the REMS Document and REMS materials (*Prescriber Agreement Forms, Patient Agreement Form,* and *Pharmacy Agreement Forms*).

Your proposed modified REMS, received on June 22, 2022, amended and appended to this letter, is approved. The modified REMS consists of the elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

The modification of the approved REMS must be fully implemented within 120 calendar days of this letter.

This shared system REMS, known as the Mifepristone REMS Program, currently includes those products listed on the FDA REMS website[3].

Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS must be revised to one year from the date of the approval of the modified SSS REMS (1/3/2023) and annually thereafter.

The revised REMS assessment plan must include, but is not limited to, the following:

Program Implementation and Operations

1. REMS Certification Statistics
   a. Prescribers
      i. Number of certified prescribers who have certified with the Sponsor's distributor(s) and number who have submitted *Prescriber Agreement Forms* to Certified Pharmacies
      ii. Number and percentage of newly certified prescribers
      iii. Number and percentage of active certified prescribers (i.e., who ordered mifepristone or submitted a prescription during the reporting period)

   b. Pharmacies

[3] https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

i. Number of certified pharmacies
ii. Number and percentage of newly certified pharmacies
iii. Number and percentage of active certified pharmacies (i.e., that dispensed mifepristone during the reporting period)

c. Wholesalers/Distributors
i. Number of authorized wholesalers/distributors
ii. Number and percentage of newly authorized wholesalers/distributors
iii. Number and percentage of active authorized wholesalers/distributors (i.e. that shipped mifepristone during the reporting period)

2. Utilization Data
a. Total number of tablets shipped by wholesalers/distributors, stratified by Certified Prescriber or Certified Pharmacy location
b. Number of prescriptions dispensed from pharmacies

3. REMS Compliance Data
a. Audits: Summary of audit activities for each stakeholder (i.e., certified pharmacies and wholesalers/distributors) including but not limited to:
i. A copy of the final audit plan for each stakeholder type (provide for the current reporting period)
ii. The number of audits expected, and the number of audits performed
iii. The number and type of deficiencies noted
iv. For those with deficiencies noted, report the corrective and preventive actions (CAPAs) required, if any, to address the deficiencies, including the status (e.g., completed, not completed, in progress) (provide for the current reporting period)
v. For any stakeholders that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken (provide for the current reporting period)
vi. A summary report of all resulting changes to processes and procedures necessary to ensure compliance with the REMS requirements (provide for the current reporting period)

b. A summary report of non-compliance, associated corrective action plans (CAPAs), and the status of CAPAs including but not limited to:
i. A copy of the final non-compliance plans for Pharmacies and Distributors (provide for the current reporting period)
ii. For each instance of noncompliance below (iii-v), report the following information (provide for the current reporting period):
1. A unique, anonymized ID for the stakeholder(s) associated with the non-compliance event to enable tracking over time
2. The source of the non-compliance data (e.g., self-reported, audit, other)
3. A root cause analysis of the non-compliance

4. Actions to prevent future occurrences and outcomes of such actions

iii. Prescriber compliance

1. Number and percentage of certified prescribers who became decertified as a result of non- compliance
   - Provide a summary of reasons for decertification (provide for the current reporting period)
2. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

iv. Pharmacy compliance

1. Number and percentage of prescriptions dispensed that were written by prescriber(s) who did not submit a Prescriber Agreement to the dispensing Certified Pharmacy
2. Number and percentage of mifepristone tablets dispensed by non-certified pharmacies
3. Number and percentage of pharmacies that became decertified as a result of non- compliance
   - Provide a summary of reasons for decertification (provide for the current reporting period)
4. An assessment of prescription delivery timelines, including percentage delivered more than four days after receipt of the prescription, duration and causes for delay. A proposal for this assessment will be submitted within 60 days of the approval of the REMS Modification.
5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

v. Wholesaler/distributor compliance

1. Number of healthcare providers who successfully ordered mifepristone who were not certified
2. Number of non-certified pharmacies that successfully ordered mifepristone
3. Number of shipments sent to non-certified prescriber receiving locations
4. Number of shipments sent to non-certified pharmacy receiving locations
5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

Overall Assessment of REMS Effectiveness

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a

proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively,

updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **NDA 020687 REMS ASSESSMENT METHODOLOGY**
> **(**insert concise description of content in bold capital letters, e.g.,
> **ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

> **NDA 020687 REMS ASSESSMENT**
>
> ***or***
>
> **NEW SUPPLEMENT FOR NDA 020687/S-000**
> **CHANGES BEING EFFECTED IN 30 DAYS**
> **PROPOSED MINOR REMS MODIFICATION**
>
> ***or***
>
> **NEW SUPPLEMENT FOR NDA 020687/S-000**
> **PRIOR APPROVAL SUPPLEMENT**
> **PROPOSED MAJOR REMS MODIFICATION**
>
> ***or***
>
> **NEW SUPPLEMENT FOR NDA 020687/S-000/**
> **PRIOR APPROVAL SUPPLEMENT**

PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 020687/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 020687

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov
.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call (b) (6)

Sincerely,

{See appended electronic signature page}

(b) (6)

Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - REMS Document
  - Prescriber Agreement
  - Patient Agreement Form
  - Pharmacy Agreement Form

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (6)

01/03/2023 05:35:41 PM

GUIDANCE FOR INDUSTRY

FOR THE SUBMISSION OF AN ENVIRONMENTAL ASSESSMENT IN HUMAN DRUG APPLICATIONS AND SUPPLEMENTS

WITHDRAWN

Center for Drug Evaluation and Research (CDER)

November 1995

CMC 6

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GUIDANCE FOR INDUSTRY [1]

FOR THE SUBMISSION OF AN ENVIRONMENTAL ASSESSMENT IN HUMAN DRUG APPLICATIONS AND SUPPLEMENTS

I. INTRODUCTION

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impacts of their actions and to ensure that the interested and affected public is informed of environmental analyses. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving drug product applications as an integral part of its regulatory process. FDA's regulations in 21 CFR Part 25 specify that environmental assessments (EA's) or abbreviated environmental assessments (AEA's) must be submitted as part of certain new drug applications (NDA's), antibiotic applications, abbreviated new drug applications (ANDA's), abbreviated antibiotic applications (AADA's), investigational new drug applications (IND's) and for various other actions (see 21 CFR § 25.22(a)).

This guidance provides information on how to prepare EA's for submission to the Center for Drug Evaluation and Research (CDER) for these drug product applications. Topics covered include: 1) when categorical exclusions apply; 2) when to submit an EA or AEA; 3) the content and format of EA's or AEA's; 4) approaches to determining the environmental fate and effects of substances; 5) test methods; 6) treatment of confidential information submitted in support of an EA; 7) special considerations associated with EA's for genetically altered organisms and materials and products

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[1] This guidance has been prepared under the auspices of the Office of Pharmaceutical Science of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. The guidance is an informal communication under 21 CFR § 10.90(b)(9) that reflects the best judgment of CDER employees at this time. It does not create or confer any rights, privileges or benefits for or on any person, nor does it operate to bind or obligate FDA in any way. For further information about this guidance, contact Nancy B. Sager, Center for Drug Evaluation and Research, HFD-357, 5600 Fishers Lane, Rockville, MD 20857 (Phone: 301-594-6740; FAX: 301-594-6197, Internet: SAGERN@CDER.FDA.
GOV). For additional copies of this guidance contact the Consumer Affairs Branch, HFD-210, Center for Drug Evaluation and Research, 7500 Standish Place, Rockville, MD, 20855, 301-594-1012. An electronic version of this guidance is also available via Internet by connecting to the CDER file transfer protocol (FTP) server (CDVS2.CDER.FDA.GOV).

derived from natural sources; 8) EA documentation for foreign manufacturing facilities; and 9) Drug Master Files (DMF's).

Information in this guidance, in addition to the Code of Federal Regulations (CFR) and the FDA EA Technical Handbook (NTIS Publication Number PB 87 175345/AS) which provides information on acceptable test methods, represents the core information available from CDER to assist industry in preparing an EA.

Under the President's reinventing government (REGO) initiatives announced in April, 1995, CDER is reevaluating its environmental regulations and plans to revise the regulations to reduce the number of EA's required to be submitted by industry and, consequently, the number of finding of no significant impacts (FONSI's) prepared by the agency under NEPA. FDA will issue for public comment a notice of proposed rulemaking that will propose additional categorical exclusions for those actions CDER has determined normally do not individually or cumulatively have a significant effect on the quality of the human environment. This guidance, explaining how to prepare an EA when required by current regulations, will remain in effect until superseded by revised final regulations or new CDER guidance.

II. WHEN IS AN ACTION CATEGORICALLY EXCLUDED?

Certain actions are subject to categorical exclusion and, therefore, ordinarily do not require the preparation of an EA because, as a class, these actions will not normally have significant effects on the environment (21 CFR § 25.24).

Submissions to CDER that are ordinarily categorically excluded under the regulations are actions on the majority of: 1) ANDA's and AADA's; 2) NDA supplements; and 3) IND's. ANDA's/AADA's and NDA supplements are categorically excluded from the requirement for preparation of an EA if they meet certain criteria (21 CFR 25.24(c)). The criteria include that the drug product will not be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect, and if data available to the agency do not establish that, at the expected levels of exposure, the substance may be toxic to organisms in the environment. In such cases, no EA or AEA need be submitted unless the agency has sufficient evidence to establish that the specific proposed action may significantly affect the quality of the human environment. Supplements for chemistry, manufacturing and controls changes, such as manufacturing site changes, typically meet the categorical exclusion criteria.

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Action on an IND is categorically excluded from the requirement for preparation of an EA (21 CFR § 25.24(c)(4)) if the drug shipped under such notice is intended to be used for clinical studies or research in which waste will be controlled or the amount of waste expected to enter the environment may reasonably be expected to be nontoxic.

When requesting a categorical exclusion, the applicant should cite the categorical exclusion used and certify that the drug product meets the criteria for the categorical exclusion defined in the regulations. An applicant ordinarily need not provide data to demonstrate that it qualifies for a categorical exclusion. CDER will deny a categorical exclusion, however, and require an EA if there is sufficient available information that suggests that the substance may be toxic to organisms in the environment at the expected levels of exposure. Available information includes information submitted as part of the application as well as data available to the agency on the same or similar drugs. CDER will request additional information when warranted. If an applicant has information that indicates that a substance may be toxic to organisms in the environment at the expected level of exposure, the information should be provided to CDER.

CDER considers any action that, directly or indirectly, affects a species or the critical habitat of a species determined under the Endangered Species Act (ESA) or the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES) to be endangered or threatened, or that affects properties listed in or eligible for listing in the United States' Register of Historic Places, to be an action that may significantly affect the quality of the human environment. For such actions, CDER may request additional information if a categorical exclusion is claimed.

III. PREPARING AN EA FOR SUBMISSION TO CDER

A. When is an EA or AEA required under the regulations?

Preparation of an environmental assessment is ordinarily required unless the proposed action qualifies for exclusion under 21 CFR §§ 25.23 and 25.24. EA's are submitted to CDER for among other actions: 1) NDA's and 2) efficacy or other supplements to existing NDA's or actions on ANDA's or AADA's, if the approved drug product will be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect, or if data available to the agency establish that at the established levels of exposure, the substance may be toxic to organisms in the environment.

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1. NDA's

Type 1 NDA's are for new molecular entities. NDA Types 2-7 are for drug products which have already been marketed or approved in the same form or very similar form in the U.S. **The regulations require that an EA or AEA be provided for all NDA's.**

2. NDA Supplements

Under FDA's NEPA procedures, an EA or AEA must be prepared if the supplemental application does not qualify for a categorical exclusion. If an EA or AEA has previously been submitted for the same active moiety by the applicant, the EA or AEA for the supplement need only include a copy of the original EA/AEA and a discussion of the differences/changes from the original application and the impact of these differences on the environment from those described in the original EA/AEA. For each EA format item that does not differ from the original EA/AEA, this should be stated and a reference to the previously submitted EA provided. If the applicant is abstracting information from an environmental assessment/FONSI released under the Freedom of Information Act (FOIA), a copy of the document should be included with the submission. If no previous EA/AEA can be referenced, an EA or AEA, as appropriate, should be provided in accordance with the content and format information provided in section III.D.

3. ANDA/AADA's

Under FDA's NEPA procedures, an EA or AEA must be prepared if the ANDA/AADA application or supplement to an ANDA/AADA does not qualify for categorical exclusion. If an EA or AEA has previously been submitted for the same active moiety by the applicant, the EA or AEA need only include a copy of the original EA/AEA and a discussion of the differences/changes from the original application and the impact of these differences on the environment from those described in the original EA/AEA. For each EA format item that does not differ from the original EA/AEA, this should be stated and a reference to the previously submitted EA provided. If the applicant is abstracting information from an environmental assessment/FONSI released under the Freedom of Information Act (FOIA), a copy of the document should be included with the submission. If no previous EA/AEA can be referenced, an EA or AEA, as appropriate, should be provided in accordance with the content and format information provided in section III.D.

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4. IND's

Under FDA's NEPA procedures, an EA or AEA must be prepared if the action does not qualify for a categorical exclusion.

B. What type of EA should be submitted?

FDA's NEPA procedures provide for two types of EA's: "full" EA's or abbreviated EA's. A "full" EA consists of 15 format items, including characterization of the fate and effects in the environment of the compound which is the subject of the proposed action. AEA's exclude or limit some of the information required including that in EA format items 7 and 8, fate and effects testing. The information to be provided for each of the format items is described in 21 CFR § 25.31a and in section III.D of this document.

FDA believes that, as stated in 21 CFR § 25.1(b), environmental documents are to concentrate on timely and significant issues, not to amass needless detail. FDA 's regulations (21 CFR § 25.31a(b)) provide that for various actions, certain format items of the EA may be abbreviated. For other drug product approvals requiring an EA pursuant to 21 CFR § 25.31a(a), the EA generally should address format items 1-15, but in some cases, not all format items may apply (see section III.D.7 for additional information). If a preparer of an EA believes that not all items in the format apply, the applicant may consult the Environmental Assessment Team at CDER to agree on a different format.

FDA's regulations at 21 CFR §25.31a(b) describe three types of CDER actions which are eligible for an AEA: 1) infrequent uses; 2) naturally occurring substances; and 3) products approved by the Environmental Protection Agency (EPA).

The basis for an AEA should be stated in EA format item 4.a. After CDER evaluates the environmental information submitted in an EA in which one or more EA format items are abbreviated, CDER may require the submission of additional information.

1. Infrequent Use AEA's

The infrequent use provision allows for preparation of an AEA when the drug product is intended for the prevention, treatment, or diagnosis of a rare disease or for a similarly infrequent use; for ophthalmic or topical application; or for local or general anesthesia (21 CFR § 25.31a(b)(3)).

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For infrequent use AEA's, documentation for EA format items 7-11 and 15 is ordinarily not required. Questions have arisen regarding the interpretation of rare disease or condition under this provision. CDER is providing guidance regarding this provision as follows: "Rare disease or condition" is defined in the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 360bb(a)(2) as "any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such a drug." Criterion A may be supported by designation as an Orphan Drug by FDA's Office of Orphan Products Development or by providing the estimated patient population and supporting information from an independent source (*e.g.,* Centers for Disease Control and Prevention (CDC)). If a drug has been designated as an Orphan Drug under criterion B, an infrequent use AEA may be used.

2. Naturally Occurring Substances AEA's

An AEA may be submitted for organic or inorganic drug substances, whether obtained from a natural resource or synthesized, that will exist in the environment in the same form as a substance found naturally in the flora, fauna, atmosphere, water or soil. A modified active moiety (*e.g.,* salt) which does not occur naturally also may be supported by an AEA filed under § 25.31a(b)(5) if it is established that, *in vivo* and in the environment, the active moiety exists in a form that is found naturally.

AEA's for substances that occur naturally in the environment should discuss whether the use of the product can reasonably be expected on the basis of all available evidence to alter significantly the concentration and distribution of the product, its metabolites, degradation products or its constituent parts in the environment (EA format item 7). These AEA's may rely on **existing** data (*i.e.,* from literature or data previously generated by the applicant) to fulfill the reporting requirements of EA format item 8 (effects). If a substance does not occur naturally in the geographic area of proposed drug use and disposal, additional information may be needed.

More information is available in section V regarding drug substances that are obtained from natural resources.

3. AEA's for Products Approved by EPA

AEA's for products that have been approved by the Environmental Protection Agency (EPA) under section 4 or 5 of the Toxic Substances Control Act (TSCA) or under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) should rely on environmental information in studies submitted to EPA, in the application/ petition submitted for FDA approval, and in the scientific literature to fulfill the requirements of EA format items 7, 8 and 15 (21 CFR § 25.31a(b)(6)). The AEA should contain a

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description of any potential adverse environmental impact determined by the EPA.

C. What EA information should be provided in an application?

The applicant should determine whether a categorical exclusion, AEA or EA is appropriate for their submission and provide the required information in the initial filing. **Failure to provide: 1) a claim of categorical exclusion with certification of compliance with the categorical exclusion criteria; or 2) an adequate EA or AEA (*e.g.,* information for each required EA format item), is grounds for refusing to file the application (21 CFR §314.101(d)(4) and §25.23(d)).**

If the submission is eligible for more than one type of environmental assessment format (*e.g.,* a naturally occurring substance for a rare disease for which one could prepare an AEA either under 21 CFR § 25.31a(b)(3) or (5)), the applicant should submit the information in the format with the fewest reporting requirements and state which EA format is being used. CDER will request additional information if warranted.

D. Content and Format

This section describes the basic information that should be submitted for each format item in an EA or AEA and follows the formats described in FDA's NEPA procedures (21 CFR § 25.31a). Attachment A contains an outline of the format for an EA.

1. Date

The EA should include the date the EA was originally prepared and the date(s) of any subsequent amendments.

2. Name of Applicant/Petitioner

The EA should identify the applicant who is submitting the application.

3. Address

The EA should contain the address where all correspondence is to be directed.

4. Description of Proposed Action

a. Requested Approval

The description of the requested approval should include the drug product application number (if available), drug product name, dosage form, strength, a brief description of the drug product packaging, whether an EA or AEA is provided and, if applicable, the basis for the AEA. For example, "XYZ Pharmaceuticals has filed an NDA pursuant to

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section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADE NAME® (established name), 250 mg and 500 mg, packaged in OHDPE bottles. An EA has been submitted pursuant to 21 CFR § 25.31a(a)."

b. Need for Action

The EA should briefly describe the drug's intended uses in the diagnosis, cure, mitigation, treatment or prevention of disease. If attempting to qualify an action for an abbreviated environmental assessment because it is used to treat a rare disease or condition (see section III.B.1), it should be indicated if the drug is for acute or long-term use, the current and/or expected patient population (*i.e.,* total patient population, not marketing estimate) and Orphan Drug status, if applicable.

c. Production Locations

The EA should identify the location of both the drug substance and the drug product manufacturing facilities. The location of production facilities for isolated drug substance intermediates should also be provided if the intermediates are not commercially available to all parties in the open marketplace (*i.e.*, proprietary drug substance intermediates). The EA should include a statement whether any intermediates are considered proprietary. The specific street address(es) should be provided. A brief description of the environments at and adjacent to the facilities should be provided. The zoning (*e.g.*, industrial, commercial, residential) and any geographic features (*e.g.*, mountains, lakes, rivers, forests) in proximity to the manufacturing facilities should be identified.

If primary packaging operations are conducted at locations other than the drug product manufacturing facility, the sites of those operations should be identified.

Information ordinarily need not be provided for secondary packaging operations, labeling, testing, quality control, distribution and warehousing operations which are performed at locations other than the manufacturing facilities, or primary packaging facilities where the introduction of drug substance, proprietary drug substance intermediate or drug product into the environment is minimal (*e.g.*, due to accidental breakage, emission from nondestructive testing). If standard procedures at any of these facilities allow for introduction of other than incidental quantities of these compounds into the environment, then information should also be included for those facilities.

The names and addresses of manufacturers or suppliers that are excluded from public release under FOIA procedures may be treated as confidential information when preparing an environmental assessment and may be included in a confidential appendix (see section III.G for a discussion of confidential and non-confidential

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information). All other information regarding these facilities (*e.g.,* EA format item 6) should be included in the non-confidential EA summary document and identified in such a manner to clearly indicate the operation conducted at the facility (*e.g.,* Contract Manufacturer - Drug Substance, Contract Primary Packager #1, Contract Primary Packager #2).

Note that for each facility identified in this section, information should be provided under EA format item 6 unless it is a foreign site with appropriate certification (see section VI).

d. Locations of Use

The EA should identify the location(s) of end use of the drug product. Typically, the locations of use are identified as hospitals, clinics and/or patients in their homes. If use is expected to be concentrated in a particular geographic region, this fact should be included.

e. Disposal Sites

The EA should describe the method(s) of disposal of rejected, expired, returned or waste drug substance, proprietary drug substance intermediate, and drug product. The applicant should provide a brief, general description of the method(s) of disposal including whether the facilities that will be used are permitted by an appropriate authority to destroy hazardous or non-hazardous material. The company/facility currently responsible for disposal should be identified as should: 1) the license or permit number; 2) the EPA or other issuing authority's identification number, if any; 3) the license or permit expiration dates; and 4) the issuing agent. For example, "Returned, expired or rejected drug product will be disposed of by high temperature incineration at a facility which is licensed by the EPA or an appropriate state authority to destroy hazardous materials. The facility currently being used is XYZ Incinerators, 1234 Good Ave., Burn, AK which is licensed by the EPA to destroy hazardous material under permit 1234 (expiration date 12/1999))." **Copies of the actual permits/licenses do not need to be submitted.** A reference to EA format item 6.b, "Controls Exercised," may be provided if the disposal operations are described there. Specific information regarding contract disposal facilities (*e.g.,* identification, licensing information) may be included in a confidential appendix. (See section III.G for a discussion of confidential and non-confidential information).

Unless other disposal methods by the end user are anticipated, it is sufficient to state that at U.S. hospitals, pharmacies or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy or clinic procedures and/or that in the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, although minimal quantities of unused drug may be disposed of in the

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sewer system.

5. Identification of Chemical Substances that are the Subject of the Proposed Action

The EA should contain information to allow for accurate location of data about the chemical in scientific literature and to allow for identification of closely related compounds. At a minimum, the information listed below should be provided. Other information, such as the International Nonproprietary Name (INN) or nonsystematic/ semisystematic chemical names, should be included if deemed useful in the identification of the compounds.

Usually this information need only be provided for the drug substance, but the same information should also be provided for the form of the active ingredient in the drug product if it is different from the drug substance (*e.g.*, a salt formed *in situ* from a free base) or for a pharmacologically active related substance formed by conversion from a pharmacologically inactive parent compound (*e.g.*, a prodrug product is converted to the pharmacologically active form). Although the following information is generally self-explanatory, explanation is provided, where appropriate:

a. Nomenclature

i. Established Name (U.S. Adopted Name-USAN)

ii. Brand/Proprietary Name

iii. Chemical Names

(1) Chemical Abstracts (CA) Index Name (inverted form)

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(2) Systematic Chemical Name (uninverted form)

b. Chemical Abstracts Service (CAS) registration number

c. Molecular Formula

d. Molecular Weight

e. Structural (graphic) Formula

f. Physical Description

For example, white to off-white powder

g. Additives

The EA should identify by name and CAS registration number any substance added to the described chemical substance in relatively small amounts to impart or improve desirable properties or suppress undesirable properties (*e.g.,* formulation excipients, preservatives) which is expected to be emitted into the environment. A reference to EA format item 6.a is acceptable as long as the additives are included in the list of "Substances Expected to be Emitted."

h. Impurities

Impurities in drug substances and products are controlled and are typically found at very low levels (*i.e.,* much less than 1%). The EA should only identify impurities likely to be found in the described chemical substance at levels > than 1%. CAS registration numbers should be provided, if available. Reference in the EA document to a confidential appendix which provides this information is adequate. Identification in this section of the EA of potential residual solvents is not necessary if solvents are adequately addressed in EA format item 6.a.

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6. Introduction of Substances into the Environment

Information should be provided in EA format items 6.a through 6.e for all facilities identified in EA format item 4.c, unless a facility is a foreign facility with appropriate certification (see section VI). The information should be presented separately for each facility. The extent/detail of information necessary for primary packaging operations depends on the dosage form and the potential for introduction of chemical substances into the environment.

The obligation for a company to obtain the proper emission permits and comply with all applicable Federal, State and local emission requirements is not negated by FDA review of an environmental assessment or approval of an application.

a. Substances Expected to be Emitted

The substances expected to be emitted from the facilities should be listed. Substances that are emitted at low levels need not be listed unless they are likely to have a significant environmental impact. The list(s) should include the CAS registration number for each and the manner in which they are expected to be emitted (*e.g.*, organic solvent waste stream). Reference in the EA document to a confidential appendix which provides this information is adequate.

b. Controls Exercised

The EA should contain a brief description of the controls associated with the air, liquid, and solid emission waste streams identified in EA format item 6.a. Descriptions of control efficiencies (*e.g.*, emission of airborne particulate material is controlled by HEPA filtration with a 99.9% operating efficiency) or treatment prior to emission (*e.g.*, neutralization of aqueous waste streams) should be included, if applicable. Disposition of unused product or rejected packaged goods, including those at contract packagers, should be discussed in EA format item 6.b if it has not been described in EA format item 4.e. Disposal of manufacturing aids, emission controls or other items (*e.g.*, resins, filters, clothing) which may contain residual drug substance or proprietary drug substance intermediates should be discussed.

c. Citation of and Statement of Compliance with Applicable Emission Requirements

A citation (*i.e.*, list of regulations/laws) of all applicable Federal, State and local emission requirements, including occupational, should be provided, as well as a statement of compliance with, or being on an enforceable schedule to be in

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compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the manufacturing operations.

Material safety data sheets (MSDS) should be provided in a non-confidential appendix for the drug substance and if appropriate, drug product.

A list of emission permits and/or licenses should be provided along with the number, authorizing agency and expiration dates. **Inclusion of the actual permit and/or license is not necessary.** Any of the requested information that is not applicable or not current for a specific permit/license (*e.g.*, expired permit) should be explained. If no permits are required, this should be stated (e.g., air emissions are below the level that requires a permit). For ease of review, CDER prefers that this information be presented in a table format (see Attachment B for a sample table).

d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements

The EA should state whether approval and the subsequent increase in production at the facility is expected to affect compliance with current emission requirements and should contain a brief supporting discussion based on the estimated fifth year production volume (*e.g.*, waste water emission will increase to approximately 60% of the permit limit).

e. Expected Introduction Concentrations

For the drug substance and/or active moiety entering the environment as a result of use and disposal, expected introduction concentrations for use and disposal should be estimated, either through use of calculations or direct measures. The estimates for use should be based on total fifth year production estimates for all dosage forms and strengths included in the application or related (companion) applications. All concentrations should be reported as the concentration of active moiety rather than, for example, the salt or complex. The specific calculations and the basis for the calculations (*e.g.,* 5th year production estimates) may be included in a confidential appendix.

Based on the identification of and literature about emitted substances other than the drug substance/active moiety, CDER can determine whether it needs more information about the potential environmental impacts of these other emissions (see EA format item 6.a). Such additional information generally will not be needed.

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Note: for substances occurring naturally in the environment, calculations may aid in preparing the discussion of the concentration and distribution of the substance in the environment which is called for in EA format item 7 (21 CFR § 25.31a(b)(5)) .

i. Expected Introduction Concentration from Use

The calculation of the expected introduction concentration (EIC) entering into the aquatic environment from patient use may include consideration of metabolism to less pharmacologically active or inactive compounds and the environmental depletion mechanisms that occur in the waste treatment process (*e.g.,* adsorption, degradation, hydrolysis), if the information is available. Information should be provided regarding the metabolic profile and pharmacological activity of the metabolites relative to the active moiety if metabolism is considered.

The EIC for the aquatic environment, assuming all drug substance produced is used, even distribution throughout the U.S. per day, and no metabolism or depletion mechanisms, should be calculated as follows:

EIC-Aquatic (ppm) = A x B x C x D

where A = kg/year production
B = 1/liters per day entering POTW's*
C = year/365 days
D = 10^6 mg/kg (conversion factor)

* 1.115 x 10^{11} liters per day entering publicly owned treatment works (POTW's), Source: 1992 Needs Survey, Report to Congress, September 1993, EPA 832-R-93-002

This equation should be used when determining if the Tier 0 approach will be used unless localized use is expected (see section III.D.7.c). If an alternative calculation is used in addition to the equation provided above, it should be clearly indicated in the EA and the source and/or basis for the alternative calculation provided. An alternative calculation should be used if localized use of the drug product is expected.

Some drug substance and/or active moiety may enter the terrestrial environment when sludge from waste water treatment facilities, which contains adsorbed material, is applied to land. Although application of sludge to land is regulated by EPA or an appropriate State authority, controls similar to those at landfills are not in place to limit the release of materials in the environment after application. Sludge is generally subjected to some form of aerobic or anaerobic digestion in the waste treatment facility, and only a fraction of the sludge may be applied to soil while the remainder is incinerated or landfilled. The EIC for the terrestrial compartment should be estimated if, based on the available physical/chemical properties of the compound, significant

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quantities of the active moiety are expected to adsorb to sludge and typical POTW procedures allow for significant quantities of sludge to be disposed of in this manner. The calculations used depend on the treatment/disposal process. Depletion mechanisms (*e.g.,* biodegradation, hydrolysis) that occur in the waste treatment process may be considered when calculating the EIC for the terrestrial compartment, if the information is available.

The concentration expected in the atmospheric compartment should be considered for products that are released primarily into the air (*e.g.,* medical gases).

ii. Expected Introduction Concentration from Disposal

Normally, the EIC from disposal need not be calculated since the majority of pharmaceutical waste will be disposed of in landfills or at incineration facilities which are regulated by the EPA or appropriate State agencies. These agencies have considered the environmental impacts from the operation of these facilities in their licensing process and require controls (*e.g.,* scrubbers, lined landfills, migration tests) to limit the release of materials into the environment. The EIC for disposal should be calculated if significant quantities of material (*e.g.,* rejected batches) are expected to be disposed of in the sewer system.

7. Fate of Emitted Substances in the Environment

a. Tiered Approach to Determining Environmental Fate (EA format item 7) and Effects (EA format item 8)

The Center encourages the use of a logical, tiered approach to testing so that adequate information is available to assess the potential environmental fate (EA format item 7) and effects (EA format item 8) of pharmaceuticals while minimizing the cost to industry. Information is provided in EA format item 7.c (Tier 0) and EA format item 8 (Tiers 1-3) regarding an acceptable approach to tier testing. Figure 1 provides an illustration of this tiered approach. Alternative, scientifically justified approaches may also be used.

If EA format items 7 and 8 are needed, the information provided should focus on the fate and effect of the drug substance and/or structurally related substances (SRS's) rather than, for example, excipients, solvents or raw materials used in producing the drug substance, proprietary drug substance intermediate, or drug product. Based on the identification of and literature about emitted substance

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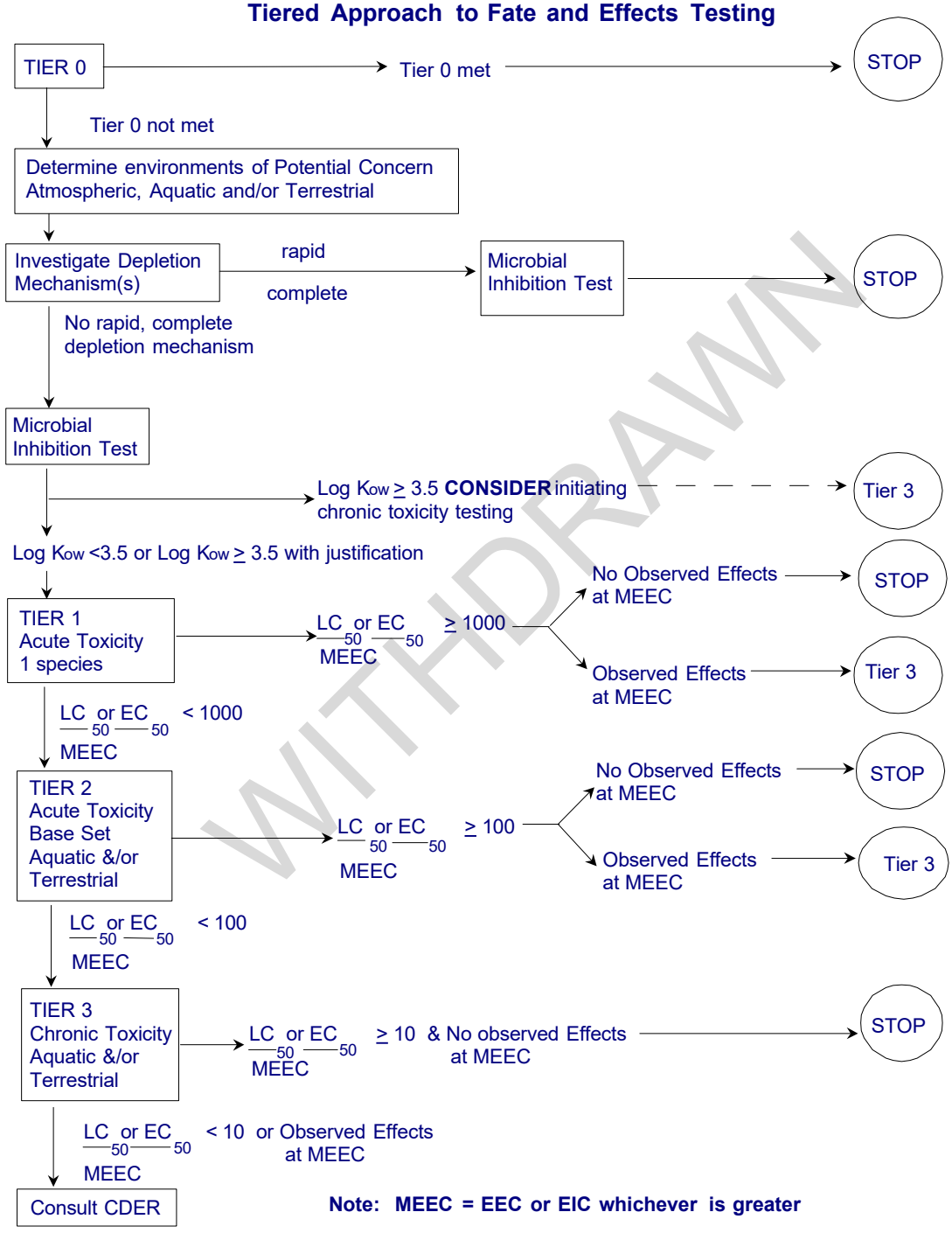
other than the drug substance or SRS's, CDER can determine whether it needs more information about the potential environmental impacts of these other emissions. Such additional information generally will not be needed.

Figure 1
Tiered Approach to Fate and Effects Testing



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Information submitted under EA format items 7 and 8 may include specific data generated on the test substance or relevant information on analogous compounds from the submitter or from the peer reviewed literature as appropriate. Actual experimental data regarding base parameters are generally preferable to computer modeling; however, in some circumstances computer modeling may be appropriate. FDA may be consulted if a company believes computer modeling is appropriate and wishes to use modeling in an EA.

b. Type of Fate Information to be Submitted

i. EA's filed pursuant to 21 CFR § 25.31a(a)

Information listed in section III.D.7.d may not be needed if an applicant follows a tiered approach to preparing an environmental assessment (see Tier 0 approach described in section III.D.7.c).

ii. EA's filed pursuant to 21 CFR § 25.31a(b)(3)

Fate information normally need not be submitted in AEA's for drugs intended for the prevention, treatment, or diagnosis of a rare disease or for a similarly infrequent use; for ophthalmic or topical application; or for local or general anesthesia (21 CFR § 25.31a(b)(3)).

iii. EA's filed pursuant to 21 CFR § 25.31a(b)(5)

AEA's for substances that occur naturally in the environment should contain a discussion of whether, on the basis of all available evidence, the use of the product can reasonably be expected to alter significantly the concentration and distribution of the product, its metabolites, degradation products, or its constituent parts in the environment (21 CFR § 25.31a(b)(5)). The natural source of the substance (*e.g.*, endogenous to all mammalian cells), and the production volume relative to the estimated quantity occurring naturally in the environment, if known, should be provided. Information in section III.D.7.d may not be needed if an applicant follows a tiered approach to preparing an environmental assessment (see Tier 0 approach described in section III.D.7.c).

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iv. EA's filed pursuant to 21 CFR § 25.31a(b)(6)

AEA's for products that have been approved by the Environmental Protection Agency (EPA) under section 4 or 5 of the TSCA or under FIFRA should rely on environmental information in studies submitted to EPA, in the application/ petition submitted for FDA approval and in the scientific literature (21 CFR § 25.31a(b)(6)).

c. Tier 0

CDER has performed a retrospective review of toxicity information available in EA's previously submitted in support of NDA's and NDA supplements. Data are available from each reviewing division and are representative of pharmacological drug classifications. The data have routinely shown no observed effects on relevant standard environmental test organisms at drug concentrations below 1 part per billion (ppb). Because CDER has routinely found that drugs at concentrations less than 1 ppb have no significant effect on relevant standard test organisms, and, therefore, are unlikely to have a significant effect on the environment, CDER has determined that information for EA format items 7, 8, 9, 10, 11 and 15 will normally not be needed for drugs whose maximum expected environmental concentration (EEC or EIC whichever is greater) is less than 1 part per billion.

EA format items 7, 8, 9, 10, 11 and 15 will normally not be needed when the expected environmental concentration due to entry into the environment is less than one (1) ppb from use and/or disposal or at any point where higher concentrations are expected as a result of bioaccumulation or other types of concentration processes. Additionally, for those actions involving genetically modified organisms and cells, the applicant should be using a containment class for manufacturing established by a recognized authority (*e.g.,* National Institutes of Health's Recombinant DNA Advisory Committee) or consideration of the fate and effects of the use of the modified organisms or cells should be included as an integral part of the CDER application review process (*e.g.,* manufacturing process validation) if the Tier 0 approach is used to limit the information submitted in EA format items 7, 8, 9, 10, 11 and 15.

Under specific circumstances, such as those identified in section II as reasons for denying a categorical exclusion, EA format items 7, 8, 9, 10, 11 and 15 may have to be submitted even if the Tier 0 approach is used. CDER encourages consultation if there are any questions regarding the applicability of Tier 0 to a particular drug product.

See EA format items 6.e and 7.d.iv for information regarding concentration calculations.

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d. Fate information to be submitted for an EA filed pursuant to 21 CFR § 25.31a(a)

If the Tier 0 approach (see section III.D.7.c) cannot be used by an applicant, the following information should be provided.

i. Identification of Substances of Interest

The actual substances which will enter or exist in the environment (*i.e.,* atmospheric, aquatic, terrestrial) may include the parent compound (*i.e.*, drug substance) or SRS's such as the dissociated parent compound, metabolites or degradants. The EA should list the drug substance and the **predominant** SRS's expected to enter or exist in the environment, provide the name, chemical structure and CAS number when possible, and provide a rationale for the decision as to which substance(s) will be studied. Predominant SRS's should be considered those greater than 10% of dose.

In most cases, fate (and effects) information should be provided on the parent (or active) drug substance, as representative of substances entering the environment. Such information is relevant to SRS's when these possess the same fundamental structure and are comparably or more polar than the parent drug substance. At a minimum, the EA should contain a discussion of the potential fate and effects of the predominant SRS's based on their structural differences/similarities to the parent compound *(e.g.*, due to a functional group change, the metabolite should be more soluble than the parent compound, the SRS is more polar). Computerized structure/activity relationship modeling programs may be useful in supporting extrapolation of fate and effects information from the parent (or active) drug substance to the SRS. Relevant available pharmacologic activity and toxicity information should be provided for the SRS's. Specific toxicity/activity information for SRS's may be included in a confidential appendix. Additional environmental information on a predominant SRS may be warranted, following consultation with the Environmental Assessment Team at CDER, if the fate of the compound is expected to differ from the parent compound or there is an indication that the SRS's effect on the environment would be substantially greater than from the parent drug substance.

ii. Physical/Chemical Characterization

The following tests should be conducted to determine if the compound is most likely to amass predominantly in aquatic, terrestrial and/or atmospheric environments:

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(a) Water Solubility

(b) Dissociation Constant(s)

(c) Octanol/Water Partition Coefficient

(d) Vapor Pressure or Henry's Law Constant

If there is a scientific basis for not performing a test, the justification should be included in the EA (*e.g.*, water solubility was not determined because the compound is hydrolytically unstable). For a test compound that associates or dissociates in water, water solubility and the octanol/water partition coefficient may have to be determined at pH 5 and 9 as well as pH 7.

The octanol/water partition coefficient (K_{ow}) is an indicator of a nonionized compound's potential to adsorb to the organic fraction of soil, sediment or sludge in addition to being an indicator of a compound's lipophilicity. It is not as good a predictor for inorganic chemicals, metal organic complexes, dissociating, ionic organic compounds or compounds with other mitigating structural features such as molecular size. Further study of the sorption/desorption properties (K_{oc}) of a substance to sludge should be **considered** if log K_{ow} is greater than 3 or other properties indicate that sorption/desorption may occur.

iii. Environmental Depletion Mechanisms

Depletion mechanisms should be investigated to determine if there is degradation of the compound in the environment(s) of interest. **It is not necessary to go to extraordinary effort to identify a depletion mechanism once the typical depletion mechanisms (i.e., hydrolysis, photolysis, biodegradation) have been investigated nor to continue investigating all potential depletion mechanisms once one has been identified.** Consideration should be given to the nature and extent of the degradation. If a rapid, complete depletion mechanism is identified (degradants are relatively simple, polar by-products), no testing to determine the environmental effects of the compound should be performed except for a microbial inhibition test or other appropriate test to assess the potential for the compound to disrupt waste treatment processes. Based on the estimated time prior to emission from a treatment facility, CDER considers the following to be rapid depletion mechanisms:

Hydrolysis $t_{½}$ (pH 5-9):	≤ 24 hours
Aerobic Biodegradation $t_{½}$:	≤ 8 hours
Soil Biodegradation $t_{½}$:	≤ 5 days

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It is usually sufficient to provide basic supporting information that identifies the potential for a compound to be removed from the environment by a depletion mechanism (*e.g.,* photolysis or hydrolysis based on information developed for analytical methods validation or from stability studies). If the depletion mechanism is being used to reduce the expected introduction concentration (EA format item 6.e) or to eliminate effects testing, a formal, detailed analysis of the depletion mechanism should be provided (*e.g.,* according to a standard test method, rate determination, analysis of expected exposure time in the environment).

Direct and indirect photolysis, although significant under laboratory conditions, may not be a rapid depletion mechanism in the environment due to significant variation in light intensity (*e.g.*, related to weather, latitude, depth penetration) and duration of exposure. Efforts to characterize photolysis as a depletion mechanism should take these factors into consideration.

iv. Expected Environmental Concentration (EEC)

The expected environmental concentration is the expected concentration of the active moiety or other compound of interest (see EA format item 7.d.i) that organisms would be exposed to in the environment (*e.g.,* surface water) after consideration of, for example, spatial or temporal concentration or depletion factors such as dilution, degradation, sorption and/or bioaccumulation. A brief discussion comparing the EEC to the EIC (see EA format item 6.e) should be provided. In the majority of cases the EEC would be expected to be significantly less than the EIC due to dilution in the aquatic environment.

v. Summary

A summary discussion of the environmental fate of the substance(s) of interest should be provided for the following environmental compartments based on the information and data provided in EA format items 7.d.i-iv. In some circumstances, transport between environmental compartments should be considered when determining the fate of the substance(s) of interest in the environment.

Aquatic Environment: In general, pharmaceutical substances are expected to enter predominantly into the aquatic environment and, therefore, the focus of any effects studies will most likely be on aquatic organisms. If the substance(s) of interest rapidly degrades (see EA format item 7.d.iii) or adsorbs completely and irreversibly to sludge, then fate and effects in the aquatic environment should not usually be considered.

Terrestrial Environment: In general, substances enter the terrestrial environment predominantly from sludge removed from waste water treatment plants that is subsequently applied to land (see EA format item 6.e.i). Therefore, effects on the

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terrestrial environment are more likely if a compound adsorbs to sludge. Sludge is generally subjected to some form of aerobic or anaerobic digestion in the waste treatment facility and only a fraction of the sludge may be applied to soil while the remainder is incinerated or landfilled. Fate and effects testing in the terrestrial environment should be **considered** if testing indicates that the substance(s) of interest will significantly adsorb to sludge (*e.g.*, $K_{oc} \geq 1000$) and if based on typical POTW processes, a significant quantity of sludge is expected to be applied to land.

Atmospheric Environment: In general, substances that do not adsorb readily to soils, have a high vapor pressure and have a low water solubility are likely to volatilize significantly from the aquatic or terrestrial environments, although actual volatilization rates will depend on environmental conditions (*e.g.*, dispersion away from the evaporation site) and on factors that can lessen or enhance the effective vapor pressure or behavior of the chemical at a liquid-air or solid-air interface. The atmospheric compartment may be of interest for medical gases. But based on the polarity of the majority of compounds at relevant aquatic environmental conditions, it is unlikely that there would be substantive partitioning from the aquatic to the atmospheric environment for other pharmaceuticals. Any potential for a substance to volatilize and recycle into the aquatic or terrestrial environments should be discussed based on the information and data available for the substance.

8. Environmental Effects of Released Substances

EA's filed pursuant to 21 CFR § 25.31a(a): Information in EA format item 8 may not be needed if an applicant follows a tiered approach to preparing an environmental assessment (see Tier 0 approach described in section III.D.7.c). Guidance is provided below regarding the tiered approach to effects testing, when testing is indicated.

EA's filed pursuant to 21 CFR § 25.31a(b)(3): Effects information normally need not be submitted for AEA's for drugs intended for the prevention, treatment, or diagnosis of a rare disease or for a similarly infrequent use, for ophthalmic or topical application, or for local or general anesthesia (21 CFR § 25.31a(b)(3)).

EA's filed pursuant to 21 CFR § 25.31a(b)(5): AEA's for substances that occur naturally in the environment should report **existing** data relating to the environmental effects of substances expected to be emitted into the environment as a consequence of use of the product and report information obtained from the scientific literature on the toxicity of the product to laboratory animals, *e.g.*, that information used to satisfy human safety requirements, and to organisms in the environment, *e.g.*, fish invertebrates, plants, fungi, and bacteria, that may be exposed to the product. Information in EA format item 8 may not be needed if an applicant follows a tiered approach to preparing an environmental assessment (see Tier 0 approach described in section III.D.7.c).

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EA's filed pursuant to 21 CFR § 25.31a(b)(6): AEA's for products that have been approved by the Environmental Protection Agency (EPA) under section 4 or 5 of TSCA or under FIFRA should rely on environmental information in studies submitted to EPA, in the application/petition submitted for FDA approval and in the scientific literature (21 CFR § 25.31a(b)(6)). The EA should contain a description of any potential adverse environmental impact determined by the EPA.

Tiered approach to environmental effects testing (see below, Microbiological Inhibition Testing through Tier 3 Testing): If effects data are needed and no rapid, complete depletion mechanism has been identified, it should be assumed that the compound will persist in the environment for some time and, therefore, the toxicity of the released substances to environmental organisms should be evaluated. The fate of the substance as determined in EA format item 7 should be considered when designing the studies. For those compounds which enter the atmospheric environment, testing should be designed based on the extent to which the substance recycles into the aquatic or terrestrial environments. All toxicity test results for the drug substance should be reported in terms of the quantity/concentration of the active moiety. The results of the toxicity testing should be compared to the maximum expected environmental concentration (MEEC: EIC or EEC whichever is greater) and the difference between the values discussed (*e.g.,* in terms of the assessment factor, > 1000, > 100). When using this tiered approach to effects testing, it is important to design the test conditions appropriately so that a no observed effects concentration is determined.

Microbial Inhibition Testing: A microbial inhibition test or other appropriate test (*e.g.*, respiration inhibition testing) should be performed to assess a chemical compound's potential to inhibit microorganisms and subsequently disrupt waste treatment processes.

Assessment Factors: These assessment factors are intended to provide a consistent regulatory basis for determining when additional ecotoxicity testing should be performed (tiered approach). They are directly related to the amount of valid ecotoxicity data available. If the LC_{50} or EC_{50} or other appropriate test endpoint divided by the MEEC is less than the assessment factor, additional testing should be performed. The use of EC_{50} or test end point other than the LC_{50} should be limited to those test organisms for which the LC_{50} is not the test endpoint.

TEST TIER	ASSESSMENT FACTOR
1	1000 (see below)
2	100 (see below)

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3	10 (see below)

Alternative scientifically justified approaches may also be used.

Tier 1 Testing: Acute ecotoxicity testing should be performed on a minimum of one suitable test organism (see base set for Tier 2 Testing). If the EC_{50} or LC_{50} divided by the MEEC is greater than 1000, no further testing should be conducted unless sublethal effects are observed at the MEEC. If the EC_{50} or LC_{50} divided by the MEEC is less than 1000, Tier 2 testing should be performed. Sublethal effects (observed effects) at the MEEC indicate that chronic toxicity testing (Tier 3) should be performed. The use of the assessment factor of 100 could be used for Tier 1 Testing if there is evidence (*e.g.,* Tier 2 Testing on a similar compound) to support that the single test organism used would be expected to be the most sensitive of the base set test organisms.

Tier 2 Testing: Acute ecotoxicity testing should be performed on the minimum base set of aquatic and/or terrestrial organisms. The aquatic base set usually consists of: 1) a fish acute toxicity test; 2) an aquatic invertebrate acute toxicity test; and 3) an algal species bioassay. The terrestrial base set usually consists of: 1) plant early growth tests; 2) earthworm toxicity test; and 3) soil microbial toxicity test. Usually only an earthworm toxicity study is indicated if the substance binds tightly to soil. A rodent acute toxicity is not included in the terrestrial base set since there is usually a significant quantity of mammalian (*e.g.,* mice, rat, dog, monkey, humans) toxicity testing performed, both acute and chronic, to support the underlying application and to demonstrate the safety of the drug product. **Consultation with the Environmental Assessment Team at CDER is suggested prior to initiating any terrestrial studies.** If the EC_{50} or LC_{50} for the most sensitive organism in the base set divided by the MEEC is greater than 100, no further testing should be conducted unless sublethal effects are observed at the MEEC. If the EC_{50} or LC_{50} divided by the MEEC is less than 100, Tier 3 testing should be performed. Sublethal effects (observed effects) at the MEEC indicate that chronic toxicity testing (Tier 3) should be performed.

Tier 3 Testing: Chronic toxicity testing should be considered if the compound has the potential to bioaccumulate or bioconcentrate, if indicated based on Tier 1 and/or Tier 2 Testing, or if there are other indications that the compound undergoes biotransformation to more toxic compounds.

Bioaccumulation or bioconcentration is a complex, dynamic process which is dependant on the availability, persistence and physical/chemical properties of a compound in the environment. In general, pharmaceuticals tend not to be very lipophilic and are produced/used in relatively low quantities compared to industrial chemicals. The majority of pharmaceuticals are metabolized to some extent in humans to SRS's that are more polar, less toxic and less pharmacologically active than the parent

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compound. These factors suggest that there should be a low potential for bioaccumulation or bioconcentration of pharmaceuticals, but because of the length of time it takes to conduct chronic toxicity studies, applicants are encouraged to identify compounds which are candidates for these studies as early as possible. A primary determinant of the potential for a compound to bioaccumulate is the octanol/water partition coefficient (K_{ow}). A high octanol/water partition coefficient indicates that the compound will tend to be lipophilic. Chronic toxicity testing should be **considered** if log K_{ow} of a compound is greater than or equal to 3.5 under relevant environmental conditions (*e.g.,* pH 7), and a justification should be provided if chronic toxicity testing is not performed. Structural features (*e.g.,* molecular size, polarity) that limit passage across biological membranes or the lack of bioavailability to environmental organisms (*e.g.,* strong adsorption to soil) are mitigating factors which could be considered when determining if bioaccumulation/bioconcentration would be a concern for compounds with a K_{ow} greater than or equal to 3.5. It may be necessary to obtain acute toxicity data for the organism to be tested in order to set the concentrations for the chronic studies properly. **If the preparer of an EA is considering initiating chronic toxicity studies, consultation with the Environmental Assessment Team at CDER is recommended to ensure that such studies are appropriate and properly designed.**

For chronic toxicity testing, If the EC_{50} or LC_{50} divided by the MEEC is greater than 10, no further testing should be conducted unless sublethal effects are observed at the MEEC. CDER should be consulted if the EC_{50} or LC_{50} divided by the MEEC is less than 10 or there are sublethal effects at the MEEC.

Test Methods/Test Organisms: Studies should be performed using test organisms and methods which have been identified by the FDA EA Technical Assistance Handbook, the EPA (40 CFR § 797), the Organisation for Economic Co-operation and Development (OECD) or other peer reviewed literature as appropriate for use in environmental studies. If the drug product is intended to act upon an environmental organism (*e.g.*, antiparasitic, antibiotic), information regarding the toxicity to the target organism(s) should be included.

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9. Use of Resources and Energy

a. Natural Resources and Energy

The EA should provide the approximate energy usage associated with the manufacturing operations as a percent of the total plant consumption, or other appropriate evaluations. If the drug substance, proprietary drug substance intermediates, or precursors are derived from a natural resource (*e.g.*, plants), the source should be identified, and other pertinent information provided, if applicable, such as geographic region of source, whether the resource is cultivated or harvested from the wild and/or relevant permits (See section V).

b. Effect on Endangered or Threatened Species

The EA should state whether approval is expected to affect, directly or indirectly, endangered or threatened species. If the drug substance, proprietary drug substance intermediates or precursors are derived from a natural resource, the EA should specifically state whether the natural resource is listed as endangered or threatened under the U.S. Endangered Species Act (ESA) or the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES). Endangered or threatened species in the immediate vicinity of any of the production facilities should be identified.

c. Effect on Property Listed in or Eligible for Listing in the National Register of Historic Places

The EA should state whether approval is expected to affect properties listed in or eligible for listing in the United States' National Register of Historic Places. Historic properties in the immediate vicinity of any of the U.S. production facilities should be identified.

10. Mitigation Measures

The EA should contain a summary of measures used routinely in production to mitigate the release of materials into the environment (*e.g.*, compliance with Federal, State and local environmental laws, spill prevention plans). If applicable, a brief description of special measures used to mitigate the release of toxic or potentially toxic materials into the environment should be provided (*e.g.*, special handling information in the product labeling, Occupational Safety and Health Administration (OSHA) requirements, incineration, containment procedures). If there is a discussion of any of these mitigation measures in another section of the

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EA, reference to that information is adequate. **Actual copies of mitigation measures *e.g.*, standard operating procedures (SOP's), plans, corporate policies should not be included in the EA.**

11. Alternatives to the Proposed Action

If no potential adverse environmental impacts have been identified for the proposed action, the EA should so state. If potential adverse environmental impacts have been identified for the proposed action, the EA should contain a detailed description of the environmental impact of all reasonable alternatives to the proposed action (including no action, and including measures that FDA or another government agency could undertake as well as those the applicant/petitioner would undertake). The EA should include a description of those alternatives that will enhance the quality of the environment and avoid some or all of the adverse environmental impacts of the proposed action. The environmental benefits and risks of the proposed action and the environmental benefits and risks of each alternative should be discussed.

12. List of Preparers

The EA should include the name, job title, and qualifications (*e.g.,* educational degrees) of those persons preparing the assessment, and should identify any persons or agencies consulted. Contract testing laboratories should be included in the list of consultants, although this may be included in a confidential appendix. ***Curriculum vitae* may be included in lieu of a description of an individual's qualifications, but are not necessary.**

13. Certification

A dated certification should be signed by the responsible official, include the official's title. The following language is recommended:

> "The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of the firm or agency responsible for preparation of the EA.
>
> The undersigned official certifies that the EA summary document (pages x-x) and Appendices x-x (pages x-x) contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR § 1506.6."

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The applicant is responsible for the contents of the EA and for signing the certification, whether or not a consultant was used to prepare the EA. The certification should not predate the EA.

14. References

The EA should include a list of citations for all referenced material and standard test methods used in generating data in support of the EA. Copies of referenced articles not generally available which are used to support specific claims in the EA document should be attached in a non-confidential appendix.

15. Appendices

Both confidential and non-confidential appendices may be included (see section III.G for additional information about treatment of confidential information). A list of the appendices should be included in the EA summary document with a designation of confidential or non-confidential following each of the listings. Typically, the non-confidential appendices include Material Safety Data Sheet(s), certification and compliance statements, data summary tables, and copies of referenced articles that are not generally available or which were used in support of specific claims in the EA. Proprietary/confidential information such as emissions or identification of contract facilities and test reports should be included in the confidential appendices.

E. Data Summary Table

To facilitate review, the EA should include a data summary table in a non-confidential appendix (EA format item 15). Attachment C provides an example of a suitable data summary table. Results should not be needed for all items listed if a tiered approach to determining the environmental fate and effects of compounds is used. The table should be modified as appropriate.

F. Test Methods and Report Formats

Test methods and report formats are provided in the FDA EA Technical Assistance Handbook. Equivalent tests, such as those provided by the EPA (40 CFR §§ 796 and 797), the Organisation for Economic Co-operation and Development (OECD) or other validated, peer reviewed methods may be used. The expected minimum level of test performance and test reporting for studies performed to fulfill the requirements of EA format item 7 (fate) is the standards of good scientific practice. The reports submitted in support of fate testing (EA format item 7) should include a description of the test method sufficient for a reviewer to determine the scientific merit of the methodology. The expected minimum level of test performance and test reporting for studies performed to fulfill the requirements of EA format item 8 (effects) is the standards of

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FDA's Good Laboratory Practice (GLP) regulations. Guidance on test reporting formats is included in the FDA EA Technical Assistance Handbook or 40 CFR §§ 796 and 797. **Raw test data (*e.g.*, copies of notebook pages, HPLC chromatograms for each assay) should not be included in the EA.**

G. Confidential/Non-Confidential Information

Some of the information that is submitted in an EA is available elsewhere in an application or in a publicly available document. This information may be cross-referenced in the EA, if the information is publicly available. However, the EA should be a stand-alone document, summarizing information that is available elsewhere. The EA will be made public by the FDA as required by regulations issued by the Council on Environmental Quality. Therefore, the EA should contain three distinct parts: 1) the EA summary document which is non-confidential; 2) non-confidential appendices; and 3) appendices with confidential information used to support the EA. All confidential appendices should be at the end of the environmental assessment document. References to non-confidential and confidential appendices may be included in the EA summary document, as appropriate. Confidential data and information which are pertinent to the environmental review of a proposed action and which are submitted in confidential appendices should be summarized in the EA summary document to the extent possible. The EA summary document, non-confidential appendices and FONSI are normally made available for public inspection.

Attachment D provides general guidance as to which information may be included in confidential appendices of the EA. It is the applicant's responsibility to clearly identify the information in the EA which it believes is confidential.

IV. EA'S INVOLVING BIOTECHNOLOGY PRODUCTS

Actions for drugs derived from biotechnology products raise specific concerns regarding the release into the environment of genetically modified microorganisms and cells (*e.g.,* rDNA, bacteria, yeast and plant and animal cells), and fermentation and tissue culture waste media. The EA should: 1) clearly identify that the action involves the use of such materials (EA format item 4.a); 2) describe the biological production system including the host microorganism or cell line and genetic construct(s) (EA format item 5); 3) where appropriate, describe the physical containment and procedures used to prevent release of these materials to the environment as well as relate the containment level to that recommended in the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant

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DNA Molecules (*e.g.,* 59 FR 34496, 59 FR 40170, 60 FR 20726) which provides guidance for both research and large scale (Good Large Scale Practices-GLSP) use of organisms containing recombinant DNA molecules (EA format item 6.b);
4) include a description and validation report of the process used to inactivate these materials prior to their release into the environment (EA format item 6.b); 5) discuss the mitigation measures to be taken if the production organism becomes contaminated with other biological agents (*e.g.,* virus, prions, mycoplasma, bacteria, fungi) during production (EA format item 10); and 6) discuss the environmental fate and effect of both the active and inactivated materials if they are to be released into the environment (EA format items 7 and 8).

The discussion for actions involving genetically modified microorganisms and cells should focus on their survivability and colonization potential in the environment and their ability to transfer some or all parts of their genetic material to indigenous organisms. If live microorganisms or cells may be released post-activation or as a result of accidental release during production, studies should be performed to adequately characterize these attributes. The fate of other potentially harmful components (*e.g.,* bacterial toxins) from the genetically modified microorganisms or cells after their release into the environment should be addressed.

V. EA'S INVOLVING DRUGS DERIVED FROM NATURAL RESOURCES

Under the U.S. Endangered Species Act (ESA), Congress declared, "the United States has pledged itself as a sovereign state in the international community to conserve to the extent practicable the various species of fish or wildlife and plants facing extinction, pursuant to the Convention on International Trade in Endangered Species of Wild Fauna and Flora" [CITES] (16 U.S.C. § 1531(a)(4)(F)). Identification as an endangered or threatened species does not preclude the use of material but may necessitate submission of additional information. Under the ESA, if a species has been determined to be endangered or threatened, a federal agency is required to consult with the Secretary of Interior or Commerce to ensure that the agency's actions are not likely to jeopardize the continued existence of threatened or endangered species or their critical habitats (16 U.S.C. § 1536).

When a drug substance, drug substance intermediate, or precursor is derived from a natural resource, the source should be identified. Pertinent information, such as geographic region of source or whether the resource is cultivated or harvested from the wild, should be provided in EA format item 9.a of the EA. In EA format item 9.b it should be specifically stated whether the natural resource is subject to the U.S. ESA/CITES. For natural resources covered under CITES, CDER may request copies of relevant permits.

WITHDRAWN

VI. FOREIGN MANUFACTURING FACILITIES

Executive Order 12114, "Environmental Effects Abroad of Major Federal Actions," directs FDA to consider the environmental effects of approving drug product applications on the environment outside the United Sates. The responsible company official at each of the foreign facilities should certify that the manufacturing facilities are: 1) in compliance with all local and national environmental laws; 2) in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and 3) that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws. The statement should be signed and dated by the responsible company official and, if not in English, a certified English translation should be provided. FDA will request additional information if such information is needed to evaluate environmental effects outside the U.S.

VII. DRUG MASTER FILES

CDER does not take action on DMF's, *i.e.,* CDER does not approve or disapprove submissions to a DMF (21 CFR § 314.420(a)). Therefore, NEPA does not apply and no environmental assessment needs to be submitted for a DMF. However, CDER does take action on applications that incorporate by reference information regarding the manufacture of the drug substance or proprietary drug substance intermediates that may be submitted in Type II DMF's. In these instances, the drug product applicant should include the environmental assessment information for the manufacture of drug substance or proprietary drug substance intermediates in the EA if an EA or AEA is required for their particular application. The DMF holder may be the drug product applicant or an independent manufacturer who may want to limit the applicant's access to proprietary manufacturing information. The non-confidential information regarding the manufacture of the drug substance or proprietary drug substance intermediates should be included in the EA summary document. A DMF reference may be provided for the information which is defined as confidential in this guide (*e.g.,* substances expected to be emitted, EA format item 6.a) although this information must be summarized to the extent possible and included in the EA for public release. CDER prefers that copies of confidential information from DMF's be submitted in the EA by the drug product applicant as a confidential appendix, whenever possible, to expedite review of the EA. If a letter of authorization is provided to reference confidential information in a DMF, the specific information which is being referenced, and the submission date and page number where the information can be located, should be identified. References to DMF's should be included in a confidential appendix since such references are considered confidential commercial information under FOIA.

VIII. REFERENCES

WITHDRAWN

A. Zeeman, M. and Gilford, J., "Ecological Hazard Evaluation and Risk Assessment Under EPA's Toxic Substances Control Act (TSCA): An Introduction," *Environmental Toxicology and Risk Assessment, ASTM STP 1179*, Wayne G. Landis, Jane S. Hughes, and Michael A. Lewis, Eds., American Society for Testing and Materials, Philadelphia, 1993, pp. 7-21.

B. Rand, Gary and Petrocelli, Sam., *Fundamentals of Aquatic Toxicology*, Hemisphere Publishing Corporation, 1987.

Submitted by:

_____

Nancy B. Sager
Acting Supervisor, Environmental Assessment Team

Approved by Director, Office of Pharmaceutical Science:

_____

Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

WITHDRAWN

ATTACHMENT A

FORMAT

AEA's:

Infrequent Use:

Complete EA format items 1 - 6 and 12 - 14. Documentation of EA format items 7 - 11 and 15 is ordinarily not required.

Naturally Occurring Substances:

Complete EA format items 1 - 6.d and 7.e - 15, while relying on available information for EA format items 7 and 8 (see 21 CFR § 25.31a(b)(5) for additional guidance).

Products Approved by EPA:

Complete EA format items 1 - 15, while relying on information in studies submitted to other federal or state agencies for items 7, 8 and 15 (see 21 CFR § 25.31a(b)(6) for additional guidance).

EA's: Generally, complete EA format items 1 - 15. If the Tier 0 approach is used, information in EA format items 7 - 11 and 15 may not be needed.

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EA FORMAT ITEMS 1-15

1. Date
2. Name of Applicant/Petitioner
3. Address
4. Description of Proposed Action
- **a. Requested Approval**
- **b. Need for Action**
- **c. Production Locations**
- **d. Locations of Use**
- **e. Disposal Sites**

5. Identification of Chemical Substances that are the Subject of the Proposed Action
- **a. Nomenclature**
  - **i. Established Name (U.S. Adopted Name - USAN)**
  - **ii. Brand/Proprietary Name**
  - **iii. Chemical Names**

(1) Chemical Abstracts (CA) Index Name
(2) Systematic Chemical Name

b. Chemical Abstracts Service (CAS) registration number
c. Molecular Formula
d. Molecular Weight
e. Structural (graphic) Formula
f. Physical Description
g. Additives
h. Impurities

6. Introduction of Substances into the Environment
a. Substances Expected to be Emitted
b. Controls Exercised
c. Citation of and Statement of Compliance with Applicable Emission Requirements
d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements
e. Expected Introduction Concentrations
i. Expected Introduction Concentration from Use
ii. Expected Introduction Concentration from Disposal

7. Fate of Emitted Substances in the Environment
(Note: the following are included in the text of the guidance as section III.D.7.d.i-v)
a. Identification of Substance(s) of Interest
b. Physical/Chemical Characterization
i. Water Solubility
ii. Dissociation Constant(s)
iii. Octanol/Water Partition Coefficient
iv. Vapor Pressure or Henry's Law Constant
c. Environmental Depletion Mechanisms
d. Expected Environmental Concentration (EEC)
e. Summary

8. Environmental Effects of Released Substances
9. Use of Resources and Energy
a. Natural Resources and Energy
b. Effect on Endangered or Threatened Species
c. Effect on Property Listed in or Eligible for Listing in the National Register of Historic Places
10. Mitigation Measures
11. Alternatives to the Proposed Action
12. List of Preparers
13. Certification
14. References

WITHDRAWN

15. Appendices

WITHDRAWN

ATTACHMENT B

SAMPLE EMISSION PERMIT TABLE

PERMITS FOR XXXX FACILITY			
EMISSION	AUTHORIZING AGENCY	PERMIT #	EXPIRATION DATE

WITHDRAWN

ATTACHMENT C

SAMPLE DATA SUMMARY TABLE

PHYSICAL/CHEMICAL CHARACTERIZATION	
Water Solubility[1]	
Dissociation Constant(s)	
Octanol/Water Partition Coefficient (Log K_{ow})[1]	
Vapor Pressure or Henry's Law Constant	
Sorption/Desorption (K_{oc})[1]	
DEPLETION MECHANISMS	
Hydrolysis	
Aerobic Biodegradation	
Soil Biodegradation	
Photolysis	
Metabolism	
ENVIRONMENTAL EFFECTS[2]	
Microbial Inhibition	
Acute Toxicity	
Chronic Toxicity	

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[1]Depending on dissociations constant(s), water solubility and octanol/water partition coefficient may have to be determined at pH 5 and 9, in addition to pH 7 or K_{oc} may have to be determined in acidic and/or alkaline soil in addition to neutral soil. See section III.D.7.d.ii for guidance.

[2]Identify organism(s) and report results, *e.g.,* NOEC, MIC, $EC_{50,}$ LC_{50} in ppm of active moiety.

ATTACHMENT D

CONFIDENTIAL/NON-CONFIDENTIAL

EA FORMAT ITEM	SUBSECTION	NON-CONFIDENTIAL	CONFIDENTIAL
1.Date	***	X	
2. Name of Applicant/Petitioner	***	X	
3. Address	***	X	
4. Description of Proposed Action	a. Requested Approval	X	
	b. Need for Action	X	
	c. Production Locations	* Names and addresses of facilities released under FOIA procedures	* Names and address of facilities excluded from public release under FOIA procedures
	d. Locations of Use	X	
	e. Disposal Sites	* Disposal method(s) * Statement regarding licensing/ permitting of disposal facilities	* Specific information regarding contract disposal companies/facilities

WITHDRAWN

ATTACHMENT D

CONFIDENTIAL/NON-CONFIDENTIAL

EA FORMAT ITEM	SUBSECTION	NON-CONFIDENTIAL	CONFIDENTIAL
5. Identification of Chemical Substances that are the Subject of the Proposed Action	a. Nomenclature	X	
	b. CAS Number	X	
	c. Molecular Formula	X	
	d. Molecular Weight	X	
	e. Structural Formula	X	
	f. Physical Description	X	
	g. Additives	* General discussion or reference to confidential appendix	* Specific information
	h. Impurities	* General discussion or reference to confidential appendix	* Specific information

WITHDRAWN

ATTACHMENT D

CONFIDENTIAL/NON-CONFIDENTIAL

EA FORMAT ITEM	SUBSECTION	NON-CONFIDENTIAL	CONFIDENTIAL
6. Introduction of Substances into the Environment	a. Substances Expected to be Emitted	* General discussion or reference to confidential appendix	* Specific information
	b. Controls Exercised	X	
	c. Citation/Statement of Compliance	* Citations * Signed statements for facilities released under FOIA procedures * General statements and reference to confidential appendix for facilities not released under FOIA procedures	* Signed statements for facilities excluded from release under FOIA procedures
	d. Effect of Approval on Compliance with Current Emission Requirements	X	
	e. Expected Introduction Concentrations	* Summary discussion	* Specific calculations * 5th year production estimates

WITHDRAWN

ATTACHMENT D

CONFIDENTIAL/NON-CONFIDENTIAL

EA FORMAT ITEM	SUBSECTION	NON-CONFIDENTIAL	CONFIDENTIAL
7. Fate of Emitted Substance in the Environment	a. Identification of Chemical Compounds of Interest	* Substances expected to enter or exist in the environment. * Summary discussion of toxicity/activity of predominant SRS's relative to the parent (active) compound	* Specific toxicology/ pharmacological activity data for SRS's
	b. Physical/ Chemical Characterization	* Test results	* Test reports
	c. Depletion Mechanisms	* Test results	* Test reports
	d. Expected Environmental Concentrations	* Summary discussion	* Specific information that would disclose production volumes
	e. Summary	X	
8. Environmental Effects of Released Substances	***	* Test results and summary discussion	Test reports

WITHDRAWN

ATTACHMENT D

CONFIDENTIAL/NON-CONFIDENTIAL

EA FORMAT ITEM	SUBSECTION	NON-CONFIDENTIAL	CONFIDENTIAL
9. Use of Resources and Energy	a. Natural Resources & Energy	X	
	b. Effect on Endangered or Threatened Species	X	
	c. Effect on Property Listed in or Eligible for Listing in the National Register of Historic Places	X	
10. Mitigation Measures	***	X	
11. Alternatives to the Proposed Action	***	X	
12. List of Preparers	***	X	
13. Certification	***	X	
14. References	***	X	

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ATTACHMENT D

CONFIDENTIAL/NON-CONFIDENTIAL

EA FORMAT ITEM	SUBSECTION	NON-CONFIDENTIAL	CONFIDENTIAL
15. Appendices	***	For example: * Material Safety Data Sheets * Certifications or statements of compliance from manufacturers that have been disclosed in the EA summary document * Referenced articles not generally available or which are used to support specific claims in the EA document * Data summary table	For example: * Confidential production information * Test reports * Identification of facilities that are considered confidential under FOIA procedures and any other information which would disclose this information (e.g., statement of compliance) * Letters of authorization to DMF's

WITHDRAWN

ATTACHMENT E

GLOSSARY OF TERMS

Active Moiety: The molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance (21 CFR § 314.108(a)). The active moiety is the entire molecule or ion, not the "active site."

Bioaccumulation: The process by which industrial waste, chemicals and other substances gradually accumulate in living tissue.

Bioconcentration: The process by which industrial waste, chemicals and other substances accumulate directly from water into and onto aquatic organisms.

Drug product: A finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more ingredients (21 CFR § 314.3(b)).

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR § 314.3(b)).

Expected environmental concentration (EEC): The expected concentration of the active moiety or other structurally related substance of interest that organisms would be exposed to in the environment (*e.g.,* surface water) after consideration of spatial or temporal concentration or depletion factors such as dilution, degradation, sorption, bioaccumulation. This is sometimes referred to as the predicted environmental concentration (PEC).

Expected introduction concentration (EIC) for disposal: The expected introduction concentration of the active moiety which may enter the environment due to disposal. Depletion mechanisms that occur prior to introduction into the environment may be considered in the calculation.

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Expected introduction concentration (EIC) for use: The expected introduction concentration, based on fifth year marketing estimates, of the active moiety which may enter the environment due to use. Depletion mechanisms that occur prior to introduction into the environment and human metabolism may be considered in the calculation.

Half-life ($t_{½}$): Time required to reduce by one-half the concentration of a material.

Lowest observed effect concentration (LOEC): The lowest concentration of a material used in a toxicity test that has a statistically significant adverse effect on the exposed population of the test organisms as compared with the controls.

Maximum expected environmental concentration (MEEC): The expected introduction concentration (EIC) or expected environmental concentration (EEC), whichever is greater.

Median effective concentration (EC_{50}): The concentration of material to which organisms are exposed that is estimated to be effective in producing some sublethal response in 50% of the test organisms. The EC_{50} is usually expressed as a time-dependent variable (*e.g.,* 24 hour EC_{50}).

Median lethal concentration (LC_{50}): The concentration of material to which organisms are exposed that is estimated to be lethal to 50% of the test organisms. The LC_{50} is usually expressed as a time-dependent variable (*e.g.,* 24 hour LC_{50}).

Minimum inhibitory concentration (MIC): The lowest concentration of a chemical that inhibits the visible growth of the test organisms.

No observed effect concentration (NOEC): The highest concentration of a material used in a toxicity test that has no statistically significant adverse effect on the exposed population of test organisms as compared with the controls.

Octanol/water partition coefficient (K_{ow}): The ratio of a chemical's solubility in n-octanol and water at equilibrium; also expressed as P. A measurement of a drug's lipophilicity and an indication of its ability to cross cell membranes. The logarithm of P or K_{ow} is used as an estimate of the tendency of the chemical to bioaccumulate or adsorb to soil or sediments.

Parts per billion (ppb): One unit of chemical (usually expressed as mass) per 1,000,000,000 (10^9) units of medium (*e.g.,* water) or organism (*e.g.,* tissue) in which it is contained. For water 1 µg/L = 1 ppb; for tissue 1 µg/kg = 1 ng/g = 1 ppb.

Parts per million (ppm): One unit of chemical (usually expressed as mass) per

WITHDRAWN

1,000,000 (10^6) units of medium (*e.g.,* water) or organism (*e.g.,* tissue) in which it is contained. For water 1 mg/L = 1 ppm; for tissue 1 mg/kg = 1 µg/g = 1 ppm.

Parts per trillion (pptr): One unit of chemical (usually expressed as mass) per 1,000,000,000,000 (10^{12}) units of medium (*e.g.,* water) or organism (*e.g.,* tissue) in which it is contained. For water 1 ng/L = 1 pptr; for tissue 1 ng/kg = 1 pptr.

Primary packaging operations: Manufacturing operations which result in the drug product being placed into the immediate container (*i.e.,* container which is in direct contact with the drug product).

Secondary packaging operations: All packaging operations other than the primary packaging operation.

Soil or sediment/water partition coefficient (K_{oc}): The ratio of chemical adsorbed per unit weight of organic carbon in soil or sediment to the concentration of the chemical in solution at equilibrium.

"Substance that occurs naturally in the environment": In the context of § 25.31a(b)(5) this refers to organic or inorganic drug substances, whether obtained from a natural resource or synthesized, that will exist in the environment in the same form as the substance found naturally in the flora, fauna, atmosphere, water or soil.

Toxicity: The inherent potential or capacity of a material to cause adverse effects in a living organism.

Type 1 NDA[2]**:** A new drug application (NDA) for a drug for which the active moiety (present as the unmodified base [parent] compound, or an ester or a salt, clathrate, or other noncovalent derivative of the base [parent] compound) has not been previously approved or marketed as the active moiety in the United States for use in a drug product, either as a single ingredient or as part of a combination product or as part of a mixture of stereoisomers.

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[2]For complete definitions of Type 1-7 NDA's see Center for Drug Evaluation and Research, Staff Manual Guide, 4820.3, “Drug Classification and Priority Review.”

Type 2 NDA: A new drug application (NDA) for a drug for which the active moiety has been previously approved or marketed in the United States but for which the particular ester, or salt, clathrate, or other noncovalent derivative or unmodified base (parent) compound has not yet been approved or marketed in the United States, either as a single ingredient, part of a combination product, or part of a mixture of stereoisomers.

Type 3 NDA: A new drug application (NDA) for a new dosage form or formulation, including a new strength, where the drug has already been approved or marketed in the United States by the same or another manufacturer. The indication may be the same as that of the already marketed drug product or may be new.

Type 4 NDA: A new drug application (NDA) for a drug product containing two or more active moieties that have not been previously approved or marketed together in a drug product by any manufacturer in the United States. The new product may be a physical or a chemical (ester or non-covalent) combination of two or more active moieties.

Type 5 NDA: A new drug application (NDA) for a drug product that duplicates a drug product already approved or marketed in the United States by another firm.

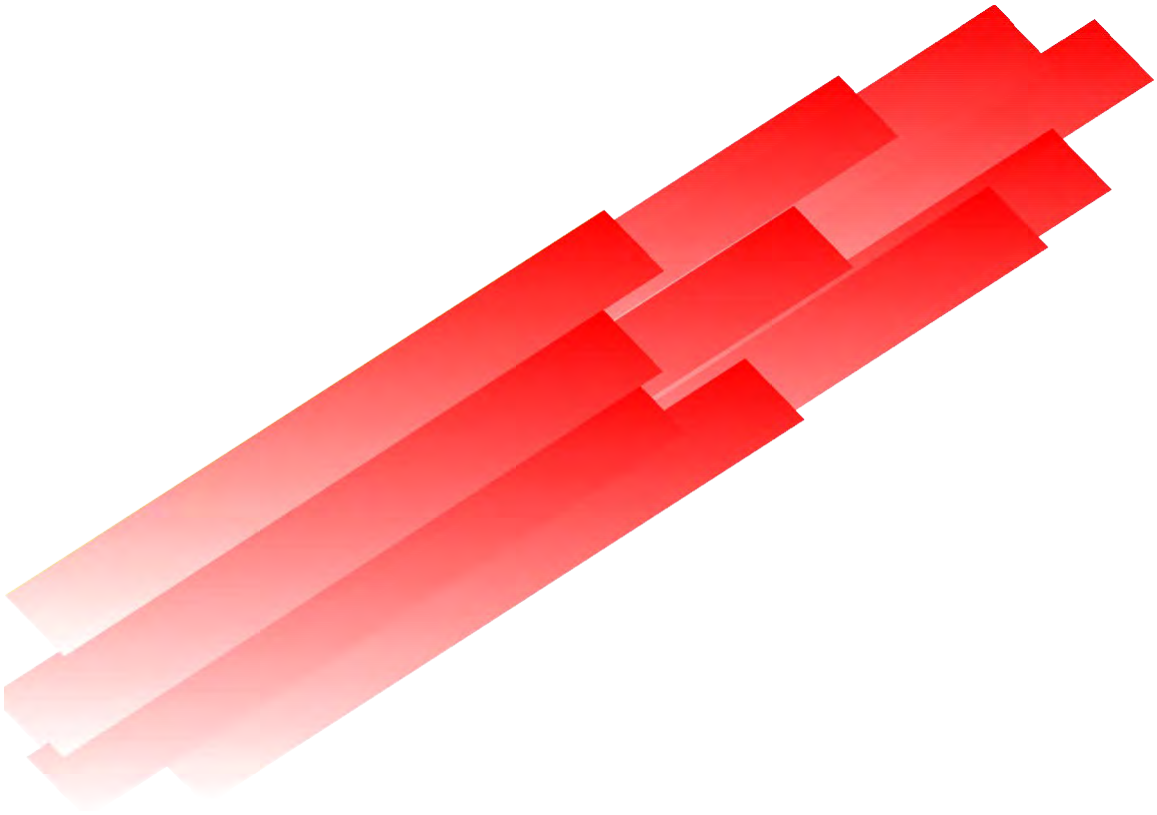
Type 6 NDA: A new drug application (NDA) for a drug product that duplicates a drug product (same active moiety, same salt, same formulation, or same combination) already approved or marketed in the United States by the same or another firm except that it provides for a new indication.

Type 7 NDA: The first new drug application (NDA) for a drug product containing one or more drugs marketed at the time of application or in the past without an approved NDA.

WITHDRAWN

Guidance for Industry

Environmental Assessment of Human Drug and Biologics Applications



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
July 1998
CMC 6
Revision 1

Guidance for Industry

Environmental Assessment of Human Drug and Biologics Applications

Copies of this guidance are available from the Office of Training and Communications, Division of Communications Management, Drug Information Branch, HFD-210, 5600 Fishers Lane, Rockville, MD 20857 (Phone 301-827-4573) or from the Internet at http://www.fda.gov/cder/guidance/index.htm.

Copies also are available from the Office of Communication, Training and Manufacturers Assistance, HFM-40, CBER, FDA, 1401 Rockville Pike, Rockville, MD 20852-1448, or from the Internet at http://www.fda.gov/cber/guidelines.htm. Copies also may be obtained by fax from 1-888-CBERFAX or 301-827-3844 or from Voice Information at 800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
July 1998
CMC 6
Revision 1

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GUIDANCE FOR INDUSTRY[1]

Environmental Assessment of Human Drug and Biologics Applications

I. INTRODUCTION

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impacts of their actions and to ensure that the interested and affected public is informed of environmental analyses. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impacts of approving drug and biologics applications as an integral part of its regulatory process. FDA's regulations in 21 CFR part 25 specify that environmental assessments (EAs) must be submitted as part of certain new drug applications (NDAs), abbreviated applications, applications for marketing approval of a biologic product, supplements to such applications, investigational new drug applications (INDs) and for various other actions (see 21 CFR 25.20), unless the action qualifies for categorical exclusion.

Under the President's reinventing government (REGO) initiatives, announced in April 1995, FDA reevaluated and revised its environmental regulations to reduce the number of EAs required to be submitted by industry and, consequently, the number of findings of no significant impact (FONSIs) prepared by the Agency under NEPA. FDA issued for public comment a notice of proposed rulemaking on April 3, 1996 (61 FR 14922) (republished May 1, 1996 (61 FR 19476)), that proposed additional categorical exclusions for those actions that have been identified as normally not having a significant effect, individually or cumulatively, on the quality of the human environment. The final rule was published on July 29, 1997 (62 FR 40569), and became effective August 28, 1997. All applications or petitions requesting Agency action (e.g., NDAs, abbreviated new drug applications (ANDAs), INDs, biologics license applications (BLAs), supplements to such applications) must be accompanied by either an EA or a claim of categorical exclusion. Failure to provide (1) a claim of categorical exclusion or (2) an adequate EA, is sufficient grounds for ***refusing to file or approve*** the application (21 CFR 314.101(d)(4), 601.2(a) and (c), and 25.15(a)). An EA that is adequate for filing is one that addresses the relevant environmental issues. An EA adequate for approval is one that contains sufficient information to enable the Agency to determine whether the proposed action may affect significantly the quality of the human environment. This guidance provides information on when an EA should be submitted; it also makes recommendations on how to prepare EAs for submission of drug or biologics applications to the Center for Drug Evaluation and Research (CDER) and the Center for

[1] This guidance has been prepared under the direction of the Chemistry Manufacturing Controls Coordinating Committee, Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on environmental assessments. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Biologics Evaluation and Research (CBER). Topics covered include (1) when categorical exclusions apply, (2) when to submit an EA, (3) the content and format of EAs, (4) specific guidance for the environmental issues that are most likely to be associated with human drugs and biologics, (5) test methods, (6) an applicant's treatment of confidential information submitted in support of an EA, and (7) master files for drugs and biologics.

This guidance, which is based on the July 1997 final rule, will remain in effect until superseded by new regulations or new guidance. The guidance is intended to supersede CDER's *Guidance for Industry For the Submission of an Environmental Assessment in Human Drug Applications and Supplements,* which was published in November 1995. Information in this guidance, along with information in the Code of Federal Regulations (CFR) at 21 CFR part 25 and 40 CFR parts 1500-1508 and the FDA *Environmental Assessment Technical Handbook* (NTIS Publication Number PB 87 175345/AS), which provides information on acceptable test methods, represents the core information available from CDER and CBER to assist industry in preparing an EA.

II. WHAT TYPES OF ACTIONS ARE SUBJECT TO CATEGORICAL EXCLUSION?

Certain classes of actions are subject to categorical exclusion and, therefore, ordinarily do not require the preparation of an EA because, as a class, these actions, individually or cumulatively, do not significantly affect the quality of the human environment (21 CFR 25.5(c)). However, as required under 21 CFR 25.21 and 40 CFR 1508.4, FDA will require "at least an EA" for any specific action that ordinarily would be excluded if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment.[2] See section III.C for additional information regarding extraordinary circumstances.

Submissions to CDER or CBER that ordinarily are excluded categorically under the regulations include actions on (1) NDAs, abbreviated applications, applications for marketing approval of a biologic product, and supplements to such applications if FDA's approval of the application does not increase the use of the active moiety; (2) NDAs, abbreviated applications, and supplements to such applications if FDA's approval of the application increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb); (3) NDAs, abbreviated applications, applications for marketing approval of a biologic product, and supplements to such applications for substances that occur naturally in the environment when the approval of the application does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment; (4) INDs; and (5) applications for marketing approval of a biologic product for transfusable human blood or blood components and plasma. An applicant is eligible

[2] Regulations would require an EIS (environmental impact statement) when "evaluation of data or information in an EA or otherwise available to the agency leads to a finding by the responsible agency official that a proposed action may significantly affect the quality of the human environment (21 CFR 25.22(b)).

to file a claim of categorical exclusion from the requirement to submit an EA if the action meets the criteria of at least one categorical exclusion.

A person submitting an application or petition of a type subject to categorical exclusion under 21 CFR 25.31 is not required to submit an EA if the person states that the action requested qualifies for categorical exclusion, citing the particular categorical exclusion that is claimed, and states that to the applicant's knowledge, no extraordinary circumstances exist (21 CFR 25.15(d)). An applicant ordinarily need not provide data to demonstrate that the action qualifies for categorical exclusion. CDER and CBER can rely on other information submitted in an application to evaluate the appropriateness of a claim for categorical exclusion. In the limited instances when it may be necessary, CDER or CBER will request additional information as needed to establish to their satisfaction that the criteria for categorical exclusion have been met.

III. WHEN IS AN EA REQUIRED?

Preparation of an environmental assessment ordinarily is required unless the proposed action qualifies for an exclusion under 21 CFR 25.30 or 25.31. An EA would also be required if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment (21 CFR 25.21).

Detailed information is provided below for the most common situations when actions would not qualify for categorical exclusion.

A. NDAs, Abbreviated Applications, and Supplements

Note: Section 1, below, should be used to assess increased use of a biological product as referenced in 21 CFR 25.31(a). Section 2 does not apply to biologics license applications (BLAs) because BLAs are not included in the categorical exclusion on which this section is based (21 CFR 25.31(b)). BLAs should be evaluated for whether they are eligible for categorical exclusion using 21 CFR 25.31(a) or (c) or other appropriate categorical exclusions found in 21 CFR 25.30 and 25.31.

NDAs, abbreviated applications, and supplements to such applications would not qualify for categorical exclusion if FDA's approval of the application increases the use of the active moiety ***and*** the estimated concentration of the substance at the point of entry into the aquatic environment will be 1 ppb or greater.

1. Increased Use

Increased use of an active moiety may occur if the drug will be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect, or if the drug is a new molecular entity. The term *use* also encompasses disposal of FDA-regulated articles by consumers.

Attachment A contains examples of actions that would not be considered to increase the use of a drug and Attachment B contains examples of actions that would be considered to increase the use of a drug or biologic. These lists are not inclusive. An applicant is encouraged to contact the appropriate Center if any questions arise as to whether a particular action is considered to increase the use of a drug or biologic.

2. Estimating the Concentration of a Substance at the Point of Entry into the Aquatic Environment

The expected introduction concentration (EIC) of an active moiety into the aquatic environment should be calculated as follows:

EIC-Aquatic (ppb) = A x B x C x D where

A = kg/year produced for direct use (as active moiety)
B = 1/liters per day entering POTWs*
C = year/365 days
D = 10^9 µg/kg (conversion factor)

* 1.214 x 10^{11} liters per day entering publicly owned treatment works (POTWs), Source: *1996 Needs Survey, Report to Congress.* Information regarding the *Needs Survey* is available on the Internet at http://www.epa.gov/owm. It is updated periodically.

This calculation assumes:

- All drug products produced in a year are used and enter the publicly owned treatment works (POTW) system.

- Drug product usage occurs throughout the United States in proportion to the population and amount of waste water generated.

- There is no metabolism.

The estimate of the kilogram/year active moiety should be based on or include (1) the highest quantity of the active moiety expected to be produced for direct use in any of the next five years. *Produced for direct use* means the quantity intended for use in humans during a given year (i.e., excludes any quantity produced for inventory buildup), (2) the quantity used in all dosage forms and strengths included in the application, and (3) the quantity used in an applicant's related applications. Related applications include those for other dosage forms using the same active moiety and for products using different forms of the active moiety (e.g., level of hydration, salt, free acid/base). All concentrations should be reported as the

concentration of active moiety, rather than the salt or complex.

The calculation of the expected introduction concentration (EIC) of an active moiety entering into the aquatic environment from patient use can consider the extent of metabolism of the active moiety to less pharmacologically active or inactive compounds, if that information is available. The pharmacological activity of metabolites relative to the active moiety should be considered when calculating the EIC. The weighted contribution of the metabolite to the EIC should be calculated (e.g., kg/year active moiety x 10% x 0.5 for a metabolite found at a level of 10% and that has half the pharmacological activity of the active moiety). If the pharmacological activity of the metabolite is unknown, it can be assumed to be the same as the active moiety.

An alternative calculation should be used if the drug product is intended for use in a specific geographic location (e.g., use an alternative value for the amount of liters per day entering POTWs — term B in the EIC calculation above). Moreover, if an alternative calculation is used to estimate localized use, or for any other reason, the calculation and the source and basis for the alternative calculation should be provided when filing an EA or a claim of categorical exclusion and would be subject to review.

B. Applications for Substances that Occur Naturally in the Environment

NDAs, abbreviated applications, applications for marketing approval of a biologic product and supplements to such applications for substances that occur naturally in the environment would not qualify for categorical exclusion under 21 CFR 25.31(c) when FDA's approval of the application alters significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. This might be the case when the use and disposal occur in a geographic area where the substance does not naturally occur. However, the application may be eligible for a categorical exclusion under other provisions in 21 CFR 25.31.

In addition to drug and biologic products derived from natural sources or from biological systems, substances can be considered naturally occurring even if they are chemically synthesized. The Agency will consider the form in which the FDA-regulated article will exist in the environment when determining whether the drug or biologic is a naturally occurring substance. For example, a modified active moiety (e.g., salt) that does not occur naturally could be considered a naturally occurring substance if it is established that, in vivo and in the environment, the active moiety exists in a form that is found naturally.

Biological and biotechnological products will be similarly evaluated. For example, a protein or DNA comprising naturally occurring amino acids or nucleosides, but having a sequence different from that of a naturally occurring substance, will normally qualify as a

naturally occurring substance after consideration of metabolism. The same principle would apply to synthetic peptides and oligonucleotides and living and dead cells and organisms. CDER and CBER may rely on other information submitted in an application (e.g., information about metabolism, excretion, and stability; viability (if applicable); and physical and/or chemical characteristics of the product) in determining whether the FDA-regulated article would be considered a naturally occurring substance.

CDER and CBER will evaluate on a case-by-case basis the appropriateness of categorical exclusions claiming that the quantity of the naturally occurring substance that is expected to enter the environment as a result of an action will not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

C. Extraordinary Circumstances

As stated in 21 CFR 25.21 and 40 CFR 1508.4, FDA will require at least an EA for any specific action that ordinarily would be categorically excluded if extraordinary circumstances indicate that the specific proposed action could significantly affect the quality of the human environment. Extraordinary circumstance can be shown by data available either to the Agency or the applicant and can be based on the production, use, or disposal from use of the FDA-regulated article. Data available to the Agency can include public information, information submitted in the application, and data available to the Agency on the same or similar products.

1. Actions for which available data establish that there is a potential for serious harm to the environment at the expected level of exposure.

FDA considers harm to the environment to include not only toxicity to environmental organisms but also environmental effects other than toxicity, such as lasting effects on ecological community dynamics.

2. Actions that adversely affect a species or the critical habitat of a species determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora to be endangered or threatened, or wild fauna or flora that are entitled to special protection under some other Federal law.

Actions that adversely affect a species or the critical habitat of a species determined under the Endangered Species Act to be endangered or threatened, wild fauna or flora listed in the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), or wild fauna or flora that are entitled to special protection under some other Federal law or international treaty to which the United States is a party would be considered an extraordinary circumstance, and an EA should be submitted unless there are specific exemptions relating to the

pharmaceutical substances or FDA action. An example of an exception would be when a species is afforded special protection under Federal law or international treaty, but the pharmaceutical is derived only from nonwild specimens. If nonwild specimens are exempted from Federal law or treaty, the action would be eligible for categorical exclusion as indicated in section III.C.3.a. Both direct effects (e.g., pharmaceuticals derived from fauna or flora, see section III.C.3) and indirect effects (e.g., adverse effects from manufacturing site emissions) should be considered.

Under the U.S. Endangered Species Act (ESA), Congress declared, "[T]he United States has pledged itself as a sovereign state in the international community to conserve to the extent practicable the various species of fish or wildlife and plants facing extinction, pursuant to the Convention on International Trade in Endangered Species of Wild Fauna and Flora" (16 U.S.C. 1531(a)(4)(F)). Identification as an endangered or threatened species does not preclude the use of such fauna or flora. However, under the ESA, if a species has been determined to be endangered or threatened, a Federal agency is required to consult with the Secretary of Interior or the Secretary of Commerce to ensure that the agency's actions are not likely to jeopardize the continued existence of endangered or threatened species or their critical habitats (16 U.S.C. 1536).

3. Use of Fauna or Flora

FDA intends to examine closely the proposed actions for FDA-regulated articles obtained from fauna and flora and will use the extraordinary circumstances provision to require an EA in any instance in which it appears from an examination of the proposed action that the action may jeopardize the continued existence of a species. The following sections discuss CDER's and CBER's current position on when the use of fauna or flora normally would constitute an extraordinary circumstance for which an EA should be submitted to support the application.[3]

a. Cultivated Specimens

Actions involving drug or biologic products derived from cultivated plants (e.g., plantation, nursery stock) or bred or domestic animals (e.g., laboratory breed, cows, pigs) are not normally considered an extraordinary circumstance that would require an EA for an action that is normally categorically excluded (see section III.C.2 for a possible exception).

b. Wild Specimens

[3] FDA may clarify the environmental information that must be submitted to the Agency in marketing applications for specific drug or biologic products derived from plants or animals (e.g., paclitaxel, 61 FR 58694).

i. NDAs, abbreviated applications, applications for marketing approval of a biologic product, or certain supplements to such applications.

NDAs, abbreviated applications and applications for marketing approval of a biologic product where the drug or biologic product is derived from plants or animals taken from the wild, supplements to such applications that relate to changes in the source of the wild biomass (e.g., species, geographic region where biomass is obtained), or supplements to such applications that are considered to increase the use of an active moiety or biologic substance (see Attachment B) and which will cause more harvesting than what was described in the original EA would be considered an extraordinary circumstance, and an EA should be submitted.

ii. INDs

INDs generally involve relatively small quantities of a drug or biologic product and treatment of a limited number of patients. Many INDs never result in the filing of an NDA or application for marketing approval of a biologic product, which would allow for the wide-spread commercial sale of the product. CDER and CBER will evaluate INDs on a case-by-case basis where the drug or biologic product is derived from wild plants or animals to determine whether the extraordinary circumstance provision in 21 CFR 25.21 is invoked.

To facilitate Center review, when submitting a claim of categorical exclusion for actions where the drug or biologic product is derived from plants or animals, CDER and CBER request that the applicant provide the following information with the claim, or specifically identify where the information can be located (e.g., page number of application): (1) biological identification (i.e., common names, synonyms, variety, species, genus and family); (2) a statement as to whether wild or cultivated specimens are used; (3) the geographic region (e.g., country, state, province) where the biomass is obtained; and (4) a statement indicating whether the species is (a) determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) to be endangered or threatened, (b) entitled to special protection under some other Federal law or international treaty to which the United States is a party, or (c) the critical habitat of a species that has been determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) or is entitled to

special protection under some other Federal law or international treaty to which the United States is a party. CDER and CBER will use this information to evaluate whether the claim of categorical exclusion is appropriate.

4. Production and Disposal Sites

FDA has found that regulated articles produced and disposed of in compliance with all applicable emission requirements do not significantly affect the environment and has determined it is unnecessary to review a company's compliance with Federal, State, and local environmental laws. In addition, both CDER and CBER routinely require as part of their safety evaluations that live organisms be inactivated following production and prior to release into the environment if there is a reasonable possibility that the living system may be harmful to the environment. Therefore, CDER and CBER will not routinely request submission of manufacturing and disposal information in an EA. However, if information available to the Agency or the applicant establishes that the general or specific emission requirements promulgated by Federal, State, or local environmental protection agencies do not address unique emission circumstances and the emissions may harm the environment, this would be sufficient grounds for requesting manufacturing or disposal information in an EA. Actions that threaten a violation of Federal, State, or local law or requirements imposed for the protection of the environment may constitute a significant impact (40 CFR 1508.27(b)(10)).

5. Significant Effects as Defined in 40 CFR 1508.27

The Council on Environmental Quality has provided a definition of "significantly" to aid in determining if an action may significantly affect the quality of the human environment. These examples should be considered when evaluating whether extraordinary circumstances exist that may warrant submission of at least an EA (See Attachment C).

IV. PREPARING AN EA FOR SUBMISSION TO CDER or CBER

A. Content and Format

This section describes the basic information that should be submitted in an EA if an EA is required. Attachment D contains an outline of the format for an EA. Alternative formats may be used, but the applicant should recognize that use of a standard format, such as described in this guidance, promotes efficiency in the review process.

1. Date

The EA should include the date the EA was originally prepared and the date(s) of any subsequent amendments.

2. Name of Applicant or Petitioner

The EA should identify the applicant who is submitting the application.

3. Address

The EA should contain the address where all correspondence is to be directed.

4. Description of Proposed Action

a. Requested Approval

The description of the requested approval should include the drug or biologic application number (if available), the drug or biologic product name, the dosage form and strength, and a brief description of the product packaging. For example, "XYZ Pharmaceuticals has filed an NDA pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADE NAME (established name), 250 mg and 500 mg, packaged in OHDPE bottles. An EA has been submitted pursuant to 21 CFR part 25."

b. Need for Action

The EA should briefly describe the drug's or biologic's intended uses in the diagnosis, cure, mitigation, treatment, or prevention of disease.

c. Locations of Use

The EA should identify the location(s) where the product will be used. Depending on the type of product and its use, the locations of use are typically identified as hospitals, clinics and/or patients in their homes. If use is expected to be concentrated in a particular geographic region, this fact should be included.

d. Disposal Sites

Unless other disposal methods by the end user are anticipated, it is sufficient to state that at U.S. hospitals, pharmacies, or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy, or clinic procedures and/or that in the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system, which may include landfills, incineration, and

recycling, although minimal quantities of the unused drug could be disposed of in the sewer system.

5. Identification of Substances that are the Subject the Proposed Action

The EA should contain information that allows for the accurate location of data about the substance in the scientific literature and for identification of closely related compounds. At a minimum, the information listed below should be provided, if available. For many biological products, format items 5.a.iii, b, c, and d will not apply. Other information, such as the international nonproprietary name (INN) or nonsystematic or semisystematic chemical names should be included if deemed useful in the identification of the compounds.

Usually this information need only be provided for the drug or biologic substance, but the same information also should be provided for the form of the active ingredient in the drug or biologic product if it is different from the drug or biologic substance (e.g., a salt formed in situ from a free base) or for a pharmacologically active related substance formed by conversion from a pharmacologically inactive parent compound (e.g., a prodrug product is converted to the pharmacologically active form).

a. Nomenclature

i. Established Name (U.S. Adopted Name-USAN)

ii. Brand/Proprietary Name/Tradename

iii. Chemical Names or Genus/Species of Biologic Product (e.g., virus)

- Chemical Abstracts (CA) Index Name (inverted form)
- Systematic Chemical Name (uninverted form)

b. Chemical Abstracts Service (CAS) registration number

c. Molecular Formula

d. Molecular Weight

e. Structural (graphic) Formula/Amino Acid Sequence

6. Environmental Issues

The type of information provided will vary depending on the environmental issues associated with the particular action. In general, the EA should include a succinct description of the environmental issues. The affected environment and the environmental effects and their significance should be discussed. Data and analyses to support the discussions should be provided as appropriate. Specific guidance is provided in section IV.B for the environmental issues that are most likely to be associated with human drugs and biologics. For environmental issues not specifically addressed in section IV.B (e.g., those included in sections III.C.4 and 5), applicants are encouraged to consult the appropriate Center prior to preparing the EA.

7. Mitigation Measures

Describe measures taken to avoid or mitigate any potential adverse environmental effects associated with the proposed action. If no adverse environmental effects have been identified, it should be so stated and indicated that, therefore, no mitigation measures are needed. See section IV.B.2.b for additional information regarding the discussion of mitigation measures for actions involving fauna and flora.

8. Alternatives to the Proposed Action

If no potential adverse environmental effects have been identified for the proposed action, the EA should state this. If potential adverse environmental effects have been identified for the proposed action, the EA "shall discuss any reasonable alternative course of action that offers less environmental risk or that is environmentally preferable to the proposed actions" (21 CFR 25.40(a)). The discussion should include the no-action alternative and measures that FDA or another government agency could undertake as well as those the applicant or petitioner would undertake. The EA should include a description of those alternatives that will enhance the quality of the environment and avoid some or all of the adverse environmental effects of the proposed action. The environmental benefits and risks of the proposed action and the environmental benefits and risks of each alternative should be discussed. See section IV.B.2.c for additional information regarding the discussion of alternatives for actions involving fauna and flora.

9. List of Preparers

The EA should include the name, job title, and qualifications (e.g., educational degrees) of those persons preparing the assessment and should identify any persons or agencies consulted. Contract testing laboratories should be included in the list of consultants, although this may be included in a confidential appendix. Curriculum vitae can be included in lieu of a description of an individual's

qualifications.

10. References

The EA should include a list of citations for all referenced material and standard test methods used in generating data in support of the EA. Copies of referenced articles that are not generally available and that are used to support specific claims in the EA document should be attached in a nonconfidential appendix.

11. Appendices

Both confidential and nonconfidential appendices can be included. See section IV.E for additional information about the treatment of confidential information. A list of the appendices should be included in the EA summary document with a designation of confidential or nonconfidential following each of the listings. Typically, the nonconfidential appendices include data summary tables and copies of referenced articles that are generally unavailable or that were used to support specific claims in the EA. Proprietary or confidential information, such as use estimates and test reports, should be included in the confidential appendices.

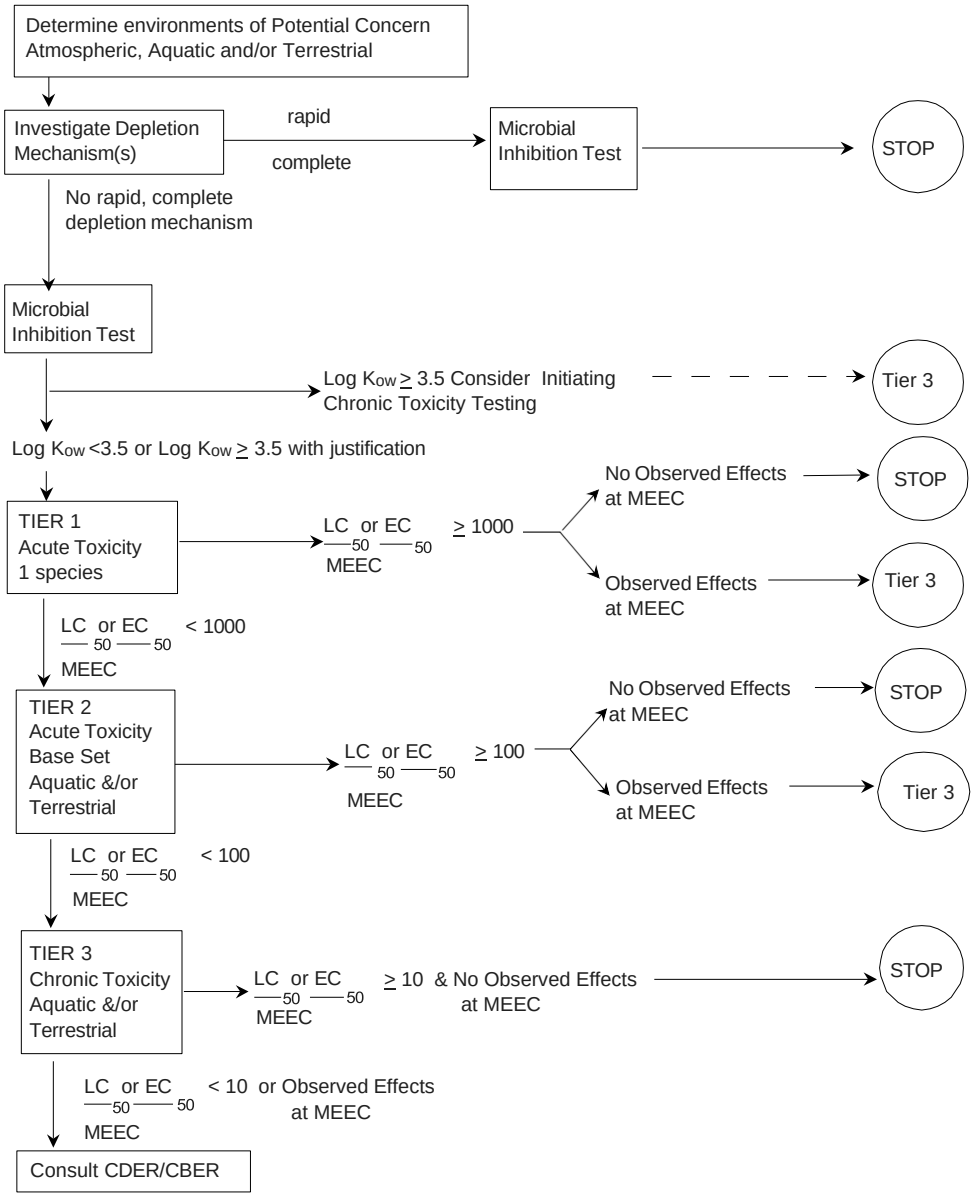
B. Specific Guidance — Environmental Issues

1. Assessing Toxicity to Environmental Organisms

If an EA is required, it normally should focus on characterizing the fate and effects of the compound of interest in the environment (1) when FDA's approval of the application increases the use of an active moiety and the estimated concentration of the active moiety at the point of entry into the aquatic environment is 1 ppb or greater (see section III.A); (2) when the substance occurs naturally in the environment and FDA's approval of the application alters significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment (see section III.B); or (3) in some cases, when data available to the Agency or applicant establish that at the expected level of exposure, there is the potential for serious harm to the environment (see section III.C.1). The provided information should focus on the fate and effects of the active moiety and/or structurally related substances (SRSs), rather than on excipients, for example.

The Centers encourage the use of a logical, tiered approach to testing so that adequate information is available to assess the potential environmental fate and effects of pharmaceuticals while minimizing the cost to industry. Figure 1 provides an illustration of a tiered approach. Alternative, scientifically justified approaches also can be used.

Figure 1
Tiered Approach to Fate and Effects Testing



Note: MEEC = EEC or EIC whichever is greater

Information submitted for fate and effects can include specific data generated on the test substance or relevant information on analogous compounds from the submitter or from peer-reviewed literature as appropriate. Actual experimental data regarding base parameters are generally preferable to computer modeling; however, in some circumstances computer modeling may be appropriate. FDA should be consulted if a company believes computer modeling is appropriate and wishes to use modeling in an EA.

a. Environmental Fate of Released Substances

i. Identification of Substances of Interest

The actual substances that will enter or exist in the environment (i.e., atmospheric, aquatic, terrestrial) can include the parent compound (i.e., drug or biologic substance) or SRSs such as the dissociated parent compound, metabolites, or degradants. The EA should list the drug or biologic substance and the predominant SRSs expected to enter or exist in the environment; provide the name, chemical structure and CAS number when possible; and provide a rationale for the decision as to which substance(s) will be studied. Predominant SRSs should be considered those greater than 10 percent of dose.

In most cases, fate (and effects) information should be provided on the parent (or active) drug or biologic substance, as representative of substances entering the environment. Such information is relevant to SRSs when the SRSs possess the same fundamental structure as the parent drug or biologic substance and are comparably or more polar. At a minimum, the EA should contain a discussion of the potential fate and effects of the predominant SRSs based on their structural differences and/or similarities to the parent compound (e.g., due to a functional group change, the metabolite should be more soluble than the parent compound, or the SRS is more polar). Computerized structure-activity relationship modeling programs may be useful in supporting extrapolation of fate and effects information from the parent (or active) drug or biologic substance to the SRS. Relevant available pharmacologic activity and toxicity information should be provided for the SRSs. Specific toxicity-activity information for SRSs may be included in a confidential appendix. Additional environmental information on a predominant SRS may be warranted, following consultation with the appropriate Center, if the fate of the compound is expected to differ from the parent compound, or there is an indication that the

SRSs effect on the environment would be substantially greater than from the parent drug or biologic substance.

ii. Physical and Chemical Characterization

The following tests should be conducted to determine if the compound is most likely to amass predominantly in aquatic, terrestrial, and/or atmospheric environments:

- Water Solubility
- Dissociation Constant(s)
- Octanol/Water Partition Coefficient
- Vapor Pressure or Henry's Law Constant

If there is a scientific basis for not performing a test, the justification should be included in the EA (e.g., water solubility was not determined because the compound is hydrolytically unstable). For a test compound that associates or dissociates in water, water solubility and the octanol/water partition coefficient may have to be determined at pH 5 and 9 as well as pH 7.

The octanol/water partition coefficient (K_{ow}) is an indicator of a nonionized compound's potential to adsorb to the organic fraction of soil, sediment, or biosolids (i.e., sludge) in addition to being an indicator of a compound's lipophilicity. It is not as good a predictor for inorganic chemicals, metal organic complexes, dissociating, ionic organic compounds, or compounds with other mitigating structural features such as molecular size. Further study of the sorption and/or desorption properties (K_{oc}) of a substance to biosolids should be considered if log K_{ow} is greater than 3 or other properties indicate that sorption or desorption may occur.

iii. Environmental Depletion Mechanisms

Depletion mechanisms should be investigated to determine if there is degradation of the compound in the environment(s) of interest. It is usually sufficient to provide basic supporting information that identifies the potential for a compound to be removed from the environment by a depletion mechanism (e.g., photolysis or hydrolysis based on information developed for analytical methods validation or from stability studies). It is unnecessary to go to

extraordinary effort to identify a depletion mechanism once the typical depletion mechanisms (i.e., hydrolysis, photolysis, biodegradation) have been investigated or to continue investigating other potential depletion mechanisms once one has been identified.

If the depletion mechanism is being used to reduce the expected introduction concentration or to eliminate effects testing, a formal, detailed analysis of the depletion mechanism should be provided (e.g., according to a standard test method, rate determination, analysis of expected exposure time in the environment).

Consideration should be given to the nature and extent of the degradation. If a rapid, complete depletion mechanism is identified (degradants are relatively simple, polar by-products), no testing to determine the environmental effects of the compound should be performed except for a microbial inhibition test or other appropriate test to assess the potential for the compound to disrupt waste treatment processes. Based on the estimated time prior to emission from a treatment facility, the following would be considered rapid depletion mechanisms:

Hydrolysis $t_{½}$ (pH 5-9):	:, 24 hours
Aerobic Biodegradation $t_{½}$:	:, 8 hours
Soil Biodegradation $t_{½}$:	:, 5 days

Direct and indirect photolysis, although significant under laboratory conditions, may not be as rapid a depletion mechanism in the environment due to significant variation in light intensity (e.g., related to weather, latitude, depth penetration) and duration of exposure. Efforts to characterize photolysis as a depletion mechanism should take these factors into consideration.

iv. Environmental Concentrations

Expected Introduction Concentration (EIC): The environmental introduction concentrations into those environments (i.e., aquatic, terrestrial, atmospheric) where the substance(s) of interest is most likely to amass (see section IV.B.1.a.ii) should be estimated. A method of calculating the expected introduction concentration of a substance into the aquatic environment is described in section III.A.2. The calculation of the expected introduction concentration (EIC) entering into the aquatic environment from patient use, in addition to considering metabolism as described in section III.A.1, may include consideration of the environmental depletion

mechanisms that occur in the waste treatment process (e.g., adsorption, degradation, hydrolysis), if the information is available (see section IV.B.1.a.iii).

Some drug or biologic substance and/or active moiety may enter the terrestrial environment when biosolids from waste water treatment facilities, which contain adsorbed material, are applied to land. Application of biosolids to land is subject to regulation by the Environmental Protection Agency (EPA) or an appropriate State authority. Biosolids are generally subjected to some form of aerobic or anaerobic digestion in the waste treatment facility. The EIC for the terrestrial compartment should be estimated if, based on the available physical or chemical properties of the compound, significant quantities of the active moiety are expected to adsorb to biosolids. The calculation used will depend on the typical treatment, disposal, and application processes. Currently, approximately 6.8 million tons of biosolids (dry basis) are generated per year with 54 percent of that quantity being applied to land. The remaining biosolids are incinerated, landfilled or disposed of by other means. Depletion mechanisms (e.g., biodegradation, hydrolysis) that occur in the waste treatment process can be considered when calculating the EIC for the terrestrial compartment, if the information is available. Additional information regarding land application of biosolids is available from EPA's Office of Wastewater Management (on the Internet at http://www.epa.gov/owm/bio.htm).

The concentration expected in the atmospheric compartment need not be routinely calculated for pharmaceutical products administered through inhalation because, for the majority of these, the active moiety or other compound of interest is not released into the air. However, the EIC should be considered for products that are released primarily into the air (e.g., medical gases).

CDER and CBER have defined *use* to encompass disposal of FDA-regulated articles by consumers. Normally, the EIC from disposal need not be calculated since the majority of pharmaceutical products will be totally consumed, and any residual waste will typically be disposed of in landfills or at incineration facilities that are regulated by the EPA or appropriate State agencies. These agencies have considered the environmental impacts from the operation of these facilities in their licensing process and require controls (e.g., scrubbers, lined landfills, migration tests) to limit the release of materials into the environment. The EIC for disposal

should be calculated if significant quantities of material are expected to be disposed of other than by landfill, incineration or other procedures regulated by the EPA or appropriate State agencies.

Expected Environmental Concentration (EEC): The expected environmental concentration (EEC), sometimes referred to as the *predicted environmental concentration* (PEC), is the concentration of the active moiety or other compound of interest that organisms would be exposed to in the environment (e.g., surface water) after consideration of, for example, spatial or temporal concentration or depletion factors such as dilution, degradation, sorption and/or bioaccumulation. Adjustments to the expected introduction concentration may be made, based on spatial and temporal concentration or depletion factors, to provide an expected environmental concentration. Supporting information and/or discussion should be provided to explain the factors used in calculating the expected environmental concentration. The concentration should be provided for each environmental compartment (aquatic, terrestrial, atmospheric) expected to be affected based on the physical and/or chemical characterization of the compound of interest. In the majority of cases, the EEC for the aquatic environment would be expected to be significantly less than the EIC for the aquatic environment due to dilution. Based on dilution factors for POTWs available from the EPA, applying a dilution factor of 10 to the EIC-aquatic to estimate the EEC-aquatic is normally appropriate.

v. Summary

A summary discussion of the environmental fate of the substance(s) of interest should be provided for each environmental compartment based on the information and data provided in the EA, and the environmental compartment(s) in which the substance is expected to predominantly amass should be identified. In some circumstances, transport between environmental compartments should be considered when determining the fate of the substance(s) of interest in the environment.

Aquatic Environment: In general, pharmaceutical substances are expected to enter predominantly into the aquatic environment and, therefore, the focus of any effects studies most likely will be on aquatic organisms. If the substance(s) of interest rapidly degrades (see section IV.B.1.a.iii) or adsorbs completely and irreversibly to

biosolids, then fate and effects in the aquatic environment should not usually be considered.

Terrestrial Environment: In general, substances enter the terrestrial environment predominantly from biosolids removed from waste water treatment plants that are subsequently applied to land. Therefore, effects on the terrestrial environment are more likely if a compound adsorbs to biosolids (see section IV.B.1.a.ii). Biosolids are generally subjected to some form of aerobic or anaerobic digestion in the waste treatment facility; only a fraction of the biosolids may be applied to land, while the remainder is incinerated or land filled. Fate and effects testing in the terrestrial environment should be considered if testing indicates that the substance(s) of interest will significantly adsorb to biosolids (e.g., K_{oc} ;„ 1000).

Atmospheric Environment: In general, substances that do not adsorb readily to soils, have a high vapor pressure, and have a low water solubility, are likely to volatilize significantly from the aquatic or terrestrial environments, although actual volatilization rates will depend on environmental conditions (e.g., dispersion away from the evaporation site) and on factors that can lessen or enhance the effective vapor pressure or behavior of the chemical at a liquid-air or solid-air interface. The atmospheric compartment may be of interest for medical gases. But, based on the polarity of the majority of compounds at relevant aquatic environmental conditions, it is unlikely that there would be substantive partitioning from the aquatic to the atmospheric environment for other pharmaceuticals. Any potential for a substance to volatilize and recycle into the aquatic or terrestrial environments should be discussed based on the information and data available for the substance.

b. Environmental Effects of Released Substances

Tiered approach to environmental effects testing (see below, Microbiological Inhibition Testing through Tier 3 Testing and Figure 1): If no rapid, complete depletion mechanism has been identified, it should be assumed that the compound will persist in the environment for some time and, therefore, the toxicity of the released substances to environmental organisms should be evaluated. The fate of the substance should be considered when designing the studies. For those compounds that enter the atmospheric environment, testing should be designed based on the extent to which the substance recycles into the aquatic or terrestrial environments. All toxicity test results for the drug or biologic substance

should be reported in terms of the quantity and/or concentration of the active moiety. When using this tiered approach to effects testing, it is important to design the test conditions appropriately so that a no-observed-effects concentration is determined.

Microbial Inhibition Testing: A microbial inhibition test or other appropriate test (e.g., respiration inhibition testing) should be performed to assess the substance(s) of interest's potential to inhibit microorganisms and subsequently disrupt waste treatment processes.

Assessment Factors: The assessment factors are intended to provide a consistent regulatory basis for determining when additional ecotoxicity testing should be performed (tiered approach). They are directly related to the amount of valid ecotoxicity data available. If the LC_{50} or EC_{50} or other appropriate test endpoint divided by the maximum expected environmental concentration (MEEC: EIC or EEC, whichever is greater) is less than the assessment factor, additional testing should be performed. The use of EC_{50} or test end point other than the LC_{50} should be limited to those test organisms for which the LC_{50} is not the test endpoint.

TEST TIER	ASSESSMENT FACTOR
1	1000 (see below)
2	100 (see below)
3	10 (see below)

Alternative scientifically justified approaches also can be used.

Tier 1 Testing: Acute ecotoxicity testing should be performed on a minimum of one suitable test organism (see base set for Tier 2 testing). If the EC_{50} or LC_{50} divided by the MEEC is greater than or equal to 1000, no further testing should be conducted unless sublethal effects are observed at the MEEC. If the EC_{50} or LC_{50} divided by the MEEC is less than 1000, Tier 2 testing should be performed. Sublethal effects (observed effects) at the MEEC indicate that chronic toxicity testing (Tier 3) should be performed. The use of the assessment factor of 100 could be used for Tier 1 testing if there is evidence (e.g., Tier 2 testing on a similar compound) to support that the single test organism used would be expected to be the most sensitive of the base set test organisms. If the compound is expected to partition to both the aquatic and terrestrial environments, usually testing of an aquatic test organism is sufficient since CDER has routinely observed lower toxicity results reported for aquatic test organisms as compared to terrestrial test organisms.

Tier 2 Testing: Acute ecotoxicity testing should be performed on the minimum base set of aquatic and/or terrestrial organisms. The aquatic base set usually consists of (1) a fish acute toxicity test, (2) an aquatic invertebrate acute toxicity test, and (3) an algal species bioassay. The terrestrial base set usually consists of (1) plant early growth tests, (2) earthworm toxicity tests, and (3) soil microbial toxicity tests. Usually only an earthworm toxicity study is indicated if the substance binds tightly to soil. A rodent acute toxicity is not included in the terrestrial base set since there is usually a significant quantity of mammalian (e.g., mouse, rat, dog, monkey, human) toxicity testing performed, both acute and chronic, to support the underlying applicacton and to demonstrate the safety of the drug or biologic product. Consultation with CDER or CBER is suggested prior to initiating any terrestrial studies.

If the EC_{50} or LC_{50} for the most sensitive organism in the base set divided by the MEEC is greater than or equal to 100, no further testing should be conducted unless sublethal effects are observed at the MEEC. If the EC_{50} or LC_{50} divided by the MEEC is less than 100, Tier 3 testing should be performed. Sublethal effects (observed effects) at the MEEC indicate that chronic toxicity testing (Tier 3) should be performed.

Tier 3 Testing: Chronic toxicity testing should be considered if the compound has the potential to bioaccumulate or bioconcentrate, if indicated based on Tier 1 and/or Tier 2 testing, or if there are other indications that the compound undergoes biotransformation to more toxic compounds.

Bioaccumulation, or bioconcentration, is a complex, dynamic process that depends on the availability, persistence, and physical and/or chemical properties of a compound in the environment. In general, pharmaceuticals tend not to be very lipophilic and are produced and/or used in relatively low quantities compared to industrial chemicals. In humans, the majority of pharmaceuticals are metabolized to some extent to SRSs that are more polar, less toxic, and less pharmacologically active than the parent compound. This suggests that there is a low potential for bioaccumulation or bioconcentration of pharmaceuticals; however, because of the length of time it takes to conduct chronic toxicity studies, applicants are encouraged to identify as early as possible compounds that are candidates for these studies.

A primary indicator of the potential for bioaccumulation is a compound's octanol/water partition coefficient (K_{ow}). A high octanol/water partition coefficient indicates that the compound will tend to be lipophilic. Chronic toxicity testing should be considered if log K_{ow} of a compound is greater

than or equal to 3.5 under relevant environmental conditions (e.g., pH 7), and a justification should be provided if chronic toxicity testing is not performed. Structural features (e.g., molecular size, polarity) that limit passage across biological membranes or the lack of bioavailability to environmental organisms (e.g., strong adsorption to soil) are mitigating factors that could be considered when determining if bioaccumulation (bioconcentration) would be a concern for compounds with a K_{ow} greater than or equal to 3.5. It may be important to obtain acute toxicity data for the organism to be tested to set the concentrations for the chronic studies properly. If the preparer of an EA is considering initiating chronic toxicity studies, consultation with CDER or CBER is recommended to ensure that such studies are appropriate and properly designed.

For chronic toxicity testing, if the EC_{50} or LC_{50} divided by the MEEC is greater than or equal to 10, no further testing should be conducted unless sublethal effects are observed at the MEEC. CDER or CBER should be consulted if the EC_{50} or LC_{50} divided by the MEEC is less than 10 or there are sublethal effects at the MEEC.

Test Methods and Test Organisms: Studies should be performed using test organisms and methods that have been identified by the FDA *Environmental Assessment Technical Handbook*, the EPA (40 CFR 797), the Organization for Economic Cooperation and Development (OECD), or other peer-reviewed literature, as appropriate, for use in environmental studies. If the drug or biologic product is intended to act upon an environmental organism (e.g., antiparasitic, antibiotic), information regarding the toxicity to the target organism(s) should be included.

c. Summary

A summary discussion of the environmental fate and effect of the substance(s) of interest should be provided. Discussion of the affected environments (aquatic, terrestrial, or atmospheric) should be included. The toxicity test results should be compared to the MEEC and the difference between the values discussed (e.g., in terms of the assessment factor, > 1000, > 100). It also may be appropriate to relate the toxicity test results to other estimated environmental concentrations (see section IV.B.1.a.iv).

2. Use of Fauna or Flora

If an EA is to be submitted for an action because the use of fauna or flora is the environmental issue (see section III.C.2 or 3), the EA should include specific information regarding the source of the fauna or flora, the mitigation measures associated with the harvesting of the resources, and a discussion of the reasonable

alternatives.

a. Use of Resources

Information relating to the source of the plant or animal, such as biological identification, government oversight of harvesting, geographic region where biomass is obtained, and harvesting methods and techniques should be included in the EA. The EA should include, but not be limited to, the following types of information:

- Biological identification (i.e., common names, synonyms, variety, species, genus, and family).
- A statement as to whether wild or cultivated specimens are used.
- The geographic region (e.g., country, state, province) where biomass is obtained and whether harvesting occurred on public or private land.
- A brief description of government oversight of the harvesting including, if applicable, the identity of the authority permitting harvesting and identity of authorities consulted regarding the harvesting. Submission of copies of permits or harvesting regulations relating to the specific species is helpful. For species covered under CITES, CDER or CBER could request copies of relevant permits.
- A brief description of the applicant's oversight of the harvesting.
- A statement indicating whether the species is (1) determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) to be endangered or threatened, (2) entitled to special protection under some other Federal law or international treaty to which the United States is a party, or (3) the critical habitat of a species that has been determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) or is entitled to special protection under some other Federal law or international treaty to which the United States is a party.
- A statement describing the part of plant or animal used and whether it is a renewable resource.

- A detailed description of the method of harvest including such information as the type of harvesting (e.g., clear cut, gleaning from timber stands destined for clear cutting, salvaging, pruning), frequency of harvest, whether the harvesting technique will affect the ecosystem (and if so, how), and whether the harvesting is conducted in accordance with government regulations or guidances (include citations to applicable regulations or guidances).

- Bulk weight or other appropriate measure of biomass needed to yield one kilogram of active moiety or biologic substance, the amount that has been harvested to date to support the proposed Agency action for the product, and the amount expected to be harvested in the future.

- The amount of biomass needed to produce the active moiety or biological substance used to treat the average patient. This should be provided in terms easy to understand (e.g., 2-3 trees per patient). The expected patient population and number of kilograms of active moiety or biologic substance needed per year should be provided.

- An estimate of the total number of plants or animals in the geographic region where the biomass is obtained.

- Any uses of the plant or animal other then for the proposed use (humans, food source, habitat for fauna).

- Plant or animal growth rate and/or life span and, if applicable, the rate of reproduction/regeneration.

- A discussion of whether the harvesting provides for sustained yield (e.g., percentage of sustainable harvest needed to supply annual needs based on the proposed use and any prior approved uses).

b. Mitigation Measures

Mitigation measures taken before (e.g., developing a process that uses a renewable part of a plant), during (e.g., limiting/selecting specimens to be harvested), and after harvesting (e.g., reforestation) should be included in the discussion of mitigation measures (see 40 CFR 1508.20).

c. Alternatives to the Proposed Action

A discussion must be provided of the reasonable alternatives that were considered when deciding which biomass source would be used to produce the active moiety or biologic substance (21 CFR 25.40(a)). All alternatives that were considered (e.g., other species, wild or cultivated sources, chemical synthesis) should be discussed. A brief discussion of the factors (e.g., environmental effects) that were considered in deciding whether or not the alternative would be used should be provided. The no-action (i.e., no approval) alternative should also be discussed. It should be indicated if any of the alternatives not currently used are planned for use in the future.

C. Data Summary Table

To facilitate review, the EA, if appropriate, should include a data summary table in a nonconfidential appendix (EA format item 11). Attachment E provides an example of a suitable data summary table.

D. Test Methods and Report Formats

Test methods and report formats are provided in the FDA *Environmental Assessment Technical Handbook*. Equivalent tests, such as those provided by the EPA (40 CFR 796 and 797), the Organization for Economic Cooperation and Development (OECD), or other validated, peer-reviewed methods can be used. Environmental fate studies should be compliant with either FDA's current Good Manufacturing Practice (cGMP) regulations (21 CFR 211.194) or FDA's Good Laboratory Practice (GLP) regulations (21 CFR part 58). The reports submitted in support of fate testing should include a description of the test method sufficient for a reviewer to determine the scientific merit of the methodology. Test performance and test reporting for environmental effects studies should meet FDA's GLP standards. Guidance on test reporting formats is included in the FDA *Environmental Assessment Technical Handbook* or 40 CFR parts 796 and 797. Raw test data (e.g., copies of notebook pages, HPLC chromatograms for each assay) should not be included in the EA.

E. Confidential and Nonconfidential Information

Some of the information that is submitted in an EA may be available elsewhere in an application or in a publicly available document. This information may be incorporated by reference in the EA (21 CFR 25.40(d)). However, the EA summary document, the document that contains the information recommended in section IV.A, should be a stand-alone document that contains a summary of the public information that is incorporated by reference and, to the extent possible, a summary of the confidential information that is either incorporated by reference or included in confidential appendices to the EA (21 CFR 25.51(a)). The EA will be made public by the FDA as required by regulations issued by

the Council on Environmental Quality. Therefore, the EA should contain, if appropriate, three distinct parts: (1) the EA summary document (see section IV.A), which is nonconfidential; (2) nonconfidential appendices; and (3) appendices with confidential information used to support the EA. Confidential data and information pertinent to the environmental review of a proposed action should be included in confidential appendices whenever possible to facilitate review of the EA. All confidential appendices should be at the end of the environmental assessment document. References to nonconfidential and confidential appendices may be included in the EA summary document, as appropriate. The EA summary document, nonconfidential appendices, and FONSI are made available for public inspection to the extent allowed by applicable laws (21 CFR 25.50(a) and (b)).

Attachment F provides general guidance as to which information can be included in confidential appendices of the EA. It is the applicant's responsibility to clearly identify the information in the EA that it believes is confidential.

F. Master Files for Drugs and Biologics

CDER and CBER do not take action on drug master files (DMFs) or master files (MFs) (i.e., they do not approve or disapprove submissions to a DMF (21 CFR 314.420(a)) or MF). Therefore, NEPA does not apply, and no EA needs to be submitted for a master file.

However, if an EA is required for the particular application, certain information that is included in a master file may be needed to address the relevant environmental issue(s). In these instances, the applicant seeking marketing approval should include the nonconfidential information in the EA summary document, rather than provide reference to the master file. The master file holder may be the applicant or an independent manufacturer who wants to limit the applicant's access to proprietary information. A master file reference may be provided for the confidential information, although this information must be summarized to the extent possible and included in the EA for public release. To expedite review of the EA, CDER and CBER prefer that copies of confidential information from master files be submitted in confidential appendices to the EA, whenever possible. If a letter of authorization is provided to reference confidential information in a master file, the specific type of information that is being referenced, the submission date, and page number where the information can be located should be stated. References to master files should be included in a confidential appendix since such references are considered confidential commercial information under the Freedom of Information Act (FOIA).

REFERENCES

1. FDA, "National Environmental Policy Act; Revision of Policies and Procedures; Final Rule," *Federal Register*, July 29, 1997 (62 FR 40569).

2. FDA, "National Environmental Policy Act; Proposed Revision of Policies and Procedures; Proposed Rule," *Federal Register*, April 3, 1996 (61 FR 14922); (republished May 1, 1996 (61 FR 19476)).

3. Rand, G., and S. Petrocelli, *Fundamentals of Aquatic Toxicology*, Hemisphere Publishing Corporation, 1987.

4. Zeeman, M., and J. Gilford, "Ecological Hazard Evaluation and Risk Assessment Under EPA's Toxic Substances Control Act (TSCA): An Introduction," *Environmental Toxicology and Risk Assessment, ASTM STP 1179*, Wayne G. Landis, Jane S. Hughes, and Michael A. Lewis, Eds., American Society for Testing and Materials, Philadelphia: 1993, pp. 7-21.

ATTACHMENT A: NO INCREASED USE

The following are types of actions that are not considered to result in increased use of an active moiety if approved by the Agency:

- Chemistry, manufacturing and control supplements (§§ 314.70, 601.12).
- Abbreviated applications.
- Lower doses than previously approved for the same indication (i.e., total daily dose).
- Shorter duration of use than previously approved for the same indication (e.g., number of days).
- Exclusion of a patient population in the labeling (e.g., by age, sex, complicating medical conditions).
- A prodrug for which the active metabolite is an approved product in the United States and which is intended to substitute directly[4] for that approved product. An active moiety which is the active metabolite of an approved prodrug in the United States would be considered similarly.
- New dosage forms that substitute directly for an approved product.
- Product reformulations in which the labeled amount of active moiety/biologic substance remains constant.
- Packaging changes/dosage form product line extensions that substitute directly for an approved product (e.g., new delivery system, addition of a different vial fill size).
- Combination drugs in which the single product substitutes directly for two approved products that would be administered separately.

[4] In context of Attachments A and B, substitute directly means that the drug or biologic product (i.e., active moiety or biologic substance) will be used for the same indication, at the same or lower dosage levels (i.e., total daily dose), and for the same or shorter duration of use (e.g., number of days) as previously approved by the Agency for the same active moiety or biologic substance.

ATTACHMENT B: INCREASED USE

The following are types of actions that are considered to result in increased use of an active moiety if approved by the Agency:

- New molecular entities.
- A new indication for a drug that was previously approved. This includes those actions requesting approval of off-label uses and switches from a second-line to first-line indication.
- R to OTC switches.
- Higher doses than were previously approved (i.e., total daily dose).
- Longer duration of use than previously approved (e.g., number of days).
- Inclusion of a patient population in the labeling that had previously been ***specifically excluded*** (e.g., by age, sex, complicating medical conditions).
- New dosage forms/routes of administration that increase the amount of active ingredient/biologic substance used. For example, the use of the active moiety or biologic substance for the same indication will normally increase if a switch is made from an injectable dosage form to an oral dosage form.

ATTACHMENT C: 40 CFR 1508.27

§ 1508.27 Significantly.

"Significantly" as used in NEPA requires considerations of both context and intensity:

(a) *Context.* This means that the significance of an action must be analyzed in several contexts such as society as a whole (human, national), the affected region, the affected interests, and the locality. Significance varies with the setting of the proposed action. For instance, in the case of a site-specific action, significance would usually depend upon the effects in the locale rather than in the world as a whole. Both short- and long-term effects are relevant.

(b) *Intensity.* This refers to the severity of impact. Responsible officials must bear in mind that more than one agency may make decisions about partial aspects of a major action. The following should be considered in evaluating intensity:

(1) Impacts that may be both beneficial and adverse. A significant effect may exist even if the Federal agency believes that on balance the effect will be beneficial.

(2) The degree to which the proposed action affects public health or safety.

(3) Unique characteristics of the geographic area such as proximity to historic or cultural resources, park lands, prime farmlands, wetlands, wild and scenic rivers, or ecologically critical areas.

(4) The degree to which the effects on the quality of the human environment are likely to be highly controversial.

(5) The degree to which the possible effects on the quality of the human environment are highly uncertain or involve unique or unknown risks.

(6) The degree to which the action may establish a precedent for future actions with significant effects or represents a decision in principle about a future consideration.

(7) Whether the action is related to other actions with individually insignificant but cumulatively significant impacts. Significance exists if it is reasonable to anticipate a cumulatively significant impact on the environment. Significance cannot be avoided by terming an action temporary or by breaking it down into small component parts.

(8) The degree to which the action may adversely affect districts, sites, highways, structures, or objects listed in or eligible for listing in the National Register of Historic Places or may cause loss or destruction of significant scientific, cultural, or historical resources.

(9) The degree to which the action may adversely affect an endangered or threatened species or its habitat that has been determined to be critical under the Endangered Species Act of 1973.

(10) Whether the action threatens a violation of Federal, State, or local law or requirements imposed for the protection of the environment.

ATTACHMENT D: EA FORMAT

1. **Date**
2. **Name of Applicant/Petitioner**
3. **Address**
4. **Description of Proposed Action**
   - a. **Requested Approval**
   - b. **Need for Action**
   - c. **Locations of Use**
   - d. **Disposal Sites**
5. **Identification of Substances that are the Subject of the Proposed Action**
   - a. **Nomenclature**
     - i. **Established Name (U.S. Adopted Name - USAN)**
     - ii. **Brand/Proprietary Name/Tradename**
     - iii. **Chemical Names or Genus/Species of Biologic Product (e.g., virus)**
       - **Chemical Abstracts (CA) Index Name**
       - **Systematic Chemical Name**
   - b. **Chemical Abstracts Service (CAS) Registration Number**
   - c. **Molecular Formula**
   - d. **Molecular Weight**
   - e. **Structural (graphic) Formula/Amino Acid Sequence**
6. **Environmental Issues**
7. **Mitigation Measures**
8. **Alternatives to the Proposed Action**
9. **List of Preparers**
10. **References**
11. **Appendices**

ATTACHMENT E: SAMPLE DATA SUMMARY TABLE

SAMPLE DATA SUMMARY TABLE	
PHYSICAL/CHEMICAL CHARACTERIZATION	
Water Solubility[1]	
Dissociation Constant(s)	
Log Octanol/Water Partition Coefficient (Log K_{ow})[1]	
Vapor Pressure or Henry's Law Constant	
Sorption/Desorption (K_{oc})[1]	
DEPLETION MECHANISMS	
Hydrolysis	
Aerobic Biodegradation	
Soil Biodegradation	
Photolysis	
Metabolism	
ENVIRONMENTAL EFFECTS[2]	
Microbial Inhibition	
Acute Toxicity	
Chronic Toxicity	

[1]Depending on dissociations constant(s), water solubility and octanol/water partition coefficient may have to be determined at pH 5 and 9, in addition to pH 7 or K_{oc} may have to be determined in acidic and/or alkaline soil in addition to neutral soil. See section IV.B.1.a.ii for guidance.

[2]Identify organism(s) and report results, e.g., NOEC, MIC, EC_{50}, LC_{50} in ppm of active moiety.

ATTACHMENT F: CONFIDENTIAL/NONCONFIDENTIAL

EA FORMAT ITEM	SUBSECTION	NONCONFIDENTIAL	CONFIDENTIAL
1.Date	***	X	
2. Name of Applicant/Petitioner	***	X	
3. Address	***	X	
4. Description of Proposed Action	a. Requested Approval	X	
	b. Need for Action	X	
	c. Locations of Use	X	
	d. Disposal Sites	X	
5. Identification of Substances that are the Subject of the Proposed Action	a. Nomenclature	X	
	b. CAS Number	X	
	c. Molecular Formula	X	
	d. Molecular Weight	X	
	e. Structural Formula	X	

EA FORMAT ITEM	SUBSECTION	NONCONFIDENTIAL	CONFIDENTIAL
6. Environmental Issue (Specific environmental issues identified in section IV.B)	a. Assessing Toxicity to Environmental Organisms	For example: * Substances expected to enter or exist in the environment. * Summary discussion of toxicity/activity of predominant SRSs relative to the parent (active) compound * Test results physical/chemical characterization * Method of calculating estimates of environmental concentration * Supporting information for spatial/temporal depletion factors * Environmental effects test results	For example: * Specific toxicology/ pharmacological activity data for SRSs * Test reports * Environmental concentration estimates
	b. Use of Fauna or Flora	For example: * Biological identification and other information relating to species used (e.g., plant growth rate) * Geographic region of the source * Government oversight * Method of harvesting	For example: * Bulk weight of biomass needed to produce a kg of active moiety * Amount harvested * The expected patient population and kg of active moiety expected to be used per year
7. Mitigation Measures	***	X	
8. Alternatives to the Proposed Action	***	X	
9. List of Preparers	***	X	

EA FORMAT ITEM	SUBSECTION	NONCONFIDENTIAL	CONFIDENTIAL
10. References	***	X	
11. Appendices	***	For example: * Referenced articles not generally available or which are used to support specific claims in the EA document * Data summary table	For example: * Estimates of the kg of active moiety to be used/year * Test reports * Letters of authorization to DMFs

ATTACHMENT G: GLOSSARY OF TERMS

Active Moiety: The molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance (21 CFR 314.108(a)). The active moiety is the entire molecule or ion, not the "active site."

Bioaccumulation: The process by which industrial waste, chemicals, and other substances gradually accumulate in living tissue.

Bioconcentration: The process by which industrial waste, chemicals, and other substances accumulate directly from water into and onto aquatic organisms.

Biological (biologic) product: Any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component, derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of a disease or condition of human beings (section 351 of the Public Health Service Act).

Biomass: The plant, plant part (e.g., bark, leaves, flower, seed), animal, or animal part (e.g., skin, liver, stomach) that is collected for processing into a drug or biologic.

Drug product: A finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more ingredients (21 CFR 314.3(b)).

Drug substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b)).

Expected environmental concentration (EEC): The expected concentration of the active moiety or other structurally related substance of interest that organisms would be exposed to in the environment (e.g., surface water) after consideration of spatial or temporal concentration or depletion factors such as dilution, degradation, sorption, bioaccumulation. This is sometimes referred to as the predicted environmental concentration (PEC).

Expected introduction concentration (EIC) for disposal: The expected introduction concentration of the active moiety that may enter the environment due to disposal. Depletion mechanisms that occur prior to introduction into the environment may be considered in the calculation as indicated in the text.

Expected introduction concentration (EIC) for use: The expected introduction concentration, based on fifth-year marketing estimates, of the active moiety that can enter the environment due to use. Depletion mechanisms that occur prior to introduction into the environment and human metabolism may be considered in the calculation as indicated in the text.

Half-life ($t_{½}$): Time required to reduce by one-half the concentration of a material.

Lowest observed effect concentration (LOEC): The lowest concentration of a material used in a toxicity test that has a statistically significant adverse effect on the exposed population of the test organisms as compared with the controls.

Master file: A submission of information to the FDA by a person who intends it to be referenced during the review of an application. See 21 CFR 314.420 for specific information on drug master files.

Maximum expected environmental concentration (MEEC): The expected introduction concentration (EIC) or expected environmental concentration (EEC), whichever is greater.

Median effective concentration (EC_{50}): The concentration of material to which organisms are exposed that is estimated to be effective in producing some sublethal response in 50 percent of the test organisms. The EC_{50} is usually expressed as a time-dependent variable (e.g., 24 hour EC_{50}).

Median lethal concentration (LC_{50}): The concentration of material to which organisms are exposed that is estimated to be lethal to 50 percent of the test organisms. The LC_{50} is usually expressed as a time-dependent variable (e.g., 24 hour LC_{50}).

Minimum inhibitory concentration (MIC): The lowest concentration of a chemical that inhibits the visible growth of the test organisms.

New molecular entity: An active moiety (present as the unmodified base [parent] compound, or an ester or a salt, clathrate, or other noncovalent derivative of the base [parent] compound) that has not been previously approved or marketed as the active moiety in the United States for use in a drug product, either as a single ingredient or as part of a combination product, or as part of a mixture of stereoisomers.

No observed effect concentration (NOEC): The highest concentration of a material used in a toxicity test that has no statistically significant adverse effect on the exposed population of test organisms as compared with the controls.

Octanol/water partition coefficient (K_{ow}): The ratio of a chemical's solubility in n-octanol and water at equilibrium; also expressed as P. A measurement of a drug's or biologic's lipophilicity and an indication of its ability to cross cell membranes. The logarithm of P or K_{ow} is used as an estimate of the tendency of the chemical to bioaccumulate or adsorb to soil or sediments.

Parts per billion (ppb): One unit of chemical (usually expressed as mass) per 1,000,000,000 (10^9) units of medium (e.g., water) or organism (e.g., tissue) in which it is contained. For water 1 µg/L = 1 ppb; for tissue 1 µg/kg = 1 ng/g = 1 ppb.

Parts per million (ppm): One unit of chemical (usually expressed as mass) per 1,000,000 (10^6) units of medium (e.g., water) or organism (e.g., tissue) in which it is contained. For water 1 mg/L = 1 ppm; for tissue 1 mg/kg = 1 µg/g = 1 ppm.

Parts per trillion (pptr): One unit of chemical (usually expressed as mass) per 1,000,000,000,000 (10^{12}) units of medium (e.g., water) or organism (e.g., tissue) in which it is contained. For water 1 ng/L = 1 pptr; for tissue 1 ng/kg = 1 pptr.

Soil or sediment/water partition coefficient (K_{oc}): The ratio of chemical adsorbed per unit weight of organic carbon in soil or sediment to the concentration of the chemical in solution at equilibrium.

Toxicity: The inherent potential or capacity of a material to cause adverse effects in a living organism.

Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

July 2024
Real-World Data/Real-World Evidence (RWD/RWE)

Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products

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Food and Drug Administration
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Center for Biologics Evaluation and Research (CBER)
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July 2024
Real-World Data/Real-World Evidence (RWD/RWE)

GBP-PET01211

Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products
Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION AND SCOPE

The 21st Century Cures Act (Cures Act),[2] signed into law on December 13, 2016, is intended to accelerate medical product development and bring innovations faster and more efficiently to the patients who need them. Among other provisions, the Cures Act added section 505F to the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355g). Pursuant to this section, FDA created a framework for a program to evaluate the potential use of real-world evidence (RWE) to help support the approval of a new indication for a drug[3] already approved under section 505(c) of the FD&C Act or help support or satisfy postapproval study requirements.

FDA is issuing this guidance as part of its RWE Program[4] and to satisfy, in part, the mandate under section 505F of the FD&C Act to issue guidance about the use of RWE in regulatory decision-making.[5] The RWE Program will cover clinical studies that use real-world data (RWD) sources, such as information from routine clinical practice, to derive RWE.

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) and Oncology Center for Excellence (OCE) at the Food and Drug Administration.

[2] Public Law 114-255.

[3] For the purposes of this guidance, all references to *drugs* include both human drugs and biological products. This guidance does not apply to medical devices. For information on medical devices, see the guidance for industry and FDA staff *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices* (August 2017). We update guidances periodically. For the most recent version of the guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] See *Framework for FDA's Real-World Evidence Program*, available at https://www.fda.gov/media/120060/download. The framework and RWE Program also cover biological products licensed under the Public Health Service Act.

[5] See section 505F(e) of the FD&C Act.

This guidance is intended to provide sponsors and other interested parties with considerations when proposing to use electronic health records (EHRs) or medical claims data[6] in clinical studies[7] to support a regulatory decision on effectiveness or safety of a drug.

For the purposes of this guidance, FDA defines RWD and RWE as follows:[8]

- RWD are data relating to patient health status or the delivery of health care routinely collected from a variety of sources.

- RWE is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Examples of RWD include data derived from EHRs, medical claims data, data from product and disease registries,[9] patient-generated data including from in-home use settings, and data gathered from other sources that can inform on health status, such as digital health technologies.[10] This guidance focuses on health-related data recorded by providers that can be extracted from two sources: EHRs and medical claims data. EHRs and medical claims data are types of electronic health care data that contain patient health information, and these data are widely used in safety studies and increasingly being proposed for use in effectiveness studies. EHRs and medical claims data can be considered as data sources in various clinical study designs.

This guidance discusses the following topics related to the potential use of EHR and medical claims data in clinical studies to support regulatory decisions:

(1) Selection of data sources that appropriately address the study question and sufficiently characterize study populations, exposure(s), outcome(s) of interest, and key covariates.

(2) Development and validation of definitions for study design elements (e.g., exposures, outcomes, covariates).

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[6] For purposes of this guidance, the term *medical claims data* (sometimes referred to as *administrative healthcare claims data*) refers to information submitted to insurers to receive payment for treatments (e.g., pharmacy claims data) and other interventions.

[7] For the purposes of this guidance, the term *clinical studies* refers to all study designs, including, but not limited to, interventional studies where the treatment is assigned by a protocol (e.g., randomized or single-arm trials, including those that use RWD as an external control arm) and non-interventional (observational) studies where treatment is determined in the course of routine clinical care (e.g., case-control or cohort studies). Throughout the guidance, FDA uses the terms *clinical studies*, *studies*, and *study* interchangeably.

[8] See *Framework for FDA's Real-World Evidence Program*, available at https://www.fda.gov/media/120060/download.

[9] For additional discussion, see the guidance for industry *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products* (December 2023).

[10] For additional discussion, see the guidance for industry, investigators, and other stakeholders *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* (December 2023).

(3) Data traceability[11] and quality during data accrual, data curation, and incorporation into the final study-specific dataset.

This guidance does not provide recommendations on choice of study design or type of statistical analysis, and it does not endorse any type of data source or study methodology. For all study designs, it is important to ensure the reliability and relevance of the data used to help support a regulatory decision. For the purposes of this guidance, the term *reliability* includes accuracy, completeness, and traceability. The term *relevance* includes the availability of data for key study variables (exposures, outcomes, covariates) and sufficient numbers of representative patients for the study.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The FDA guidance for industry and FDA staff *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data* (May 2013) focuses on the use of electronic health care data in pharmacoepidemiologic safety studies. The 2013 guidance includes recommendations for documenting the design, analysis, and results of pharmacoepidemiologic safety studies to optimize FDA's review of protocols and study reports that are submitted to FDA.

This guidance complements the 2013 guidance by expanding on certain aspects of that guidance relating to the selection of data sources, and provides additional guidance for evaluating the relevance and reliability of both EHRs and medical claims data for use in a clinical study. This guidance also provides a broader overview of considerations relating to the use of EHRs and medical claims data in clinical studies more generally, including studies intended to inform FDA's evaluation of product effectiveness.

III. GENERAL CONSIDERATIONS

For all studies using EHRs or medical claims data that will be submitted to FDA to support a regulatory decision, sponsors should submit protocols and statistical analysis plans before conducting the study. Sponsors seeking FDA input before conducting the study should request comments or a meeting to discuss the study with the relevant FDA review division. All essential elements of study design, analysis, conduct, and reporting should be predefined, and, for each study element, the protocol and final study report should describe how that element was

[11] For the purposes of this guidance, traceability is the method (e.g., audit trail) that allows for knowledge of data provenance (i.e., the origin of a piece of data and how it got to the electronic health record or medical claim).

ascertained from the selected RWD source, including applicable validation studies. More information about study elements is provided in section V, Study Design Elements.

This guidance provides recommendations on selecting data sources to maximize the completeness and accuracy of the data derived from EHRs and medical claims for clinical studies. The use of certain study design features or specific analyses to address misclassified or missing information, as well as methods to achieve covariate balance are out of scope of this guidance. Instead, this guidance addresses issues that are essential to determining the reliability and relevance of the data and that should be addressed in the protocol, including:

(1) The appropriateness and potential limitations of the data source for the study question and to support key study elements.

(2) Time periods for ascertainment of study design elements.

(3) Conceptual definitions and operational definitions for study design elements (e.g., inclusion/exclusion criteria for study population, exposures, outcomes, covariates) and the results of validation studies. See section V, Study Design Elements, for examples of conceptual and operational definitions for study design elements.

(4) Quality assurance and quality control (QA/QC) procedures for data accrual, curation, and incorporation into the final study-specific dataset.

IV. DATA SOURCES

Protocols submitted to FDA should identify all data sources proposed for the study, as well as other relevant descriptive information (discussed below). FDA does not endorse one data source over another or seek to limit the possible sources of data that may be relevant to answering study questions.

Each data source should be evaluated to determine whether the available information is appropriate for addressing a specific study question. Given that existing electronic health care data were not developed for research purposes or to support regulatory submissions to FDA, it is important to understand their potential limitations when they are used for that purpose. Examples of potential limitations include:

(1) The purpose of medical claims data is to support payment for care; claims may not accurately reflect a particular disease or the comprehensive management of a disease (e.g., the transcription and classification practices of clinical coders may differ), or a patient may have a particular disease or condition that is not reflected or well-reflected in claims data. In addition, medical claims data can change during the run-off period and claims adjudication process, as initial submissions may be adjusted or corrected, leading to variations in reported diagnoses and procedures over time.

(2) EHR data are generated for use in clinical care and may also serve as a basis for billing and for auditing of practice quality measures. Structured and unstructured data recorded in an EHR system depend on each health care system's practices for patient care, the clinical and documentation practices of its providers, and the functionality and configuration of the EHR system. In addition, data collection is limited to the data captured within an EHR system or network, and may not represent comprehensive care (e.g., care obtained in different facilities in the same or outside of the health care system). Similar to claims data, EHR data may not accurately reflect the presence, characteristics, or severity of a particular disease.

(3) For prospective clinical studies proposing to use EHRs, it may be possible to modify the EHR system for the purpose of collecting additional patient data during routine care through an add-on module to the EHR system. However, given the limited ability to add modules to collect extensive additional information, EHR-based data collection may still not be comprehensive.

(4) Information regarding continuity of care depends on patients remaining within the specific health care system and engaging with the health care system for continuing care.

Prior use of the selected data source for research purposes (e.g., previous submissions to FDA by the sponsor or relevant examples in the published literature) should be described in the protocol. This description should include how well the selected data source has been shown to capture study variables (e.g., inclusion and exclusion criteria, exposures, outcomes, key covariates) and how the study variables can be validated for a particular research activity.

A. Relevance of the Data Source

There are differences in the practice of medicine around the world and between health care systems that may affect the relevance of the data source to the study question. Patients in different types of commercial or government health care payment programs can differ in a range of characteristics, such as age, socioeconomic status, health conditions, risk factors, and other potential confounders. Various factors in health care systems and insurance programs, such as patient out-of-pocket expenses, formulary decisions, and patient coverage, can influence the degree to which patients on a given therapy in one health care system might differ in disease severity, or other disease characteristics, from patients on the same therapy in another health care system. It is also important to identify whether the data sources cover all populations relevant to the study if those sources are to be used to address the study question. Differences in terminology and coding systems used in different health care systems should also be considered.

FDA recommends including the following in the protocol:

(1) The reason for selecting the particular data sources, and the time frame of data that are available, to address the specific study question.

(2) Relevant background information about the health care system(s), including (if available) any specified method of diagnosis and preferred treatments for the disease of interest, and

the degree to which such information is collected and validated in the proposed data sources.

(3) A description of any available information on prescribing and utilization practices (e.g., stepped therapy, prior authorizations, formulary restrictions) that may impact feasibility of the study in the data source or interpretation of study findings.

(4) A discussion on how factors relating to the health care system, including its practices, might affect the generalizability of the study findings from the selected data sources. When non-U.S. data sources are proposed, additional explanation (e.g., demographic factors, standard of care) should be provided to support the generalizability to the U.S. population.

B. Data Capture: General Discussion

A record in EHR systems or medical claims databases is generated only if there is an interaction of the patient with the health care system. Because EHRs and medical claims data are collected during routine care and not according to a prespecified research protocol, information needed to address certain questions in a proposed study may not be present in EHRs and medical claims data sources. Sponsors should demonstrate that the proposed data source(s) contain the detail and completeness needed to capture the study populations, exposures, key covariates, outcomes of interest, and other important parameters (e.g., time periods) that are relevant to the study question and design.

1. Enrollment and Comprehensive Capture of Care

The capture of patients' health care information in a medical claim or EHR data source depends on *continuity of coverage* (i.e., enrollment and disenrollment from the health insurance plan) and *continuity of care* (i.e., continuous interaction with the health care system). When using medical claims data sources, continuity of coverage should be addressed, given that patients often enroll and disenroll in different health plans when they experience changes in employment, or other life circumstances. When using EHR data sources, continuity of care should be discussed**,** specifically, whether patients receive all types of health care services within the same health system or network of facilities that contribute to the same EHR data source. The validity of findings from a study using these data depends in part on the documentation of the migration of patients into and out of health plans and health care systems. Such documentation allows for the identification of time periods during which data are and are not available on the patients of interest. Definitions of continuity of coverage and continuity of care should be developed and documented in the protocol. Of note, information on continuity of care may be difficult to accurately capture (e.g., data do not differentiate discontinuation of care and lack of encounters due to worsening or resolution of existing health conditions) and might need to be approximated in an EHR data source.

FDA recommends addressing the comprehensiveness of the data sources in capturing aspects of care and outcomes that are relevant to the study question. This information will help evaluate the likelihood that all exposures and outcomes of interest will be captured for

regulatory decision-making. For example, outpatient data sources that do not include hospitalization data would generally not be appropriate for studying outcomes likely to result in hospitalization. A second example is a study where an outcome is dependent on a specific frequency of laboratory tests, and clinicians do not typically order those tests at such a frequency.

FDA recommends specifying how all relevant populations, exposures, outcomes, and covariates will be captured during the study period, particularly in situations where data availability varies greatly over time. The data sources should contain adequate numbers of patients with adequate length of continuous follow-up to ascertain outcomes of interest based on the biologically plausible time frame when the outcome, if associated with the exposure, might be expected to occur. Information should be provided about the distribution of length of follow-up for patients in the data sources because the length of follow-up may inform whether the selected data sources are adequate or whether additional supportive data are needed to ascertain long latency outcomes.

In general, EHRs and medical claims data may not systematically capture the use of nonprescription drugs or drugs that are not reimbursed under health plans, episodes of medical tourism outside the U.S., or immunizations offered in the workplace, at pharmacies or public health clinics, or through government immunization programs. If these exposures are particularly relevant to the study question, the data source may not be suitable, or the protocol should describe how this information gap will be addressed (e.g., by building additional modules into the EHR system, linking, or collecting additional data).

Obtaining comprehensive drug coverage and medical care data on patients with certain types of privacy concerns (e.g., sexually transmitted infection, substance abuse, mental health conditions) can be challenging and failure to do so can result in incomplete or erroneous information. Patients with these conditions may receive treatment in federally qualified health centers, or in private clinics where an insurance claim may not be generated if self-payment is used. In addition, certain populations (e.g., patients with rare cancers) more often enroll in experimental clinical trials. In such cases, patients' health data may not be fully captured in electronic health care data. If these issues are relevant to the study question of interest, the protocol should describe how the issues will be addressed.

2. Data Linkage and Synthesis

Data linkages can be used to increase the amount of data available to capture the longitudinal patient journey, increase the amount of data available on individual patients, and provide additional data for validation purposes. If the study involves establishing new data linkages within the same data sources (e.g., mother-infant linkages) or across different data sources (e.g., vital records, disease and product registries, biobank data), the protocol should describe each data source, the information that will be obtained, linkage methods, and the accuracy and completeness of data linkages over time. Probabilistic and deterministic approaches to data linkage may result in different linkage quality, albeit both approaches can have value depending on the scenario. The deterministic approach for data linkage uses records that have an exact match to a unique or set of common identifiers. The probabilistic approach for data linkage uses less restrictive steps in which the linkage can be established by exact matching of

fewer identifiers or matching part of the information on the identifiers (e.g., the first several letters of a name) (Carreras et al., 2018). When a probabilistic approach is used, the analysis plan should include testing the impact of the degree of match and robustness of findings. In addition, if the study involves generating additional data (e.g., interviews, mail surveys, computerized or mobile-application questionnaires, measurements through digital health technologies), the protocol should describe the methods of data collection and the methods of integrating the collected data with the proposed EHRs or medical claims data.

For studies that require combining data from multiple data sources or study sites, FDA recommends demonstrating whether and how data from different sources can be obtained and integrated with acceptable sample size and quality, given the potential for heterogeneity in clinical and coding practices across data sources or systems.

Because patients typically visit multiple health care sites, especially in geographically contiguous areas, the inclusion of de-identified data from many sites creates the possibility that there will be multiple records from different health care sites for a single individual. The existence of multiple records of the same person in different sites can result in overcounts of a particular data measure or, alternatively, if some site records are not available, can result in a collection of patient histories that reflect only a fraction of the patient's total health care history. Specific attention to data curation[12] including individual level and population level linkages and understanding of many-to-one and 1:1 linkage is fundamental to assessing the appropriateness of a new data linkage. Even where multiple data sources are linked by a unique patient identifier or where the patient information is coming from only one data source, there still can be an issue with multiple records or duplicate records. FDA recommends considering and documenting the type of curation performed to address duplication or fragmentation issues and documenting approaches taken to address issues that cannot be fully rectified by curation. See section VI, Data Quality During Data Accrual, Curation, and Transformation into the Final Study-Specific Dataset.

3. Distributed Data Networks

Distributed data networks (or systems) of EHRs and medical claims data systems, often combined with the use of common data models (CDM), have been increasingly used for medical product safety surveillance and research purposes. A CDM standardizes a variety of electronic health care data sources into a common format to ensure interoperability across all sites providing data. The primary benefit of using a distributed network in which data from multiple sites are transformed into a single CDM, is the ability to execute an identical query (without any or substantial modifications) on multiple datasets. In some distributed data networks, queries can be run simultaneously at all network sites or at each site asynchronously, with results combined at a coordinating center for return to the end user. There are a number of the commonly used operational models employed by distributed data networks. Some networks are managed by a single business entity using a consistent EHR system or medical claims database structure and while data are maintained at many locations, they are structured and managed in a consistent manner (e.g., the U.S. Department of Veterans Affairs Veterans Health

[12] For the purposes of this guidance, data curation is the processing of source data through the application of standards for exchange, integration, sharing, and retrieval.

Administration). Another approach is a hybrid distributed model in which a subset of data from many remote sites is sent to a centralized repository that allows for research to be conducted on a combined dataset (e.g., U.S. Centers for Disease Control and Prevention's National Syndromic Surveillance System). A third commonly used approach is seen in networks of data systems with multiple owners and database structures, with data structured and managed differently from location to location (e.g., the member sites of FDA's Sentinel system). In this model, research queries are sent to the various network member sites and results returned to a central location for collation and reporting.

The latter type of networks, comprised of disparate data systems such as the Sentinel system, are facilitated by the use of CDMs. Networks using CDMs also typically provide tools and methodologies for analysis, a consistent level of data curation, unified QA/QC procedures, and periodic revision of the data model to incorporate new data concepts as needed. Additionally, methodologies have been developed that allow the ability to translate data from one CDM to another, however these involve additional data transformations,[13] which present added quality considerations. Data curation and transformation into a CDM, as well as general QA/QC procedures, are discussed in section VI, Data Quality During Data Accrual, Curation, and Transformation into the Final Study-Specific Dataset.

Distributed data networks are typically comprised of EHR, medical claim, or registry data. Nevertheless, combining many data sources, especially with the addition of data transformation into a CDM, adds a layer of complexity that should be considered. Because there are many different configurations of distributed health data networks, the configurations discussed in this guidance should not be considered comprehensive.

Transforming disparate database structures into a common health network with a CDM allows research across health care sites that would otherwise be more complex and costly. However, CDMs can introduce additional challenges to consider. Many CDMs, including those developed for FDA's Sentinel system, Biologics Effectiveness and Safety Initiative, and the National Patient-Centered Clinical Research Network, were created to satisfy a specific set of research purposes; the choice of data captured in a CDM is optimized for the types of data measures and detail needed for the intended use (e.g., Sentinel system for postmarket safety surveillance to inform regulatory decision-making, the National Patient-Centered Clinical Research Network for patient-centered outcomes research). Therefore, data in CDM-driven networks rarely contain all the source information present at the individual health care sites, and the data elements chosen for a given CDM network may not be sufficient for all research purposes or questions. Furthermore, CDMs often have many data elements within the model that are optional—that is, although the model has such data elements available to be filled with data, the individual sites can choose whether to put their original data into the optional fields.

Before using a CDM-driven network, data elements collected by the CDM should be considered—including whether needed data elements exist in the model and, if so, whether they are required or optional elements—to determine suitability for the study and whether identified deficiencies can be addressed by supplementing with customized study-specific data elements,

[13] For the purposes of this guidance, data transformation is the process of converting data from one format or structure into another format or structure.

collecting additional data, or using other data elements present in the dataset that are reasonable proxies for the missing information. It should be noted, however, that such workarounds involve additional considerations by the sponsor such as the work involved with validating proxy endpoints or any human subject research considerations that involve additional data. Suitability may also be improved with more flexible CDMs that are frequently expanded for new uses. For information on proxy variables, see section IV.C, Missing Data: General Considerations.

4. Computable Phenotypes

A computable phenotype identifies a clinical condition or characteristic using a computerized query to an EHR system or clinical data repository (including disease registries, claims data) using a defined set of data elements and logical expressions. Standardized computable phenotypes enable efficient selection of study populations and ascertainment of outcomes of interest or other study variables for large-scale clinical studies across multiple health care systems. A computable phenotype definition should include metadata and supporting information about the definition, its intended use, the clinical rationale or research justification for the definition, and data assessing validation in various health care settings (Richesson et al. 2016). The computable phenotype definition, composed of standardized and mapped data elements and phenotype algorithm, if applicable, should be described in the protocol and study report and should also be available in a computer-processable format. Clinical validation of the computable phenotype definition should be described in the protocol and study report. For additional information on validation, see section IV.D, Validation: General Considerations.

5. Unstructured Data

Although medical claims data are typically in structured fields, large amounts of key clinical data are unstructured data within EHRs, either as free text data fields (such as physician notes) or as other non-standardized information in computer documents (such as PDF-based radiology reports). To enhance the efficiency of data abstraction, a range of approaches, including both existing and emerging technologies and strategies, are increasingly being used to convert unstructured data into a computable format. More recent innovations include technology-enabled abstraction whereby software provides a mechanism for human data abstractors (e.g., tumor registrars) to do their work in a consistent and scalable fashion.

Technological advances in the field of artificial intelligence (AI) may permit more rapid processing of unstructured electronic health care data. AI is a branch of computer science, statistics, and engineering that uses algorithms or models to perform tasks and exhibit behaviors such as learning, making decisions, and making predictions.[14] Advances include natural language processing, machine learning, and particularly deep learning to: (1) extract data elements from unstructured text in EHRs; (2) develop computer algorithms that identify outcomes; or (3) evaluate images or laboratory results. FDA does not endorse any specific AI technology.

[14] See IMDRF/AIMD WG/N67 Machine Learning-enabled Medical Devices: Key Terms and Definitions, May 6, 2022.

All these methods are computer-assisted to various levels but require a significant amount of human-aided curation and decision-making, injecting an additional level of data variability and quality considerations into the final study-specific dataset. If the protocol proposes to use AI or other derivation methods, the protocol should specify the assumptions and parameters of the computer algorithms used, the data source from which the information was used to build the algorithm, whether the algorithm was supervised (i.e., using input and review by experts) or unsupervised, and the metrics associated with validation of the methods. Relevant impacts on data quality from use of AI or other computerized extraction methods should be documented in the protocol and analysis plan.

C. Missing Data: General Considerations

There are two broad scenarios in which information may be absent from data sources. The first scenario is when the information was intended to be collected (e.g., structured field present in EHRs), but is absent from the data sources. This is an example of traditional missing data.[15] The second case is when the information was not intended to be collected in EHRs and medical claims data and is therefore absent. The second scenario affects the relevance of the data source. Although both can have an impact on study validity, it is helpful to distinguish between these two scenarios and understand the reasons why information is present or absent in EHRs and medical claims. For example, lack of information about the result of a laboratory test could be caused by different circumstances: (1) the test might not have been ordered by the health care provider; (2) the test might have been ordered but not conducted; (3) the test might have been performed, but the result was not stored or captured in the data source; or (4) the test might have been performed and the result was stored in the data source, but data were not in an accessible format, or lost in the transformation and curation process when the final study-specific dataset was generated. Because providers might order a laboratory test based on a patient's characteristics, the decision not to order the test or a patient's decision to forgo the test may have implications on the data's fitness for use in a proposed study. An understanding of the reasons for missing data may help assess the impact of missing data on study findings.

As discussed above, data linkage is one way to address certain types of missing data. It may also be possible to identify a variable that is a proxy for the missing data. An example of a potential proxy variable includes maternal education as a proxy for socioeconomic status that often is an important confounder when evaluating child-health outcomes.

The protocol and the statistical analysis plan should be developed and based on an understanding of reasons for the presence and absence of information. Descriptive analyses should be included to characterize the missing data. Assumptions regarding the missing data (e.g., missing at random, missing not at random) underlying the statistical analysis for study endpoints and important covariates should be supported and the implications of missing data considered in the design and analysis of the study. Sensitivity analysis should be conducted to evaluate the robustness of findings.

[15] For the purposes of this guidance, missing data are data that would have been used in the study analysis but were not observed, collected, or accessible. This refers to information that is intended to be collected but is absent and information that is not intended to be collected and is therefore absent.

D. Validation: General Considerations

1. Conceptual and Operational Definitions of Study Variables

Studies using EHRs and medical claims data sources should include conceptual definitions for important study variables, including study population inclusion and exclusion criteria, exposure, outcome, and covariates. A conceptual definition should reflect current medical and scientific thinking regarding the variable of interest, such as: (1) clinical criteria to define a condition for population selection or as an outcome of interest or a covariate; or (2) measurement of drug intake to define an exposure of interest.

An operational definition should be developed based on the conceptual definition to extract the most complete and accurate data from the data source. In many studies using EHRs or medical claims data, the operational definition will be a code-based electronic algorithm using structured data elements. In other studies, the operational definition may be derived from extracting relevant information from unstructured data or constructing an algorithm that combines structured and unstructured data elements. Operational definitions can also specify additional data collection, such as a patient survey, when appropriate.

2. Selection of Study Variables for Validation

Given that operational definitions are usually imperfect and cannot accurately classify the variable of interest for every subject, a resulting misclassification can lead to false positives and false negatives (Table 1) and may bias the association between exposure and outcome in a certain direction and degree.[16] Misclassification may occur in any study variable (e.g., exposure, outcome, covariate). Understanding the implications of potential misclassification for study internal validity and study inference is the key step in determining what variables of interest might require validation and to what extent, based on the necessary level of certainty. For example, in a study to quantify a drug effect, internal validity should be optimized, and misclassification of key study variables should be minimized to accurately measure the association. Some misclassification might be tolerable in some studies when the presence of misclassification is not expected to change the interpretation of results (e.g., for signal detection, or when the hypothesized effect size is large and the impact of misclassification on the measure of association is deemed minimal).

To understand how potential misclassification of a variable of interest (e.g., exposure, outcome, covariate) might impact the measure of association and the interpretation of results, sponsors should consider: (1) the degree of misclassification; (2) differential versus non-differential misclassification (e.g., whether the degree of misclassification of an outcome may differ across treatment groups being compared); (3) dependent versus independent misclassification (e.g., correlated misclassifications of exposure and outcome when both are self-reported in the same

[16] For categorical variables, the performance of operational definitions can be measured by indices such as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). For continuous variables, indices may be based on the correlation with, or the pairwise comparison to, the reference standard. These measures inform the presence and degree of misclassification or measurement error of a variable that may in turn bias the study findings from the truth.

survey); and (4) the direction toward which the association between exposure and outcome might be biased.

3. Validation Approaches

Validation refers to the process of determining if a study variable (e.g., exposure, outcome, covariate) is correctly measured, usually according to a reference standard (Porta, 2014). Examples of validation approaches include: (1) complete verification[17] of a key study variable for all subjects; (2) verification of a study variable for all those identified by an operational definition as positive (e.g., all those identified as exposed for exposure status, or all those identified as a case for outcome status), or as negative (e.g., all those identified as unexposed for exposure status, or all those identified as a non-case for outcome status, but not necessarily all subjects; or (3) assessing the performance of an operational definition (e.g., internally in a sample of the study population for the proposed study, or externally in a prior study). The extent of effort required for validation depends on the necessary level of certainty and the implication of potential misclassification on study inference. Although complete verification of a study variable is considered the most rigorous approach, there are scenarios where verifying a key study variable for every subject might not be feasible (e.g., a very large study population, lack of reference standard[18] data for all study subjects) and assessing the performance of the variable's operational definition might suffice. Based on the performance measures described in Table 1, sponsors should consider whether validating the variable to a greater extent (e.g., all positives classified by the operational definition) is necessary and discuss options with the relevant review division.

Because the performance of an operational definition is dependent on various factors, such as data source, study population, study time frame, and choice of reference standard, FDA recommends assessing the performance of operational definitions in an adequately large and representative sample of the study population as part of the proposed study, using justified sampling methods (e.g., random sampling, stratified sampling). If sponsors propose to use an operational definition that has been assessed in a prior study, ideally, those definitions should have been assessed using the same data source and in a similar study population as the proposed study. In addition, secular trends in disease, diagnosis, and coding may necessitate assessment of the operational definition using more recent data. The quality of prior studies used to establish sensitivity, specificity, and predictive values should always be evaluated.

Choice of a reference standard may vary by study design and question, variable of interest, and the necessary level of certainty. For example, subject matter experts' review of medical records (including structured and unstructured data) may be a preferred reference standard for validation of clinical events identified by diagnosis codes or automated algorithms, or drug intake diary may be

[17] For the purposes of this guidance, complete verification involves assigning an accurate value to the variable of interest for each study subject based on a reference standard of choice. For example, medical record review can be used in conjunction with a conceptual definition to determine whether a subject meets a critical inclusion criterion or has experienced the outcome event (adjudication may be involved in this process).

[18] For the purposes of this guidance, reference standard is the best available benchmark, also referred to as a *gold standard*. When a gold standard is not clearly identified, validation may indicate concordance between methods assessed by a Kappa statistic, precent agreement, or other indices.

used to assess the validity of medication exposures identified in pharmacy dispensing data. Other examples may include broadly accepted external reference data sources, such as national or state vital statistics data sources, if appropriate. Sometimes the reference standard of choice itself may have important limitations and not be entirely valid, in which case caution should be used when interpreting validation results.

The protocol should include a detailed description of the planned validation, including justification for the choice of a validation approach, reference standard, methods, processes, and sampling strategy (if applicable). If a previously assessed operational definition is proposed, additional information should be provided, including in what data source and study population and during what time frame the assessment was conducted, the value of the assessed performance measures, and a discussion of whether the performance measures are applicable to the proposed study. FDA also recommends using quantitative approaches, such as quantitative bias analyses, either *a priori* for feasibility assessment, or to facilitate interpretation of study results, or for both purposes, to demonstrate whether and how misclassification, if present, might impact study findings. The protocol should pre-specify the indices (e.g., sensitivity, specificity) that will be used for quantifying bias and describe how the selected indices will be measured during validation.

For further discussion about the validation of study design elements, see section V.C.5, Validation of Exposure; section V.D.3, Validation of Outcomes; and section V.E.3, Validation of Confounders and Effect Modifiers.

Table 1: Schematic Representation of the Calculation of Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) for a Binary Variable

Condition based on proposed operational definition	Condition based on reference standard: Yes	Condition based on reference standard: No	Total	
Yes	a (true positive)	b (false positive)	a+b	PPV = a/(a+b)
No	c (false negative)	d (true negative)	c+d	NPV = d/(c+d)
Total	a+c	b+d	N	
	Sensitivity = a/(a+c)	Specificity = d/(b+d)		

V. STUDY DESIGN ELEMENTS

The ascertainment and validation of study design elements are discussed in detail below. The study questions of interest should be established first, and then the data source and study design most appropriate for addressing these questions should be determined. The study should not be

designed to fit a specific data source, because the limitations of a specific data source may restrict the options for study design and limit the inferences that can be drawn.

A. Definition of Time Periods

FDA recommends clearly defining the various time periods pertinent to the study design in the protocol (e.g., time periods for identifying study population, defining inclusion and exclusion criteria, assessing exposure, assessing outcome, assessing covariates, following up with patients, "washout" time period if applicable). The focus of the time scale (e.g., calendar time, age, time since exposure) should be explicitly described with adequate detail on data availability of the time unit (e.g., year, month, day, hour, minute) required to answer the study question.

The protocol should demonstrate the data availability, accuracy, and completeness for the proposed time periods and the potential impact on study validity. For example, justification should be provided regarding how data for the time period before exposure are adequate for identifying the study population and the important baseline covariates, or for the follow-up period to consider the biologically plausible time frame when the outcome (e.g., long latency events), if associated with the exposure, might be expected to occur. When the proposed outcome definition distinguishes disease onset (e.g., early symptoms) from a confirmed diagnosis, justification should be provided regarding whether the timing of disease onset can be accurately captured (e.g., for an insidious disease). In addition, when the study design involves time-varying covariates, description should be provided regarding the data availability of the time unit to capture the changes of the variable of interest (e.g., age in month as a time-varying covariate in a study among infants). The protocol should also address potential temporal changes in the standard of care, the availability of other treatments, diagnosis criteria, and any other relevant factors that are pertinent to the accuracy and completeness of data for study variables. For example, healthcare avoidance or limited access to healthcare during a pandemic may adversely impact the assessment of patients' underlying conditions for studies using RWD during or after the pandemic. Other relevant factors may include payer or provider policies (if known), such as formulary changes, step therapy, and laboratory assay changes. Before developing the study approach, sponsors should discuss with the relevant FDA review division the capability of data to capture such potential temporal changes and the impact of the potential temporal changes on internal validity.

B. Selection of Study Population

The protocol should include a detailed description of methods for determining how inclusion and exclusion criteria (e.g., demographic factors, medical condition, disease status, severity, biomarkers) will be implemented to identify appropriate patients meeting these criteria from the data source. The protocol should include a detailed description of operational definitions for inclusion and exclusion criteria to identify the eligible study population from the data source. The identification of the study population may rely on information recorded in multiple data fields such as diagnosis and procedure codes (e.g., International Classification of Diseases (ICD)-9-CM, ICD-10), laboratory tests (e.g., Logical Observation Identifier Names and Codes (LOINC)) and values, or unstructured data (e.g., physician's encounter notes, radiology and

pathology reports). The protocol should address the accuracy and completeness of the information collected in the proposed data source to fulfill the inclusion and exclusion criteria.

Operational definitions of key inclusion and exclusion criteria used to select the study population should be validated. As one example, to assess the drug effect in patients with immune thrombocytopenic purpura, the disorder ascertained by operational definition ICD-9-CM diagnosis code 287.31 or ICD-10 code D69.3 should be validated based on the conceptual definition of the disorder, which includes signs and symptoms, levels of platelets, and exclusion of other possible causes of thrombocytopenia.

In certain circumstances, key inclusion and exclusion criteria (e.g., gestational age for pregnancy studies) may be generated by the information recorded at the point of care by the health care providers. For example, health care providers may enter the calculated gestational age in EHRs based on patient self-reported last menstrual period, ultrasound dating, and other relevant information. If such data are used, the protocol should describe the source of information and the methods health care providers use to generate the data (if known).

FDA also recommends including quantitative approaches, such as quantitative bias analyses, in the protocol to demonstrate whether and how misclassification of inclusion and exclusion criteria, if present, might impact study findings. The approach can be applied *a priori* for feasibility assessment, to facilitate interpretation of study results, or for both purposes. The protocol should pre-specify the indices (e.g., sensitivity, specificity) that will be used for quantifying bias and describe how the selected indices will be measured in key inclusion/exclusion criteria validation.

C. Exposure Ascertainment and Validation

Considerations discussed in this section regarding exposure ascertainment in EHRs or medical claims data primarily apply to noninterventional studies, given that the assignment of exposure is documented in interventional studies.

1. Definition of Exposure

For the purposes of this guidance, the term *exposure* applies to the medical product or regimen of interest being evaluated in the proposed study. The product of interest is referred to as *the treatment*, and may be compared to no treatment, a placebo, standard of care, another treatment, or a combination of the above. Other variables that could affect the study outcome are considered covariates and are discussed in section V.E, Covariate Ascertainment and Validation. The exposure definition should include information about the drug dose, formulation, strength, route, timing, frequency, and duration of use for the product studied (if relevant). It may also be necessary to describe the specific manufacturer of a product (e.g., when a proper name for a vaccine is used by different manufacturers).

The description of exposure should include the intended or prescribed use of the product (e.g., the number, frequency, route of administration, and specific doses), the period between initiation of exposure and the earliest time one might reasonably expect to see an effect, and the expected duration of effect. This will usually require an understanding of the pharmacological properties

(e.g., half-life) and mechanism of action of the drug —for example, that a onetime infusion to prevent osteoporosis may have an effect for several months. See section V.C.3, Ascertainment of Exposure: Duration, and section V.C.4, Ascertainment of Exposure: Dose.

2. Ascertainment of Exposure: Data Source

Sponsors should be able to demonstrate an ability to identify the specific products of interest in the proposed data source, demonstrating that the data source contains data fields and codes that allow identification of the specific products of interest (e.g., through specific coding). For example, it is not always possible to infer a specific vaccine formulation from the billing or diagnostic code alone, such as in systems where a single billing code is used for multiple vaccines. The protocol should describe the coding system used, the level of granularity represented (e.g., using RxNorm concept unique identifiers (CUIs) mapped to the National Drug Code [NDC] codes), and the specificity attained by the coding system.

When relying on coded data, the operational exposure definitions should be based on the coding system of the selected data source and reflect an understanding of the prescription, delivery, and reimbursement characteristics of the drug (if applicable) in that data source over time. For example, in the United States, the operational definition should include the appropriate pharmacy codes (NDC or Healthcare Common Procedure Coding System (HCPCS) or other applicable codes) to capture the use of the drug in various settings. This approach is particularly important in the case of non-oral drugs that may be assigned different codes depending on how they are obtained. For example, patients using an injectable drug can obtain it from the pharmacy, in which case the NDC code would be recorded, or it can be administered by the provider, in which case the drug and its administration would be recorded using the HCPCS J code.[19]

It is also essential to report operational definitions and methods when combining information from unstructured and structured data. Emerging methods may involve review of unstructured information in medical records combined with pharmacy dispensing and physician prescribing data and notes to provide an assessment of whether a person was prescribed and received the medication of interest, as well as whether there are problems with the patient continuing the medication. An example of such methods is found in ascertainment of aspirin exposure in a retrospective cohort study of veterans undergoing usual care colonoscopy (Bustamante et al. 2019).

When using a medical claims data source, it is important to consider that there could be dispensed prescriptions that were not associated with insurance claims if these uncaptured prescriptions are relevant exposures for the study. Uncaptured prescriptions might include low-cost generic drugs, drugs obtained through discount programs, samples provided by pharmaceutical companies and dispensed by health care providers, and drugs sold via the internet or patient out-of-pocket purchases. An individual can seek care outside of the healthcare system(s), and exposure to medication prescribed by out-of-system providers would not be captured in the EHR. Lastly, nonprescription drugs and dietary supplements are not generally

[19] A drug's J code is a Healthcare Common Procedure Coding System (HCPCS) Level II code used in medical claims to report injectable drugs that ordinarily cannot be self-administered; chemotherapy, immunosuppressive drugs, and inhalation solutions; and some orally administered drugs.

captured, nor well-captured in electronic health care databases. It is important to address the likelihood of incomplete exposure ascertainment and its effect on study validity, see section V.C.5, Validation of Exposure.

3. Ascertainment of Exposure: Duration

The data source should capture the relevant exposure duration (anticipated use of a product over time). Given that some medical products are designed as onetime exposures (e.g., vaccines), and other products may be intended for use over extended periods of time, the suitability of a data source will vary with the specific medical product under investigation or the medical conditions the product is intended to treat (e.g., acute versus chronic conditions, treated daily versus as needed, or prophylaxis versus active treatment). FDA recommends describing the duration of exposure as well as the period during which the exposure is having its effect relative to the outcome of interest. Duration may refer to continuous exposure or cumulative exposure, depending on the study question. For some products, an immediate or near-immediate effect is expected; for other products, an effect is expected after a time interval (e.g., drugs that promote bone strength). FDA recommends considering the duration of continued drug effect after treatment discontinuation to include the entire period in which the drug effect may occur. For example, a vaccine effect may persist for years after vaccination, and persons might be considered exposed during that period. On the other hand, an anticoagulant's effects may not extend beyond several hours or days. FDA also recommends justifying the units (e.g., hours, days) selected for estimating the duration of exposure and ensuring the data are available in those units.

Because patients may not refill their prescriptions exactly on time or, alternatively, may refill their prescriptions early, gaps or stockpiling in therapy may exist and may be reflected in the dispensing medical claims data.[20] FDA recommends describing and justifying in the protocol how the study will measure use, address potential gaps in therapy in the data source, and handle refill stockpiling if there are early refills. Intermittent therapies (e.g., drugs used to treat pain on an as-needed basis) and therapies for which samples are often provided to patients (e.g., expensive drugs, drugs that are new to the market) present challenges in accurately assessing the actual exposure and duration of exposure, see section V.C.5, Validation of Exposure

4. Ascertainment of Exposure: Dose

Data about exposure should include information about dosing regimen (e.g., strength, dosing frequency, route of administration). Depending on the exposure and the question of interest in the study, it may be useful to describe the dose of each administration or a daily dose, as well as an estimated cumulative dose (i.e., the total amount of the drug of interest given to a patient over a specified period of time).

It is reasonable to begin with the dose information provided in the data source, and then discuss in the protocol or study report the specific assumptions made when estimating the dose of the exposures of interest, especially for pediatric patients. See section V.C.6, Dosing in Specific Populations. In addition to the dosing regimen, the data source should provide detailed and

[20] This guidance does not address issues related to medication adherence.

complete drug description information, including dosage formulation (e.g., oral solution versus injectable solution) to determine a patient's total daily dose, especially if the product has multiple formulations available.

5. Validation of Exposure

Other than for medications administered in hospital settings or infusion settings, electronic health care data capture prescriptions of drugs and the dispensing of drugs to patients, but generally do not capture actual patient drug exposure or dose consumption because this depends on patients obtaining and using the therapy as prescribed. Additionally, medical claims data do not capture dose adjustment of an existing treatment if the provider instructs patients in a clinic visit or by phone to adjust the dose without writing a new prescription. Dose adjustment for an existing treatment can be missed in the EHRs if the change was not noted in the patient's record.

Validation ideally involves a comparison of the exposure classification in the proposed data source with a reference data source,[21] and produces estimates of misclassification that can be used in qualitative or quantitative assessments of the impact on study validity. Validation might begin with defining the conceptual and operational definitions. For example, to define new use of drug X in a particular study, the conceptual definition may be "initiation of drug X and no exposure to drug X in the past 365 days," and the operational definition would be "at least one outpatient prescription claim for drug X (identified by NDC code xxx), and no claims for drug X in 365 days before the dispensing date of the prescription." For prescribed medications used in outpatient settings, dispensing or billing data would tend to be more accurate than most EHRs in reflecting exposure to a drug by documenting that the prescriptions were filled. In such cases, validation of EHRs prescribing data by examining medical claims data may be warranted. For drugs administered in the health care setting (e.g., vaccines, injectables, blood products), administration recorded in the EHRs may provide more complete information than is available in medical claims records. In these cases, it may be useful to validate medical claims data by examining the EHRs. In certain situations, when reference data sources are not available, additional studies conducted in the same population or published in the literature can provide estimates of potential misclassification of exposure status (e.g., survey of study participants to assess intake of drug, published reports of numbers of people obtaining vaccinations through pharmacies/workplaces/schools).

FDA recommends documenting the methods used to calculate and validate duration, dose, product switching, and other characteristics of exposure. Validation and misclassification issues should be addressed in appropriate study documents. FDA also recommends including in the protocol quantitative approaches, such as quantitative bias analyses, to demonstrate whether and how exposure misclassification, if present, might impact study findings. The approach can be applied *a priori* for feasibility assessment, to facilitate interpretation of study results, or for both purposes. The protocol should pre-specify the indices (e.g., sensitivity, specificity) that will be used for quantifying bias and describe how the selected indices will be measured in exposure validation.

[21] In certain cases, the RWD source may be the only reference. For example, if exposure is defined by whether the patient paid for the prescription, medical claims data may be used, and this information will be the reference source.

6. Dosing in Specific Populations

In addition to reporting validated information about the dose prescribed, dispensed, or administered, additional information may be necessary to permit an assessment of whether dosing was appropriate for specific populations (e.g., if there was significant underdosing or overdosing). For example, for patients with compromised renal function, it may be necessary to have access to measurements of serum creatinine, creatinine clearance, or estimated glomerular filtration rate to determine whether the recommended dose based on product labeling was used. Another example is when assessing exposure in pediatric populations where it may be necessary to obtain the patient's weight and describe the dose within weight categories. The need for additional data to permit appropriate assessment of dosing may occur more frequently with claims data, but can also occur when using EHRs, if necessary, data are absent.

7. Other Considerations

The patients providing comparator data should be defined clearly and with adequate detail in the protocol. The protocol should discuss the reasoning for selecting the: (1) source of comparator data; and (2) the time period (if the comparator group is not concurrent with the treatment group). Because a comparator agent may differ from the product of interest in specific indication within a disease, contraindication, safety profile, or user's disease severity or comorbidity, as well as other patient, physician, and healthcare system characteristics (e.g., timing of exposure relative to the onset of disease, disease status, prior treatment, patient's socioeconomic status, physician's prescribing behavior, drug availability and treatment guideline based upon particular healthcare system, etc.), it is important to ensure adequate data are available for FDA to assess the comparability of the exposed and comparator populations.

Relevant concomitant medication use (e.g., combination therapy components, standard of care therapy, etc.) should be described and ascertained from the data source. A study's definition of concomitant medication use should be described in detail. Definitions of concomitant medication use might include instances when drugs are dispensed on the same day, when drugs have overlapping days' supply, or when patients have filled prescriptions for two or more drugs during the study period. Limitations to ascertainment of concomitant drugs (e.g., nonprescription drugs) should also be described.

D. Outcome Ascertainment and Validation

A crucial step in selecting a data source is determining whether it captures the clinical outcome of interest. Because electronic health care data typically capture outcomes that are brought to the attention of a health care professional and documented in the medical record, outcomes representing mild symptoms or events occurring outside of medical care (e.g., out-of-hospital death) will not generally be well-captured. Conversely, discrete outcomes or acute events (e.g., stroke, myocardial infarction, new infection) are more likely to be captured than worsening of existing problems (e.g., depression, psoriasis, arthritis) that may not be discerned by a new diagnosis code. In general, the likelihood of capturing outcomes may vary by disease type and the extent to which the patient has ongoing encounters with health care professionals that could lead to additional information being documented in medical records. Unlike traditional clinical

trials, studies exclusively using electronic health care data to ascertain outcomes likely do not have protocol-defined follow-up visits and may not have monitoring of events at intervals necessary for outcome ascertainment; further, the severity of disease and responses to treatment may impact the frequency of follow-up visits, and hence the data available. In addition, the assessment of the outcome of interest is likely more standardized and comprehensive in traditional clinical trials. Therefore, the availability, accuracy, and completeness of data on the outcome of interest as well as the need for external data linkage should be carefully considered. Whether and to what degree a data source captures the outcome of interest should be assessed before study initiation and be independent of the exposure of interest.

1. Definition of Outcomes of Interest

Many outcomes involve diagnoses recorded by physicians as part of routine care. To minimize the effect of variability in practice by different physicians and over time (e.g., using different diagnosis and classification criteria, coding the same event in different ways), FDA recommends defining an outcome of interest based on the clinical, biological, psychological, and functional concepts of the condition, as appropriate. The conceptual definition for the outcome of interest (also referred to as the *case definition*) should reflect the medical and scientific understanding of the condition and might vary by study. For example, for anaphylaxis, the conceptual definition (or case definition) may include the following clinical criteria: sudden onset, rapid progression of signs and symptoms, ≥1 major dermatological criterion, and ≥ 1 major cardiovascular or respiratory criterion. The protocol should include a detailed description of the conceptual definition, including the signs, symptoms, and laboratory and radiology results that would confirm the outcome status.

Conceptual definitions should be able to be operationalized in RWD sources. For example, randomized controlled trials in oncology typically use tumor-based outcomes of interest in the setting of specific timing and frequency of follow-up assessment and often include molecular or other biomarker testing that may not be standard of care in all clinical practice settings. Since achievement of an objective response (tumor shrinkage), or the date of tumor progression based on standardized clinical trial criteria (e.g., RECIST 1.1) is not typically captured in RWD sources, proxy measures or multi-component definitions may need to be explored and their use justified. As mentioned above, it is more feasible to capture outcomes that have well-defined diagnostic criteria that are likely to be consistently captured in RWD. Sponsors should discuss the proposed outcomes definitions and the appropriateness of proxy measures with the FDA review division.

2. Ascertainment of Outcomes

To help identify potential cases in the selected data source and study population, operational definitions using diagnosis and procedure codes (e.g., ICD-9-CM, ICD-10), laboratory tests (e.g., LOINC) and values, or unstructured data (e.g., physician's encounter notes, radiology and pathology reports) should be developed based on the conceptual definition of the outcome of interest. If the operational definition includes information abstracted from unstructured data in the EHRs or another data source (e.g., mention of spina bifida in birth certificate records for the identification of neural tube defects in infants), the protocol should provide a detailed description

and rationale for the methods and tools used to process the unstructured data and the validation of those methods. See section IV.B.5, Unstructured Data, for additional information on unstructured data. When patient- or physician-generated data (e.g., data required for subjective end points) are proposed to assess the outcome of interest or to complement operational definitions, the protocol should specify how the outcome measure (e.g., sign score, severity index) will be defined and constructed and validated, if applicable, and how the data will be collected.

The sensitivity and specificity of an operational definition may both be reduced when there is outcome misclassification. Given that it is usually not possible for sensitivity and specificity to be perfect (i.e., 100%), outcome misclassification might result in both false positives and false negatives. FDA recommends considering the potential impact of outcome misclassification on study validity and inference when developing or selecting an operational definition for the proposed study. For example, when studying infrequently occurring outcomes in a cohort study, given the low prevalence of the outcome event, it is important to achieve high specificity to minimize false positive cases and high sensitivity so that more true cases can be captured. If the study is designed to estimate a risk ratio, selecting an operational definition with high specificity may be more important than high sensitivity, because imperfect sensitivity (some false negatives) may not bias the risk ratio, provided the outcome misclassification is non-differential and specificity is very high (almost no false positives), regardless of outcome prevalence. Thus, focusing on very high specificity in this scenario will help ensure the study result is correct even if data are imperfect, while high sensitivity is still important to ensure the precision of the estimates.

Operational definitions developed for one data source or study population might not perform as well in other sources or populations, due to database-specific sensitivity and specificity as well as variable disease prevalence. PPV and NPV are functions of sensitivity and specificity as well as prevalence of the outcome in the population in which the predictive values are measured. Therefore, PPV and NPV are variable by data source and study population characteristics (e.g., demographic factors, underlying diseases, comorbidities, clinical settings).

The protocol should include a detailed description of the operational definition, the coding system, the rationale, and associated limitations of information selected to construct the operational definition (e.g., selection of primary or secondary diagnosis codes for which the order may not correspond to their medical importance), and the potential impact on outcome misclassification. If the performance of the operational definition has been assessed in prior studies, the applicability to the proposed study should be discussed. Furthermore, because the case definition used in prior studies to establish sensitivity, specificity, and predictive values might include different diagnostic criteria from the conceptual definition developed for the proposed study, proper use of the performance measures assessed in prior studies should be carefully considered.

3. Validation of Outcomes

FDA expects validation of the outcome variable to address outcome misclassification. The extent of validation, such as complete verification of the outcome variable for all subjects, verification

of all potential cases (or non-cases) identified by an operational definition, or assessing the performance of an operational definition depends on the necessary level of certainty and the implication of potential misclassification on study inference.

Although complete verification of the outcome variable is considered the most rigorous approach, there are scenarios where verifying outcome for every subject might not be feasible and assessing the performance of the operational definition of the outcome might suffice. Outcome validation involves using a clinically appropriate conceptual outcome definition to determine whether a patient's status, classified by an operational definition, truly represents the outcome of interest, typically by reviewing clinical details recorded in the patient's medical records in either electronic or paper format.

FDA recommends using standardized medical record review processes, including the use of standardized tools, documentation of process, and training of personnel. A standard and reproducible process is critical for minimizing intra- and inter-rater variability, especially for multi-site studies in which medical records usually cannot be shared across systems and a centralized medical record review is not possible. Even with a centralized medical record review, a standardized process helps to ensure that the same criteria are applied by different adjudicators or a single adjudicator over time. Reporting of comparison metrics (e.g., kappa statistic) is useful to ensure replicability. An estimated medical record retrieval rate (e.g., when requesting medical records from health facilities for a study using claims-based databases) should be justified in the protocol, and the implications for internal and external validity should be discussed. In addition, because knowledge of a patient's exposure status may influence the observer and result in differential misclassification, blinding of the abstractor and adjudicator to exposure status should be considered by masking the study question or redacting the exposure information, especially when the abstractor or adjudicator may associate the exposure with the outcome of interest. The protocol should provide a description of how observer bias will be handled.

Ideally, through complete verification of the outcome variable, the outcome status is accurately classified for each subject to minimize outcome misclassification and improve study internal validity. In practice, a more commonly used approach is to assess the performance of an operational definition in validation studies. Performance measures, such as sensitivity, specificity, and predictive values, do not accurately classify cases and non-cases; rather, they inform the degree of outcome misclassification and facilitate the interpretation of results in the presence of misclassification.

PPV is often assessed in validation studies. PPV is the proportion of potential cases identified by an operational definition that are true positive cases. Therefore, PPV informs the degree to which false-positive cases are included among the identified cases. When the concern with false negative cases is negligible (e.g., when the sensitivity is deemed sufficiently high so that the number of false-negative cases is minimal), a high PPV might be adequate to provide confidence in the validity of the outcome variable, whereas a moderate-to-low PPV might warrant verification of the outcome variable for all potential cases. When the extent of false-positive cases and the extent of false-negative cases are both of concern, sponsors should consider assessing all performance measures needed for quantitative bias analysis to evaluate the impact of outcome misclassification on the measure of association or take a more rigorous

approach by validating the outcome variable for all potential cases and non-cases to accurately classify the outcome variable for each subject. Overall, the required extent of validation should be determined by the necessary level of certainty and the implication of potential misclassification on study inference.

In general, sponsors should consider the tradeoff between false-positive and false-negative cases when selecting an operational definition and identify the proper outcome validation approach to support internal validity. For example, to identify neural tube defects in infants, an operational definition that includes a spectrum of inpatient and outpatient diagnosis codes might have a high sensitivity, low specificity, and low PPV; restricting the operational definition to inpatient diagnosis codes only or a combination of diagnosis and procedure (e.g., surgical repair) codes might increase the PPV but miss a substantial proportion of true cases (low sensitivity). Because missing true cases is particularly a concern for infrequently reported outcomes, one approach is to select an operational definition of high sensitivity and perform verification of the outcome variable for all potential cases identified by the sensitive operational definition to maximize the likelihood that the true cases are all identified and that the false-positive cases are minimized through validation. Unlike rare disease outcomes, when an outcome of interest involves a more common event (e.g., disease-specific hospitalization) or improvement or worsening of a condition, the operational definitions for common diagnoses are likely to generate false-positive and false-negative cases to a considerable extent because both true cases and true non-cases are prevalent. Therefore, it might be difficult to obtain accurate and complete information (e.g., laboratory test results, functional measures) for the operational definition to accurately classify cases and non-cases. For such outcomes, measuring PPV alone will be inadequate to inform outcome misclassification.

In scenarios where complete verification of the outcome variable for each study subject is infeasible, the performance of an operational outcome definition should be assessed in the proposed study population using a justified sampling strategy. As stated earlier, use of an operational definition that has been assessed in a prior study should ideally be in the same data source and in a similar study population, because the performance of an operational definition may vary substantially by data source and study scenario, and more recent data may be needed if there are secular trends in disease, diagnosis, and coding. The quality of prior studies used to establish sensitivity, specificity, and predictive values should be evaluated. In particular, the case definition used in the prior study to establish these measures should be compatible with the conceptual outcome definition developed for the proposed study. The applicability of these measures to the proposed study should be justified, and sensitivity analyses can be considered.

Without complete patient information and complete verification of the outcome variable, outcome misclassification remains a threat to the study internal validity, and the impact on the measure of association between exposure and outcome varies depending on whether the degree of misclassification differs between the exposure groups. Differential misclassification involves a complex interplay of differences in sensitivity, specificity, and disease prevalence between the exposure groups, and thus may bias the association either toward or away from the null.[22] Because it is difficult to predict the direction of the bias, differential misclassification is a concern for both safety and effectiveness studies. Unlike differential misclassification, non-

[22] Null refers to no association between exposure and outcome of interest.

differential misclassification tends to bias the association toward the null; as a result, a true risk might be missed in safety studies, whereas a larger study population might be needed to demonstrate the drug effect in effectiveness studies.

Non-differential outcome misclassification might occur when the outcome definition is not adequately refined and includes conditions that have different magnitude of association with the exposure of interest. For example, neural tube defects include primary neurulation defects and post-neurulation defects. Primary neurulation defects are directly attributed to failure of primary neurulation (i.e., neural tube closure), which occurs between approximately 18 and 28 days after fertilization. The pathophysiology of post-neurulation defects is less understood. Therefore, drug exposure during the critical period for primary neurulation in gestation might not affect post-neurulation in the same manner. When the outcome definition includes both primary and post-neurulation defects, the risk of primary neurulation defects, if any, is likely not detected.

Differential outcome misclassification might be minimized in studies in which the exposure status is blinded. However, even when data collection methods seem to preclude the likelihood of differential outcome misclassification, it is not guaranteed that the only misclassification of the actual data will be non-differential outcome misclassification. For example, the physician who observed, diagnosed, and documented whether or not an outcome occurred could have been the same physician who made a decision as to which patients received the treatment meant to prevent that outcome, or the physician could have monitored disease progression or treatment side effects differently, given the knowledge as to which treatment they received. Therefore, the direction of the outcome misclassification might remain unpredictable when using RWD. In addition, when more than one misclassification exists in a study, sponsors should consider how they might be related to each other. For example, whereas non-differential exposure misclassification and non-differential outcome misclassification each might bias the association toward the null, when the two misclassifications are dependent, overall it can create a bias away from the null (Lash et al. 2009). Therefore, when evaluating the implication of potential misclassification on study inference, sponsors should consider how the individual non-differential misclassifications are interrelated, rather than assuming that the association is biased toward the null. Under such circumstances, assessing the performance of the operational outcome definition according to exposure status in the proposed study population might be necessary.

Regarding outcome validation, sponsors should justify the proposed validation approach, such as verifying the outcome variable for all potential cases or non-cases, versus assessing the performance of the proposed operational definition; if the latter will be done, justify what performance measures will be assessed. The protocol should include a detailed description of the outcome validation design, methods, and processes, as well as sampling strategy (if applicable). If a previously assessed operational definition is proposed, additional information should be provided, including: (1) data source and study population; (2) during what time frame validation was performed; (3) performance characteristics; (4) the reference standard against which the performance was assessed; and (5) a discussion of whether prior validation data are applicable to the proposed study.

FDA recommends including in the protocol quantitative approaches, such as quantitative bias analyses, to demonstrate whether and how outcome misclassification, if present, might impact study findings. The approach can be applied *a priori* for feasibility assessment, to facilitate interpretation of study results, or for both purposes. The protocol should pre-specify the indices (e.g., sensitivity, specificity) that will be used for quantifying bias and describe how the selected indices will be measured in outcome validation.

4. Mortality as an Outcome

In the United States, death and cause of death are generally not included in electronic health care data, with exceptions being made for death occurring while a patient is under medical care. Ascertainment of death (fact of death and cause of death) can be accomplished through linkage with public or commercial vital statistics data sources, to increase the completeness and recency of the death variables. The use of external mortality data, however, is subject to all of the limitations of such data and data linkage methods (Haynes 2019; Navar et al. 2019; Curtis et al. 2018). Careful documentation of mortality data quality and its implications should be included in the protocol.

If the death is not captured in the electronic health care data systems, patients who die after having been exposed to the study drug might be observed in electronic health care data as either not filing any further medical claims or not receiving any additional care past a particular date. For studies in which the outcome or outcomes of interest (e.g., myocardial infarction or stroke) include fatal outcomes, either excluding patients who appear to be lost to follow-up at any time following their exposure to the study drug or classifying patients who are lost to follow-up as deceased in the absence of data to the contrary, is likely to create bias. Searches of vital statistics systems may be considered to see whether their absence (disenrollment) from the system is because of death.

E. Covariate Ascertainment and Validation

For the purposes of this guidance, covariates in a particular study can include two types of elements: confounders and effect modifiers.

1. Confounders

Information on potential confounders is collected in a nonrandomized study to support appropriate efforts to balance treatment and comparator groups in the analysis.

After identifying the potential confounders in a study, the proposed data source should be evaluated to determine whether it is adequate to capture information on important factors which may contribute to confounding. These include confounders that are well-captured in the proposed data source (measured confounders) and those that are not well-captured (unmeasured or imperfectly measured confounders). Examples of confounders that can be unmeasured or imperfectly measured in electronic health care data, especially in claims data, include race/ethnicity, family history of disease, lifestyle factors (e.g., smoking, alcohol use, nutrition intake, physical activity), certain physical measurements (e.g., body mass index), drugs obtained

without insurance, and indication for drug use. FDA recommends considering potential linkages with other data sources or additional data collection to expand the capture of important confounders that are unmeasured or imperfectly measured in the original data source. The protocol should clearly disclose all known unmeasured confounders in the proposed data source(s), as well as approach(es) to supplement information on unmeasured confounders and justify the appropriateness of any proxy measure(s) for specific unmeasured confounder(s).

2. Effect Modifiers

Studies of drug effectiveness or safety usually report an average treatment effect, even though the same treatment can have different effects in different groups of people. Information on potential effect modifiers is used to better understand heterogeneity of treatment effect, the nonrandom, explainable variability in the direction and magnitude of treatment effects for individuals within a population (Velentgas et al. 2013). The potential for effect modification by demographic variables (e.g., age, sex, race, ethnicity) or pertinent comorbidities should be examined in the study, and relevant effect modifiers should be available in the chosen data source. The protocol should clearly disclose all known unmeasured effect modifiers, when relevant, in the proposed data source(s), as well as approach(es) to supplement information on unmeasured effect modifiers and justify the appropriateness of any proxy measure(s) for specific unmeasured effect modifier(s).

3. Validation of Confounders and Effect Modifiers

For all key covariates, including confounders and effect modifiers, FDA recommends providing and justifying the validity of operational definitions in the protocol and study report. Selection of such covariates depends on the study question, study design, and the impact of misclassification on study internal validity and study inference. For example, when a genetic factor is a key confounder for a study question, it may be implicitly adjusted as a time-fixed covariate in a self-controlled design, even if data are imperfect. If the measured covariates can change during a patient's follow-up period (time-varying covariates) and are important to the analysis, the protocol should describe whether and how frequently the information on time-varying covariates can be captured, particularly since capture of time-varying covariates in RWD can be differential by severity of illness (e.g., more testing in more seriously ill patients).

When evaluating the validity of covariate operational definitions, FDA recommends identifying the best reference data source based on the nature of the covariates. When validating operational definitions of covariates that are medical events or procedure utilizations (e.g., comorbidities, past medical history), the same principles apply as in section V.D.3, Validation of Outcomes. For discussion on validating operational definitions of covariates that are associated with drug uses, such as concurrent medications or past drug uses, see section V.C.5, Validation of Exposure. When assessing the validity of other covariate operational definitions, such as family history of disease, lifestyle factors, or indication for drug use, the appropriate reference may include a patient or provider survey or appropriate data linkages.

When supplemental information is needed to capture important covariates or is used for covariate validation, FDA recommends describing the likelihood of obtaining the supplemental

information for the overall study population. If this supplemental information is only available for part of the study population, FDA recommends discussing the potential effect on internal validity in relevant study documents.

Quantitative approaches, such as quantitative bias analyses, are encouraged to demonstrate whether and how misclassification of key covariate(s), if present, might impact study findings. The approach can be applied *a priori* for feasibility assessment, to facilitate interpretation of study results, or for both purposes. The protocol should pre-specify the indices (e.g., sensitivity, specificity) that will be used for quantifying bias and describe how the selected indices will be measured in key covariate(s) validation.

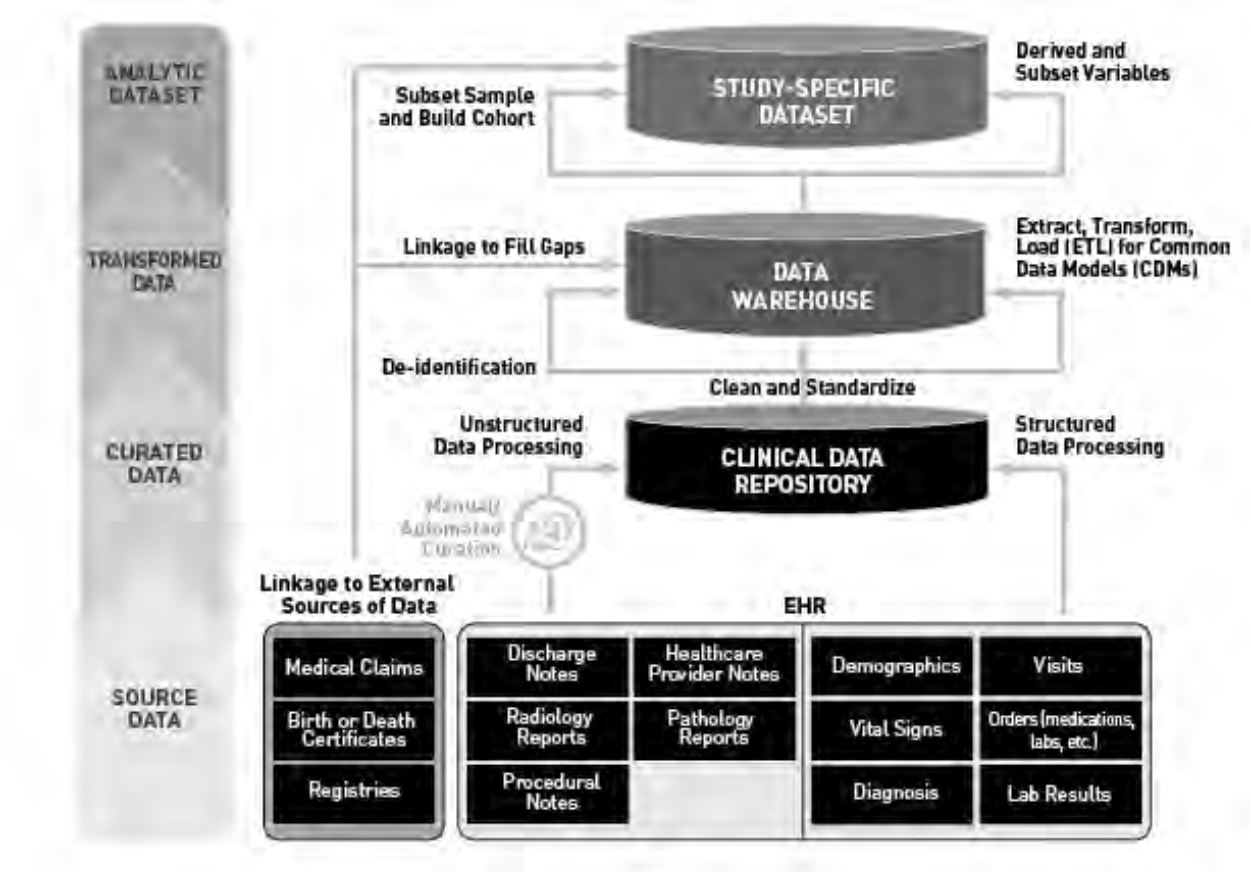
VI. DATA QUALITY DURING DATA ACCRUAL, CURATION, AND TRANSFORMATION INTO THE FINAL STUDY-SPECIFIC DATASET

This section discusses points for consideration when examining the quality of data over the course of the data life cycle. Although the data life cycle may vary depending on the type of data and setting (i.e., health care settings such as pharmacies, clinics, emergency departments and hospitals), in general, the life cycle involves multiple phases: data accrual from the original source data; curation of data to the clinical data repository; transformation and de-identification of data where necessary, creation of a data warehouse; and production of a study-specific dataset for analysis (see Figure 1).

The concept of the data life cycle illustrates the iterative nature of the process for examining the quality of data. The process is not a onetime assessment; rather, it is an ongoing process in which data quality checks, cleansing,[23] and monitoring occur at each phase in the cycle, and some checks may be repeated (i.e., occur in multiple phases of the cycle).

[23] Data cleansing (sometimes referred to as data scrubbing) is the process of correcting or removing inaccurate data (or improperly formatted, duplicate data or records) from a database. The data requiring correction/removal is sometimes referred to as "dirty data." Data cleansing is an essential task for preserving data quality.

Figure 1: Illustrative Example of the Life Cycle of EHR Data[24]



Guidelines that evaluate the quality of EHRs and medical claims data primarily focus on distributed data networks in which disparate data sources are aggregated, linked, and processed to create a comprehensive data warehouse (Miksad and Abernethy 2018; Girman et al. 2018; Daniel et al. 2018; Kahn et al. 2016; Wang et al. 2017; Mahendraratnam et al. 2019). Although FDA does not endorse any particular set of guidelines or checklists, sponsors should evaluate the completeness, accuracy, and plausibility of the data, including verifying data against its original source (e.g., discharge notes, pathology reports, registry records) and conforming to consensus-based data standards, where applicable. Sponsors should provide scientific justifications for choosing these standards and should articulate how these standards are adequate to ensure the completeness, accuracy, and plausibility of the relevant data source.

The study protocol and analysis plan should specify the traceability (curation and transformation procedures used throughout the data life cycle) and describe how these procedures could affect the integrity of the data and the overall validity of the study. Below are points for consideration when examining data at each step in the data life cycle, including (A) characterizing the data with respect to completeness, conformance, and plausibility of data values, (B) documenting the

[24] This figure illustrates some of the processes applied to EHR data to produce a dataset that may be appropriate for research use (i.e., steps from original source data through the final analytic dataset). This figure shows processes for EHR data; the process may differ for claims data. Quality checks for each process step are described in this section.

QA/QC plan that includes transformation processes; and (C) defining a set of procedures for ensuring integrity of the data.

A. Characterizing Data

The format and traceability of EHRs and medical claims data can vary significantly across health care entities (e.g., insurer, practice, provider, data vendor). In general, sponsors should address the procedures used to ensure completeness and accuracy of study data, as well as processes for data accrual, curation, and transformation over the data life cycle. The FDA recommends automated data quality reports that include the following characteristics and processes in a standardized way, when applicable to the chosen data source:

- Data accrual

  (1) Methods for data retrieval and processes to minimize missing data extraction, implausible values, and data quality checks in data captured at the point of care (e.g., during clinical practice for manual or automated health care data collection processes) to ensure accuracy and completeness of data elements.

  (2) Traceability of data elements to allow tracking of these elements back to their respective points of origin, with clear documentation of modifications that may have occurred.

  (3) Timeliness of data availability, data years spanned, and continuity of coverage (e.g., median duration of patient enrollment).

  (4) Handling data discrepancies and duplicate records. RWD may stem from multiple data streams, across various settings and platforms, which may present data discrepancies for the same variable (e.g., when the information for the same element is entered differently in different data sources) or even duplicate records for the same patient within the same data source.

  (5) The reason for and timing of data error corrections implemented by data holders during the relevant period of data collection.

  (6) The reason for and timing of changes in processes implemented by data holders during the relevant period of data collection that may impact data accrual and/or data quality checks.

  (7) Any updates or changes in coding practices and versioning (e.g., ICD diagnosis codes, Healthcare Common Procedure Coding System codes) across the study period that are relevant to variables of interest.

  (8) Any other changes in the data (e.g., collection, reporting, definitions) during the study period and their potential impact on the study results.

- Data curation

  (1) Routine migration of data from various sources over time.

  (2) QA testing and data quality checks employed across sites, as well as the criteria used in determining whether data quality techniques are appropriate for the intended purpose of the data.

  (3) Data elements that are well-defined with consistent and known clinical meaning and understanding of data traceability, as well as documentation of clinical definitions used.

  (4) Assessment of completeness of data elements including trends over time.

  (5) Unstructured and structured data processing (e.g., abstraction and conversion of unstructured data to structured data), including manual versus automated techniques.

  (6) Harmonization of structured data across systems.

  (7) Conformance to open, consensus-based data curation standards, when applicable.

  (8) Accuracy of mappings (e.g., in the presence of different coding systems, such as Systematized Nomenclature of Medicine—Clinical Terms [SNOMED CT] versus ICD-10-CM).

  (9) Additional harmonization and mapping considerations, if applicable (if data spans multiple countries—e.g., U.K. data used in addition to U.S. data).

- Data transformation[25]

  (1) Implementation of the extract, transform, and load process applied to the whole repository population as part of data warehouse creation.

  (2) De-identification of patient records and any process that could be used to re-identify unique patients in original source data without losing traceability (e.g., use of linkage tokens).

  (3) Algorithms used to transform and cleanse the data, as well as availability of standard operating procedures, including procedures for verifying the data against its original source.

  (4) Data standardization (e.g., data types, sizes, formats) for internal consistency of data elements and semantics, including semantics of local codes to a target terminology (e.g., for laboratory data).

[25] For purposes of this guidance, data transformation is the process of converting data from one format or structure into another format or structure.

(5) When converting multiple data sources into a CDM, processes used for data transformation into a CDM (e.g., common terminology and structure), the comprehensiveness of the CDM (e.g., does the CDM contain the key data elements), approaches (e.g., algorithms/methods) for identification and handling of duplicate records within and across data sources, and potential impact of restricting to CDM on sample size and duration of patient follow-up or duration of drug exposure. See section IV.B.3, Distributed Data Networks.

(6) Implementation of data checks pertaining to data model conformance errors.

(7) Data transformation processes used in preparation for data linkage. See section IV.B.2, Data Linkage and Synthesis.

(8) Quality of record linkage (i.e., linking records from multiple datasets) and deduplication (i.e., finding duplicate records in a dataset) process, which may vary depending on the accuracy of the data used to perform the matches and the accuracy of the linkage algorithm.

(9) Quantification of linkage errors (e.g., false matches, missed matches) that may lead to biased study findings. These are important when evaluating linkage quality (Harron et al. 2017). It is important to report details of the linkage algorithm and appropriate metrics (e.g., linkage error rates, match rates, comparison of characteristics of linked and unlinked data). Additional considerations include whether the error is random or nonrandom, potential bias, and impact on risk estimates and study findings.

(10) Procedures for adjudicating discrepancies in linked data as well as plans for handling linkage discrepancies (e.g., adjusting risk estimates for the linkage error).

Sponsors should also consider issues related to the study-specific analytic dataset:

(1) Adherence to data specifications outlined in the study protocol and statistical analysis plan when compiling the analytic dataset.

(2) Additional study-specific data transformations, such as data transformations that are only done for a subset of patients of interest and that are not applied to all patient records in the data warehouse (e.g., manual extraction of data from unstructured textual pathology reports).

(3) Data checks implemented on the final analytic dataset for implausible values for data elements (e.g., height, weight, blood pressure), how such values are addressed, and the completeness of data for key analytic variables.

(4) The extent, percentage, and pattern of missingness and implausible data. Depending on the analysis plan's proposed method for handling missing data, imputations may be performed and included in the final analytic dataset and the type of imputation described.

B. Documentation of the QA/QC Plan

A QA/QC plan for construction of analytical data, the planned approach for handling quality control issues during analysis, and contemplation of differing levels of data quality by data element (and the potential implications on study findings) should be described in the study protocol and analysis plan. In general, activities to ensure the quality of the data before data-related activities are developed during the design of the study, and such activities, which include standardizing procedures for how to collect the data, may be regarded as QA (Szklo and Nieto 2006). Quality control consists of the decisions and steps taken from data collection through compilation of the final analytic dataset to ensure it meets prespecified standards and to ensure the processes used are reproducible. A multidisciplinary approach that includes clinical input is necessary to ensure adequate capture and handling of data, particularly for electronic health care systems, which inherently incorporate nuances and intricacies of health care delivery.

C. Documentation of Data Management Process

All manual and automated data retrieval and transformation processes should be thoroughly assessed from data collection through writing of the final study report to ensure integrity of the data. Sponsors should ensure that curation and transformation processes do not alter the meaning of data or cause the loss of important contextual information. Descriptions of processes should include safeguards or checks to ensure that patient data are not duplicated or overrepresented. In addition, documentation of processes used to mine and evaluate unstructured data should describe the techniques employed (e.g., natural language processing) to abstract unstructured data (e.g., clinician notes) and supplement structured data (e.g., diagnostic codes).

Processes used for managing and preparing the final study-specific analytic dataset should be described in the study protocol or analysis plan. Analysts should have appropriate training or experience with the data and software used to compile the analytic datasets. To facilitate FDA review, all submitted programs (e.g., those written by analysts) should be thoroughly annotated with comments that describe the intent or purpose of each data management and analysis step written in the program (e.g., annotate each data step in a statistical analysis program).

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	SE-2 Efficacy Supplement
Application Number(s)	NDA 020687/S-020
Priority or Standard	Standard
Submit Date(s)	May 28, 2015
Received Date(s)	May 29, 2015
PDUFA Goal Date	March 29, 2016
Division / Office	(b) (6)
Reviewer Name(s)	(b) (6) and (b) (6)
Review Completion Date	March 29, 2016
Established Name	Mifepristone
(Proposed) Trade Name	Mifeprex
Therapeutic Class	Progestin antagonist
Applicant	Danco Laboratories, LLC
Formulation(s)	Oral Tablet
Dosing Regimen	For pregnancies through 70 days gestation: Mifeprex 200 mg tablet orally followed in 24-48 hours by 800 mcg buccal misoprostol.
Indication(s)	Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.
Intended Population(s)	Pregnant women who desire a medical termination through 70 days gestation.

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1 Recommendations/Risk Benefit Assessment

This NDA supplement from the Applicant, Danco Laboratories, LLC (called Danco or the Applicant throughout this clinical review), requested the following changes to the NDA for Mifeprex, approved 15 years ago in September 2000.

Changes proposed by the Applicant:

1. Change the dosing regimen: Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally
2. Remove the statement in labeling that administration of misoprostol must be done in-clinic, to allow for administration at home or other location convenient for the woman.
3. Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex
4. Follow-up needed, but not restricted to in-clinic at 14 days after Mifeprex
5. Increase the gestational age from 49 days to 70 days
6. Change the labeled time for expulsion of the products of conception from 4-24 hours to 2-24 hours post misoprostol administration
7. Add that a repeat 800 mcg buccal dose of misoprostol may be used if needed
8. Change “physician” to “(b) (4) in the label and Risk Evaluation and Mitigation Strategies (REMS) document
9. Change indication to add reference to use of misoprostol: “Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of pregnancy through 70 days gestation.”
10. Remove references to “under Federal law” from the Prescriber’s Agreement
11. Address the Pediatric Research Equity Act (PREA) requirement for pediatric studies

Each of these 11 items will be discussed in the appropriate section of this review, generally under Section 6: Review of Efficacy and Section 7: Review of Safety. Four of the items, namely Number 8-11, are primarily regulatory and/or legal. They are discussed in Sections 1.3 and 9.4 (REMS recommendations and Prescriber’s Agreement), 7.6.4 (PREA), and 9.2 (Labeling recommendation). Additional information is found in Section 7.7 (2) on the change to “(b) (4) Section 7.7 (3) on “under Federal law”, and Section 7.7 (4) on the reference to use of misoprostol.

1.1 Recommendation on Regulatory Action

The clinical reviewers recommend an approval action for this efficacy supplement.

1.2 Risk Benefit Assessment

1. Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally.

   The Applicant has submitted sufficient evidence from the published medical literature to demonstrate that decreasing the dose of Mifeprex from 600 mg to 200 mg while increasing the dose of misoprostol from 400 to 800 mcg is safe and efficacious for termination of pregnancy through 70 days gestation. The risk/benefit balance favors approval.

   There is sufficient evidence that a dosing regimen with buccal administration of 800 mcg misoprostol is safe and effective. This change in the dosing regimen should be approved.

2. Allow administration of misoprostol outside of the clinic:

   Based on the evidence submitted by the Applicant, a dosing regimen that includes administration of misoprostol outside of the clinic is safe and effective for termination of pregnancy through 70 days gestation; labeling should be revised to remove the requirement for in-clinic dosing of misoprostol

3. Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex:

   The available evidence supports that a dosing regimen that provides for administration of misoprostol 24-48 hours after administration of Mifeprex is safe and effective. The risk/benefit assessment demonstrates that this change in the dosing regimen should be approved.

4. Follow-up needed, but not restricted to in-clinic at 14 days after Mifeprex:

   Based on the evidence submitted by the Applicant supporting this change, flexibility in timing and method of follow-up after medical abortion is safe. Labeling should be revised to remove the requirement for in-clinic follow-up at 14 days.

5. Increase the gestational age from 49 days to 70 days:

   As detailed in the following review, the Applicant has submitted sufficient evidence for the safety and efficacy of medical abortion with Mifeprex, in a regimen with misoprostol, through 70 days gestation. The risk/benefit assessment supports the approval of the new dosing regimen up through 70 days gestation.

6. Change the labeled time for expulsion of the products of conception from 4-24 hours to 2-24 hours post misoprostol administration:

   The Applicant has submitted sufficient data from the published medical literature to support approval of a change in the label to note time to expulsion ranges from 2-24 hours.

7. Add that a repeat 800 mcg buccal dose of misoprostol may be used if needed:

The Applicant has submitted sufficient evidence to support that a repeat dose of misoprostol may be used through 70 days gestation to complete expulsion of the products of conception if needed. The risk/benefit assessment supports approval of this change. There have been rare reports of uterine rupture with use of misoprostol in women with prior uterine scar(s). This information should be added to the Mifeprex label.

8. Change "physician" to "(b) (4) in the labeling and Risk Evaluation and Mitigation Strategies (REMS) document:

   The Applicant has submitted sufficient data to support that Mifeprex is safe and effective when prescribed by midlevel practitioners as well as by physicians. Therefore, the term "licensed physician" was changed in the label and REMS materials to "healthcare provider who prescribes." This broader category of providers will still have to meet the certification criteria specified in the Prescriber Agreement Form.

9. Change the approved indication to add reference to use of misoprostol: "Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation." Based on current Agency labeling practice regarding drugs used together in a treatment regimen, the addition of misoprostol to the Indication Statement for Mifeprex should be approved.

10. Remove references to "under Federal law" from the Prescriber Agreement:

    The Agency has determined that there is no precedent for using this phrase in other REMS, nor is there any clinical rationale for including it; therefore, it is acceptable to remove "under Federal law" from the Prescriber Agreement Form.

11. Address the Pediatric Research Equity Act (PREA) requirement for pediatric studies:

    The Applicant has submitted sufficient evidence from the published medical literature to address the PREA requirement for this supplemental application. The Applicant has demonstrated that Mifeprex is safe and effective in postmenarchal females, including those under 17 years of age. (b) (6) concurred with granting a partial waiver under PREA in patients ages birth to 12 years of age who are premenarche.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Changes proposed in this efficacy supplement entailed a number of modifications to the current Risk Evaluation and Mitigation Strategy (REMS) for Mifeprex. See Section 9.4 for full details. The (b) (6) ((b) (6) concurs with the (b) (6) ((b) (6) evaluation of the REMS modifications, which include:

- Removal of "under Federal law" from the Prescriber Agreement Form is acceptable (see discussion in Additional Submissions / Issues).
- The term "healthcare providers who prescribe" is preferable to the Applicant's proposed "(b) (4) (see discussion in Additional Submissions / Issues).
- It is appropriate to modify the current adverse event reporting requirements under the REMS, which are currently outlined in the Prescriber's Agreement to include "hospitalization, transfusion or other serious event." Under these requirements, healthcare providers report certain adverse events to the Applicant, which then is required to report the adverse events to FDA. FDA has received such reports for 15 years, and it has determined that the safety profile of Mifeprex is well-characterized, that no new safety concerns have arisen in recent years, and that the known serious risks occur rarely. For this reason, ongoing reporting by certified healthcare providers to the Applicant of all of the specified adverse events is no longer warranted. . It should be noted that the Applicant will still be required by law, as is every NDA holder, to report serious, unexpected adverse events as 15-day safety reports, and to submit non-expedited individual case safety reports, and periodic adverse drug experience reports.

(b) (6) concurs with the following modifications recommended by (b) (6)

- Removal of the Medication Guide (MG) from the REMS. The MG will remain a required part of labeling and will be required to be provided to patients consistent with the requirements in 21 CFR part 208. FDA has been maintaining MGs as labeling but removing them from REMS when, as here, inclusion in REMS is not necessary to ensure that the benefits of a drug outweigh the risks, such as when the MG is redundant and not providing additional use or information to the patient about the risk(s) the REMS is intended to mitigate. This is consistent with ongoing efforts to streamline REMS by allowing for updates to the MG without need for a REMS modification.
- Removal of the Patient Agreement form (ETASU D). This decision was based on the well-established safety profile of Mifeprex, as well as the fact that the small numbers of practitioners who provide abortion care in the US use informed consent practices that are duplicated of the current Patient Agreement and thus the Patient Agreement is no longer necessary to ensure that the benefits of the drug outweigh the risks.
- Revision of the Prescriber Agreement Form to reflect changes to labeling revisions pursuant to the proposed efficacy supplement, and to improve the flow of the document.
- Revision of the REMS goals to reflect the above changes

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommendations for postmarket requirements or commitments for this efficacy supplement.

2 Introduction and Regulatory Background

2.1 Product Regulatory Information

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' (7 weeks) pregnancy (NDA 20-687). The application was approved under 21 CFR part 314, subpart H, "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments." Specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the approval letter, including a requirement that Mifeprex be provided by or under the supervision of a physician who meets certain qualifications specified in the letter.

The September 28, 2000, approval letter also listed two Phase 4 commitments that the then-applicant of the Mifeprex NDA (i.e., the Population Council) agreed to meet:

1. A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention. Previous study questions related to age, smoking, and follow-up on Day 14 (compliance with return visit) were incorporated into this cohort study, as well as an audit of signed Patient Agreement forms.
2. A surveillance study on outcomes of ongoing pregnancies.

In addition, the 2000 approval letter stated that FDA was waiving the pediatric study requirement in 21 CFR 314.55.

Effective October 31, 2002, the Population Council transferred ownership of the Mifeprex NDA to Danco Laboratories, LLC (Danco).

2.2 Tables of Currently Available Treatments for Proposed Indications

In the US there are no other approved products for the medical termination of first trimester pregnancy. Misoprostol alone or in combination with methotrexate has been used for early medical abortion (MAB), with much lower success than Mifeprex.[1]

[1] American College of Obstetricians and Gynecologists. Practice bulletin No. 143: medical management of first-trimester abortion. Obstet Gynecol 2014;123(3):676-92. doi:10.1097/01.AOG.0000444454.67279.7d.

2.3 Availability of Proposed Active Ingredient in the United States

Mifepristone: The only other FDA approval for mifepristone is the product Korlym, approved under NDA 202107 on February 17, 2012 for the control of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.

2.4 Important Safety Issues with Consideration to Related Drugs

Korlym (mifepristone) is indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery. Korlym is taken in oral doses of 300 mg to 1200 mg daily. It is contraindicated in pregnancy, patients taking simvastatin, lovastatin and CYP3A substrates with narrow therapeutic ranges, patients on corticosteroids for lifesaving purposes, and women with unexplained vaginal bleeding or endometrial hyperplasia with atypia or endometrial carcinoma. The label[2] provides warnings and precautions regarding adrenal insufficiency, hypokalemia, vaginal bleeding and endometrial changes, QT prolongation, exacerbation or deterioration of conditions treated with corticosteroids, use of strong CYP3A inhibitors, and opportunistic infections with *Pneumocystis jiroveci* pneumonia in patients with Cushing's. Adverse reactions noted in ≥20% of patients in clinical trials with Korlym included nausea, fatigue, headache, hypokalemia, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite and endometrial hypertrophy.

Reviewer comment:

Some of the adverse events noted with Korlym are also seen with Mifeprex, such as nausea and vomiting. However, Korlym is taken in higher doses, in a chronic, daily fashion unlike the single 200 mg dose of Mifeprex that is the subject of this supplement; the rate of adverse events with Mifeprex is much lower.

Ella (ulipristal acetate) is a progesterone agonist/antagonist emergency contraceptive indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. The **ella** label[3] notes that in clinical trials, the most common adverse reactions (≥ 10%) in women receiving **ella** were headache (18% overall) and nausea (12% overall) and abdominal and upper abdominal pain (12% overall).

Due to **ella's** high affinity binding to the progesterone receptor, use of **ella** may reduce the contraceptive action of regular hormonal contraceptive methods. The label notes that after **ella** intake, menses sometimes occur earlier or later than expected by a few

[2] http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202107s000lbl.pdf

[3] https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022474s000lbl.pdf

days. In clinical trials, cycle length was increased by a mean of 2.5 days but returned to normal in the subsequent cycle. Seven percent of subjects reported menses occurring more than 7 days earlier than expected, and 19% reported a delay of more than 7 days. The label recommends that women rule out pregnancy if the expected menses is delayed by more than one week. Nine percent of women studied reported intermenstrual bleeding after use of **ella**.

Reviewer comment:

Ella is for occasional use and is not to be used as a regular contraceptive method. As such, the drug is not recommended for repeated use in the same menstrual cycle. The safety and efficacy of repeat use within the same cycle has not been evaluated. A single dose of ella does not appear to result in serious adverse events.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A pre-NDA meeting was held with the Applicant on January 29, 2015. The following items, among others, were discussed:

- New dosing regimen
- Proposal to have (b) (4)
- Use up to (b) (4) days' gestation
- Change in the interval between Mifeprex and misoprostol administration to 24-48 hours
- Revision of the labeled time to expulsion after misoprostol is administered
- Use of the term "(b) (4) in the approval and label to describe who may obtain and dispense Mifeprex
- Deletion of "under Federal law" in the Prescriber's Agreement
- PREA requirements
- Regulatory pathway for approval

2.6 Other Relevant Background Information

Since the approval in France and China in 1988, mifepristone for MAB is currently approved in 62 countries globally[4]; see the list and dates of approval in Appendix 9.7.

Prior to the Mifeprex approval by the FDA, mifepristone had also been approved in the UK in 1991. In the UK, the current therapeutic indications include:

- Medical alternative to surgical termination of intrauterine pregnancy up to 63 days gestation based on the first day of the last menstrual period
- Softening and dilatation of the cervix uteri prior to mechanical cervical dilatation for pregnancy termination during the first trimester

[4] Gynuity website, www.gynuity.org, Medical Abortion in Developing Countries- List of Mifepristone Approvals.

- For use with prostaglandin analogues for termination of pregnancy for medical reasons beyond the first trimester
- Labour induction in foetal death in utero[5]

The estimated cumulative use of Mifeprex in the US since the 2000 approval is 2.5 million uses. Estimated global occurence of MAB and SAB combined was 43.8 million abortionsin 2008 (Guttmacher Institute data)[6]. MAB has been increasingly used as its efficacy and safety have become well-established by both research and experience, and serious complications have proven to be extremely rare.[7] Medical abortion comprises 16.5% of all abortions in the US, 25.2% of all abortions at or before 9 weeks of gestation[1], and based on data from 40 reporting areas sending data to the CDC, 30.8% of all abortions at or before 8 weeks gestation (2012 data).[8] In 2011, approximately 239,400 medical abortions were performed, which was a 20% increase from 2008 data.[9] Data show that in the most recently reported 12 months (September 29, 2014-September 28, 2015), (b) (4) Mifeprex tablets were distributed in the US (NDA 20687 SD # 650, Annual Report-15, submitted October 09, 2015). Further, the vast majority of practitioners in the US who provide medical abortion services use a regimen other than the FDA-approved one. In 2008, Wiegerinck et al published a survey of members of the National Abortion Federation which showed that only 4% of facilities were using the current FDA-approved regimen.[10]

It is noteworthy that ten years ago, the combination of mifepristone and misoprostol for medical abortion was included on the World Health Organization (WHO) Model list of Essential Medicines for termination of pregnancy where legal and acceptable, up to 9 weeks of gestation.[11] Several other national and international organizations have also endorsed the safe use of medical abortion up to 9 and 10 weeks of gestation. This topic will be discussed thoroughly in the Efficacy and Safety Sections.

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[5] Mifegyne Summary of Product Characteristics. Exelgyn Laboratories- June 2013. *https://www.medicines.org.**uk**/emc/medicine/617*

[6] Sedgh G et al., Induced abortion: incidence and trends worldwide from 1995 to 2008. Lancet, 2012;379:625-32.

[7] Cleland K, Smith N. Aligning mifepristone regulation with evidence: driving policy change using 15 years of excellent safety data. Contraception 2015;92:179-81.

[8] Pazol K, Creanga AA, Zane SB, Burley KD, Jamieson DJ. Abortion surveillance--United States, Centers for Disease Control and Prevention (CDC). MMWR Surveill Summ 2012;61(SS-8):1–44 and Surveillance Summaries Nov 27, 2015; 64(SS10);1-40.

[9] Jones RK, Jerman J. Abortion incidence and service availability in the United States, 2011. Perspectives on Sexual and Reproductive Health 2014;46(1):3-14.doi10.1363/46e0414.

[10] Wiegerinck MMJ, Jones HE, O'Connell, K, Lichtenberg ES, Paul M, Westhoff CL. Medical abortion practices: a survey of National Abortion Federation members in the United States. Contraception 2008;78:486-491.

[11] World Health Organization April 2015 Model Lists of Essential Medicines Available online at http://www.who.int/medicines/publications/essentialmedicines/en/.

MAB is a choice that women have available in many areas, especially urban, in the US, although it should be noted that some geographical areas in the US have very limited availability of both the surgical and medical options or even one option for early pregnancy termination.

The primary advantages of having a MAB compared to a surgical abortion (SAB) are the following:

- Limited or no anesthesia
- Limited likelihood of any surgical intervention

Reviewer's Comment:

A very small number of physicians currently provide early medical terminations. In the most recent REMS update from the Applicant (stamp date June 3, 2015), the cumulative number of certified prescribers since 2000 is only (b) (4). Between May 1, 2012 and April 30, 2015, the number of new prescribers was (b) (4) and the number of prescribers ordering Mifeprex was (b) (4) during this 3-year period. The number of healthcare providers that are performing early SAB is not documented.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Because this submission did not rely on datasets from any of the clinical trials, no FDA inspections were performed at clinical sites. The authors of the numerous articles, however, have published widely in peer-reviewed medical journals.

3.2 Compliance with Good Clinical Practices

This submission relies on findings from the published medical literature. The majority of the publications included a statement that the study was conducted under institutional review board (IRB) or Ethical Review Committee approval and the women gave informed consent.

3.3 Financial Disclosures

None were submitted or required.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

On March 10, 2016, a separate supplement approved the packaging of a single 200 mg tablet of mifepristone compared to the current 3 tablets in a blister pack. Each packet will have an individual barcode.

Reviewer comment:

The approval of single tablet packaging should make recording the barcode of the mifepristone tablet in the patient record (as provided in the REMS) easier as the new proposed dosing regimen uses only one 200 mg mifepristone tablet compared to the previously approved regimen of three tablets.

(b) (6), reviewed the PLR conversion of the label. Her review, dated January 11, 2016 states the following:

> "No changes have been made in the approved chemistry, manufacturing and controls. The approved 200 mg tablet will be used. This review evaluates the PLR conversion of the labeling. Sections 3, 11, and 16 of the PLR labeling, and the Highlights of Prescribing Information, have been evaluated from a chemistry perspective.
>
> **Overall Evaluation**: Acceptable. The labeling provided in Section 3, Section 11, and Section 16, and the Highlights of Prescribing Information, is identical in content to the approved information. The PLR conversion labeling, therefore, is acceptable from a chemistry perspective. The PLR label also corresponds to the content and format required in 21 CFR 201.57.

Reviewer comment:

We agree with the conclusions in the CMC review of the PLR conversion of the label.

4.2 Clinical Microbiology

The chemistry (CMC) reviewers determined that a microbiology review was not needed for this efficacy supplement.

4.3 Preclinical Pharmacology/Toxicology

Please refer to the Pharmacology/Toxicology review by (b) (6), dated March 2, 2016. No preclinical data were submitted for this efficacy supplement.The reviewer's only recommendations were labeling changes. His comments were conveyed to the Sponsor.

Per (b) (6) review, the supplement is approvable from a Pharmacology/Toxicology standpoint.

4.4 Clinical Pharmacology

The Clinical Pharmacology review by (b) (6) concluded with the following recommendation:

> "(b) (6), (b) (6) has reviewed the available clinical pharmacology information in relation to the newly proposed regimen for Mifeprex®. We find the application to be acceptable from a Clinical Pharmacology perspective, provided that an agreement on the language in the package insert is reached between the Sponsor and the Division."
>
> No postmarketing commitments or requirement are recommended.

4.4.1 Mechanism of Action

The original approved label states:

> "The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit, and monkey), the compound inhibits the activity of endogenous or exogenous progesterone. The termination of pregnancy results.
>
> …..During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity of prostaglandins."

4.4.2 Pharmacodynamics

No new studies were submitted with this Application. See the original approved label.

4.4.3 Pharmacokinetics

(b) (6) review states the following:

> The pharmacokinetics (PK) of 200 mg mifepristone tablet has not been characterized in women. However, the PK data of 200 mg mifepristone tablet in men are available (1996 study): the mean maximum concentration (C_{max}) (± standard error) = 1.77 (±0.23) mg/L, the mean time to reach C_{max} (T_{max}) = 0.81 (±0.16) hour, and the mean area-under-the curve (AUC) = 25.8 (±2.2) mg·h/L. While the effects of sex on the disposition of mifepristone have not been evaluated using Mifeprex®, no sex differences in PK of mifepristone were seen with 300 mg mifepristone in a different NDA review (Korlym™, NDA 202107, Clinical Pharmacology review). Therefore, Section 12.3 of the proposed label in a PLR format should include the available PK data of mifepristone 200 mg tablet.
>
> Cytochrome P450 3A4 (CYP3A4) plays an important role in the metabolism of mifepristone. Therefore, concomitant intake of CYP3A4 inducers with mifepristone

is anticipated to have a significant effect on the disposition of mifepristone. However, the Sponsor did not conduct any *in vivo* studies to evaluate the effect of CYP3A4 inducers on the PK of Mifeprex®. Although the lowest effective therapeutic margin of mifepristone for termination of pregnancy has been not characterized clearly, the use of misoprostol in the regimen for Mifeprex® contributes to efficacy for inducing termination of pregnancy. In addition, concomitant intake of CYP3A4 inducers does not appear to affect the systemic exposure of misoprostol. In the proposed new regimen, another dose of misoprostol can be administered following day 7 to 14 of post-treatment of mifepristone if termination of pregnancy does not occur.

In summary, the contribution of misoprostol in termination of pregnancy and additional dosing option of misoprostol may compensate the possibly diminished efficacy of Mifeprex® in the users of CYP3A4 inducers. However, the labeling information should include the practical clinical guidance for the subject who has been exposed to CYP3A4 inducers.

Reviewers comments:

- **We agree with the Clinical Pharmacology conclusions and recommendations made by (b) (6).**

- **Within the last 10 years, administration of oral mifepristone followed by buccal misoprostol for early medical abortion has become the standard of care for MAB in many countries, including the US. This is based on 1) the PK profile of different doses and routes of administration for misoprostol, and 2) many clinical trials comparing the efficacy and safety of different dosing regimens.**

From Chen and Creinin (2015)[12]:

"With buccal administration, misoprostol is held in the buccal pouch between the teeth and gums for 30 minutes before swallowing any remaining tablets. Buccal misoprostol is slowly absorbed, unlike oral misoprostol, which is rapidly absorbed and undergoes extensive first-pass metabolism. After a dose of oral misoprostol, plasma misoprostol acid levels peak quickly at 30 minutes and decrease rapidly by 120 minutes. In contrast, after buccal administration, plasma misoprostol acid levels rise gradually to peak concentration after a median time of 75 minutes and fall slowly over several hours."

[12] Chen MJ, Creinin MD. Mifepristone with Buccal Misoprostol for Medical Abortion Obstet Gynecol: a Systematic Review. Obstet Gynecol 2015;126(1):12-21.

The PK profile of vaginal misoprostol is very similar to that of buccal misoprostol. These pharmacological differences between vaginal and buccal misoprostol do not have a clinically meaningful effect on the efficacy at different gestational weeks and the adverse event profile for the combination of mifepristone and misoprostol for early medical abortion. Those routes with rapid and significant absorption (e.g., sublingual) also have high efficacy (ACOG Bulletin[1]). This review, however, focuses primarily on the new dosing regimen proposed by the Applicant with some supportive data from studies that used vaginal and sublingual misoprostol.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

There were many studies that provided data for this NDA review. The original US trial that was reviewed for the Mifeprex approval in 2000 was performed over 20 years ago in 1994-95. Subsequently, there has been 20 years of experience with MAB, guidelines from professional organizations here and abroad, and clinical trials that have been published in the peer-reviewed medical literature. This review focuses on the information submitted by the Applicant for the change in the dosing regimen and follow-up.

For a complete list of all sources of information, see the extensive list of references in Appendix 9.6 at the end of this review.

Table 1: List of Major Studies Reviewed

USA	International
Gatter 2015[13], retrospective	Louie 2014[14], Azerbaijan, prospective
Ireland 2015[15], retrospective	Ngoc 2014[16], Vietnam, prospective
Chong, 2015[17], prospective single-arm	Raymond 2013[18], International, including US, retrospective
Winikoff 2012[19], prospective	Goldstone 2012[20], Australia, retrospective
Perriera 2010[21], prospective	Boersma 2011[22], Curacao, prospective
Winikoff 2008[23], RCT*	Middleton 2005[24], prospective
Creinin 2007[25], prospective	Spitz 1998[26], single arm trial

[13] Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.

[14] Louie KS, Tsereteli T, Chong E, Ailyeva F, Rzayeva G, Winikoff B. Acceptability and feasibility of mifepristone medical abortion in the early first trimester in Azerbaijan. Eur J Contracept Reprod Health Care 2014;19(6):457-464.

[15] Ireland LD, Gatter M, Chen AY. Medical compared with surgical abortion for effective pregnancy termination in the first trimester. Obstet Gynecol 2015;126:22-8.

[16] Ngoc NTN, et al. Acceptability and feasibility of phone follow-up after early medical abortion in Vietnam: A randomized controlled trial. Obstet Gynecol 2014;123:88-95.

[17] Chong E, Frye LJ, Castle J, Dean G, Kuehl L, Winikoff B. A prospective, non-randomized study of home use of mifepristone for medical abortion in the US. Contraception 2015;92:215-291.

[18] Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. Contraception 2013;87(1):26-37.

[19] Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012;120:1070-6.

[20] Goldstone P, Michelson J, Williamson E. Early medical abortion using low-dose mifepristone followed by buccal misoprostol: A large Australian observational study. Med J Austral 2012; 197: 282-6.

[21] Perriera LK, Reeves MF, Chen BA, Hohmann HL, Hayes J, Creinin MD. Feasibility of telephone follow-up after medical abortion. Contraception 2010;81:143-149.

[22] Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. Eur J Contracept Reprod Health Care 2011;16:61-6.

[23]Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. Obstet Gynecol 2008;112(6):1303-1310.

[24] Middleton T, et al. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. Contraception 2005;72:328-32.

[25] Creinin MD, Schreiber CA, Bednarek P, Lintu H, Wagner MS, Meyn LA. Medical Abortion at the Same

Source: compiled by clinical reviewers. *Randomized controlled trial.

Reviewer's comment:

Table 1 **above lists the major studies and review articles covering over 45,000 women who had an early MAB through 70 days gestation. Both retrospective and prospective studies were found to be valuable for this review. There are additional studies submitted by the Applicant that are not quoted or reviewed primarily because they did not use a dosing regimen relevant to that proposed by the Applicant or did not contain information pertinent to the other requested changes (e.g., less restrictive follow-up requirements or gestations through 70 days) in the NDA supplement. In some cases, studies that used variants of the proposed regimen were considered because PK, PD and clinical data indicate the relevance of data on vaginally-administered misoprostol, and because lower doses and certain other routes of administration of misoprostol are expected to have lower or similar levels of effectiveness.**

5.1.1 Submissions during the Review Process

During the course of the review, the Applicant submitted additional supportive articles from the peer-reviewed medical literature, and provided more detailed data from previously submitted articles based on direct communication with the authors. Further, the Applicant submitted changes to some of the original proposals. Below in Table 2 is a list of the clinical submissions to the NDA after the initial submission dated May 18, 2015.

Time (MAST Study Trial Group). Mifepristone and misoprostol administered simultaneously versus 24 hours apart for abortion a randomized controlled trial. Obstet Gynecol 2007;109:885-894.

[26] Spitz IM, et al. Early Pregnancy Termination with Mifepristone and Misoprostol in the United States. NEJM 1998;338(18):1241-47.

Table 2 Clinical Submissions during the Course of the Review

Item	Submission Type, Date
Additional supportive articles More detailed data from previously submitted articles	Amendment # 3, dated 9/23/2015 Amendment # 4, dated 10/13/2015 Amendment # 5, dated 11/16/2015 Amendment # 6, dated 12/8/2015
Additional supportive documents on patient counseling	Follow-up to 1/27/2016 teleconference, dated 2/2/2016
Additional supportive articles	Amendment # 8, dated 2/25/2016
Proposed Additional Changes	
REMS amendment, Revised REMS Supporting Document Additional supportive articles	Amendment # 2, dated 7/16/2015
REMS modification	Dated 11/4/2015
Labeling: (b) (4) Indication Statement	Amendment # 4, dated 10/13/2015
Labeling changes: (b) (4) the proposed new dosage regimen (b) (4)	Follow-up to 1/27/2016 teleconference, dated 2/15/2016, Also in Amendment # 9, dated 2/25/2016
Labeling: changes to Sections 2.4, 5.2, 6.1, 7, 8.1, 8.2, 8.6, 12.3, 14	Amendment # 7, dated 2/23/2016
Labeling changes: revise indication statement to state “through 70 days gestation	Amendment # 9, dated 2/25/2016
Labeling: changes to Sections 2.3, 6.1 and 14	Amendment # 10, dated 3/17/2016
REMS documents	Amendment #11, dated 3/21/2016

Source: Reviewer table.

5.2 Review Strategy

This is a joint review by two medical officers: (b) (6) reviewed the efficacy data and (b) (6) reviewed safety data and related issues. Other sections are jointly completed.

Within the last 10 years, use of buccal misoprostol with mifepristone for MAB has become commonplace. However, the published literature did not contain abundant information about medical abortion outcomes with buccal misoprostol at the time of the

original NDA review. In this review, we summarize clinical outcomes and adverse effects of medical abortion regimens consisting of oral mifepristone 200 mg followed in 24-48 hours by buccal misoprostol 800 mcg in pregnancies through 70 days of gestation.

5.2.1 Discussion of Individual Studies/Clinical Trials

Information and findings from individual clinical trials and reviews in the published medical literature, websites, the Applicant and other sources are discussed in different sections throughout this review. As acknowledged during pre-submission discussions between the Applicant and (b) (6) and as is typical for literature-based submissions, original datasets from the trials that are cited were not available for submission in this supplement.

6 Review of Efficacy

Efficacy Summary

This summary lists the final conclusions based on review of the data. Not all of the conclusions, regarding covariates such as ethnicity, parity, previous abortion, are specifically addressed in labeling, but the reviewers believe that it is important to show that we evaluated many different aspects and potential risk factors for safe and effective MAB:

- Medical termination of pregnancies through 70 days gestation is safe and effective and should be approved using the new proposed regimen.
- The original approved dosing regimen remains safe and effective but the new proposed dosing regimen is effective and should be approved for use in gestations through 70 days (10 weeks) gestation.
- 2015 Chen-Creinin review[12] of over 33,800 MABs concluded that regimens with a 24-hour time interval between mifepristone and buccal misoprostol administration are slightly less effective (94.2% success) compared to those with a 24-48-hour interval (96.8% success).
- 2013 Raymond review[18] of over 45,500 MABs using oral mifepristone 200 mg and various misoprostol doses concluded that the effectiveness decreases when:
    - misoprostol is taken orally compared to the three other routes of administration (buccal, sublingual, or vaginal)
    - the gestational age increases
    - the mifepristone-misoprostol interval is less than 24 hours
    - the total misoprostol dose is 400 mcg or less
- Efficacy in the adolescent population is the same or slightly better compared to non-adolescent women.

- Efficacy outcomes do not appear to be related to other baseline characteristics including age, race, body weight, gravidity and previous spontaneous abortions. (Spitz data[26] and many subsequent studies)
- Data from the original US trial (1994-95; Spitz 1998[26]) showed lower efficacy rates with the originally approved Mifeprex dosing than is reported in a large number of subsequent trials using different mifepristone-misoprostol dosing regimens for early MAB. There does not appear to be any change in the safety profile.
- Raymond (2013 systematic review[18]) found no significant association between abortion failure rates and the timing of the follow-up evaluation.
- Over 30% of women will completely expel the products of conception within 4-5 hours of taking the misoprostol for MAB with gestations of 57-70 days (Winikoff 2012[19]); this finding supports the proposal to allow women to choose the timing of (within the labeled range) and where to take the misoprostol.
    - Data from the original NDA review showed occurrence of a successful (complete) MAB occurred in ≤ 4 hours after misoprostol administration in 45-46% of women up to 56 days gestation and 34.9% of women at 57-63 days gestation.
- Home administration of misoprostol is efficacious, practical, and safe (see Safety Section)

Reviewer's overall comment:

Compared to the current Mifeprex approved label and regimen, the Applicant has requested less restrictive measures for location and timing of misoprostol administration and follow-up measures for early MAB. We believe that a regimen that includes these less restrictive measures is equally safe and effective, while offering women greater convenience and providing a less burdensome procedure for patients and providers.

6.1 Indication

In the initial submission of this efficacy supplement, the proposed new indication was the following: "Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (b) (4)" In Amendment # 9, submitted on February 25, 2016, the Applicant proposed (b) (4) the gestational age through 70 days.

The proposed new modified regimen uses buccal (not oral) misoprostol administered 24-48 hours after taking a lower dose, 200 mg instead of 600mg, of oral mifepristone. The labeled dose of misoprostol is increased compared to the current approved regimen, from 400 mcg to 800 mcg. (b) (4) , the

(b) (4)
.

These requests were thoroughly reviewed by the Agency and we believe the product is safe and effective for the indication, which reads:

> "Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation."

6.1.1 Methods

There were numerous articles from the peer-reviewed medical literature that were submitted by the Applicant. Articles were also cited in three letters sent to CDER Center Director Janet Woodcock, MD from 1) ACOG, 2) a group of academic professionals and women's health non-profit organizations, and 3) thirty professional and academic organizations, all of which requested changes to the Mifeprex labeling and REMS. All relevant publications cited in those three letters were also submitted by the Applicant for our review. The articles and sources of data used for this review are listed in the Reference List in Appendix 9.6 at the end of this review.

The various studies noted in the articles had slightly different designs, inclusion criteria, dosing regimens and endpoints for safety and efficacy. The review focus is on clinical trials and follow-up methods for early medical abortion, including gestations through 70 days (10 weeks).

6.1.2 Demographics

Many of the trials were randomized and some were blinded to the actual dose of the two drugs that were administered. The route of misoprostol administration could not be easily blinded. Although there may have been some small differences in the demographic data for the different arms, it is doubtful that demographic differences such as race or ethnicity are clinically meaningful in relation to the safety and efficacy of medical abortion.

6.1.3 Subject Disposition

Most of the studies noted the number of women who were lost to follow-up and did not count them in the efficacy analysis. All women with any available safety data were included in the safety analyses. See Safety Section for further discussion.

6.1.4 Analysis of Primary Endpoint(s)

The studies analyzed for data used in this NDA review almost universally defined their primary efficacy endpoint as expulsion of the pregnancy from the uterus without need for any surgical evacuation or procedure for any reason (including patient request).

6.1.5 Analysis of Secondary Endpoints(s)

In addition to the final outcome of MAB success or lack of success (i.e., surgical or medical intervention needed), there are intermediate outcomes:

- Incomplete abortion: pregnancy no longer ongoing, but only partial or non-expulsion of the products of conception has occurred
- Ongoing pregnancy based on fetal heartbeat and/or growth

In the case of incomplete expulsion but where the pregnancy is no longer ongoing, there are in the US several safe options available to the healthcare provider and the patient:

- Expectant management (in many cases, complete expulsion will occur spontaneously given additional time)
- Additional dose of misoprostol
- Minor surgical procedure such as a vacuum aspiration in the clinic/office
- Surgical procedure under anesthesia such as a dilation and curettage (D&C)

For ongoing pregnancies following the initial MAB procedure, typically one of the surgical procedures is performed.

In addition to these two intermediate outcomes, there are other cases in which a surgical intervention might be performed:

- Intervention because of bleeding or other aspect of the patient's condition: the healthcare provider judges that surgical intervention is indicated
- Patient request: the patient requests surgical intervention for any reason

6.1.6 Proposal for a New Dosing Regimen

There are five major changes proposed by the Applicant in this supplement for which efficacy data will be discussed. The changes are interrelated and, in general, the same studies usually provide evidence to support multiple changes, although data from a given study may be more or less pertinent to a specific change (e.g., extending the approved gestational age, home administration of buccal misoprostol, etc.).

Summary of changes to dosing regimen, indication, and follow-up initially requested by the Applicant in the NDA Supplement:

1. **Addition of a new dosing regimen of Mifeprex 200 mg orally followed by the buccal administration of 800 mcg misoprostol at 24-48 hours instead of 48 hours**

2. **Increase in gestational age from (b) (4)**

3. **Option to administer misoprostol outside of the clinic**

4. **Option that a repeat dose of misoprostol may be used if needed for women using the new proposed dosing regimen**

5. **Follow-up timing and methods: follow-up is needed at 7-14 days after Mifeprex administration; the specific nature and timing of the follow-up to be agreed upon by the (b) (4) and patient. The current approved label states: "Patients will return for a follow-up visit approximately 14 days after the administration of Mifeprex."**

Discussion and analysis of the data supporting the five changes follows in five individual sections.

1. **Proposal of a new dosing regimen that:**
   1) decreases the oral dose of Mifeprex from 600 mg to 200 mg orally,
   2) increases the misoprostol dose from 400 mcg orally to 800 mcg misoprostol administered buccally, and
   3) revises the interval between Mifeprex and misoprostol dosing from 48 hours to "24-48 hours."

(b) (4)
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Background on some dosing data and US practices:

There is ample medical evidence that the currently approved dose regimen (oral mifepristone 600 mg followed 2 days later with oral misoprostol 400 mcg) is safe and efficacious up to 49 days gestation. It was approved in September 2000 based on the US clinical trial of 1994-95 and two French trials. After 1995, however, more studies gradually became available using lower doses of mifepristone and different doses and routes of administration for misoprostol. These newer data were not submitted to or considered in the original NDA review. Studies also showed that with lower doses (< 600 mg) of oral mifepristone followed by oral misoprostol 400 mcg, the treatment success rate is greater than 95% up to 49 days gestation.

It is difficult to tell how many MABs in the US actually used the FDA-approved dosing regimen following the 2000 approval. It is clear that many clinics and individual practitioners did not. For example, from 2001 to March 2006, Planned Parenthood Federation of America (PPFA) health centers throughout the United States provided medical abortions principally using a regimen of oral mifepristone 200 mg, followed 24–48 hours later by 800 mcg misoprostol administered vaginally at home.[27] Of note, PPFA has been and continues to be the largest provider of MAB services in the US.

[27] Fjerstad M, Sivin I, Lichtenberg ES, Trussell J, Cleland K, Cullins V. Effectiveness of medical abortion

Reviewer's comment:

The 2009 Fjerstad article[28] states that PPFA was a federation of 97 independent local affiliates operating 880 health centers throughout the US; roughly 300 of those centers provided medical abortion. So, within one year of the FDA Mifeprex approval, PPFA was using a dosing regimen (actual doses and routes of administration) very similar to that proposed in this efficacy supplement.

Meanwhile, from September 2003 to June 2005, there were four fatalities in the US and one in August 2001 in a Canadian clinical trial, all due to a sudden and rapid sepsis secondary to the bacteria *Clostridium sordellii*. The five cases were with early MAB (all around 7 weeks gestation) in women who had used 800 mcg vaginal misoprostol. By late March 2006, consideration of these fatal uterine infections led PPFA to 1) change the route of administration of the 800 mcg misoprostol from vaginal to buccal (or, much less commonly, oral) and 2) employ additional measures (sexually transmitted infection [STI] testing and treatment if positive, or use of prophylactic antibiotics) to minimize the risk of subsequent serious uterine infections. In July 2007, PPFA began requiring routine treatment with antibiotics for all medical abortions at their health centers.[28]

Reviewer's comment:

As stated in currently approved labeling "No causal relationship between the use of Mifeprex and misoprostol and these events [serious and sometimes fatal infections and bleeding] has been established." There is no clear evidence that the vaginal use of misoprostol causes infection, and no causal association has been identified between the cases of sepsis and vaginal administration of misoprostol. While labeling was revised in November 2004 and July 2005 to recommend that providers have a high index of suspicion in order to rule out serious infection and sepsis, the Agency did not consider there was sufficient evidence to justify recommending prophylactic antibiotics.

A 2006 article showed that in pregnancies greater than 49 days gestation, compared to oral administration of misoprostol, the bioavailability and efficacy with use of misoprostol is increased by vaginal, sublingual and buccal administration, avoiding first-pass metabolism by the liver.[29] Furthermore, a 2009 review of MAB[30] noted that:

> "Consistent with other kinetic studies, clinical trials have demonstrated no change in efficacy when mifepristone doses are reduced from 600 to 200 mg. Multiple

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with mifepristone and buccal misoprostol through 59 gestational days. Contraception 2009;80:282-6.

[28] Fjerstad M, Trussell J, et al. Rates of serious infection after changes in regimens for medical abortion. NEJM 2009;361:145-51.

[29] Fiala C, Gemzell-Danielsson K. Review of medical abortion using mifepristone in combination with prostaglandin analogue. Contraception 2006;74:66-86.

[30] Bartz B, Goldberg A. Medical Abortion. Clin Obstet and Gyn 2009; 52:140-50.

> clinical studies, including a 2004 Cochrane meta-analysis, reported that a regimen of 200 mg of oral mifepristone followed 24 to 48 hours later by 800 mcg of vaginal misoprostol results in complete abortion in 96% of cases at gestations of up to 63 days and that increasing the mifepristone dose to 600 mg does not improve efficacy."

In a 2010 review article covering 25 years of the clinical development of mifepristone followed by a prostaglandin for MAB, Spitz[31] noted similar conclusions:

> "In the US, most investigators administer 200 mg rather than 600 mg mifepristone as many trials have shown equivalent results with these two dose schedules. A recent meta-analysis of four randomized controlled trials compared the two dose regimens. Endpoints were complete abortion, continuing pregnancy and side effects. The two doses *[600 v. 200 mg mifepristone]* result in similar rates of complete abortion with no difference in adverse events."

Another change in clinical practice was related to the labeling stipulation that women return to the clinic/office two days after Mifeprex was administered to take the misoprostol dose. Many experts involved with termination of early pregnancies also advocated misoprostol self-administration at home to mitigate the time, travel and inconvenience of this additional visit.

In the US, the American College of Obstetricians and Gynecologists (ACOG), National Abortion Federation[32], and PPFA currently all endorse the lower oral dose of mifepristone followed in 24-48 hours with misoprostol. According to the 2014 ACOG Practice Bulletin, the misoprostol route of administration may be oral, buccal, sublingual or vaginal; sublingual administration, however, has a more rapid absorption resulting in a higher incidence of adverse side effects.[1]

<u>European practice</u>:

In December 2011, the International Federation of Obstetrics and Gynaecology (FIGO) published revised guidelines for the use of mifepristone and misoprostol for MAB up to 63 days, 64-84 days, and after 84 days (12 weeks) gestation.[33] The FIGO recommended regimens using 200 mg of oral mifepristone followed by 800 mcg of misoprostol administered vaginally, buccally, or sublingually. Up to 57-63 days gestational age, misoprostol is taken 24-48 hours after mifepristone. Per the review of data available to them, FIGO decided additional doses of 400 mcg misoprostol may be

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[31] Spitz IM. Mifepristone: where do we come from and where are we going? Clinical development over a quarter of a century. Contraception 2010;82:442–52.

[32] National Abortion Federation Guidelines 2015.

[33] Faundes A. The combination of mifepristone and misoprostol for the termination of pregnancy. *Int J Gynecol Obstet* 2011;115:1-4.

safely used depending on gestational age, and these combinations result in a complete termination in more than 95% of cases.

Similar guidelines using either vaginal, buccal, or sublingual misoprostol are endorsed by the World Health Organization (WHO), the United Kingdom Royal College of Obstetricians and Gynecologists[34], and a recent Cochrane Review (2011, Issue11).[35]

Reviewer's Comment:

From the above discussion, it is clear that the standard of care in the US for early MAB has deviated from the FDA-approved dosing regimen. PPFA provides the largest number of medical abortions each year in the US and as early as 2001, was already using the regimen of 200 mg oral mifepristone followed 24-48 hours later by 800 mcg vaginal misoprostol.

There are a large number of studies and reviews that support the efficacy of the proposed new dose regimen through 63-70 days gestation. Efficacy was defined in these studies as a complete expulsion of the pregnancy without need for surgical intervention for any reason during the follow up period. The 2015 review by Chen and Creinin summarized clinical outcomes and adverse effects from 20 MAB studies including a total of 33,846 women using regimens consisting of 200 mg oral mifepristone followed by buccal misoprostol through 70 days gestation. All studies except two used 800 mcg misoprostol. Two studies (827 women) used 400 mcg buccal misoprostol. Six studies used a 24-hour time interval between mifepristone and buccal misoprostol administration and 14 used a 24-48 hour window for the dosing interval. The table below lists the 15 studies using the proposed doses (200 mg plus 800 mcg) with a 24-48 hour dosing interval.

[34] Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion: evidence-based clinical guideline Number 7. 3rd ed. London (UK):RCOG Press 2011.

[35] Kulier R, Kapp N, et al. Medical methods for first trimester abortion (Review). The Cochrane Library 2011, Issue 11:1-126.

Table 3: Efficacy- Mifepristone 200 mg with Buccal Misoprostol 800 mcg 24-48 Hours Later - US Studies

Study &Year	Design, Location	Gestation (maximum days)	M-M Interval (hrs)	Evaluable Subjects (N)	Success - no intervention (%)
Middleton 2005[24] US	**Prospective**	56	24-48	216	94.9
Winikoff 2008[23] US	**Prospective**	63	24-36	421	96.2
Fjerstad 2009[27] US	**Retrospective**	59	24-48	1,349	98.3
Grossman 2011[36] US - Clinic Mife v. Tele-med	**Prospective**	63	24-48	449	Clinic: 96.9% Telemed: 98.7%
Winikoff 2012[19] US	**Prospective**	57-70	24-48	629	93.2
Gatter 2015[13] US	**Retrospective**	63	24-48	13,373	97.7
Chong 2015[17] US	**Prospective**	63	24-48	357	96.7
TOTALS	**7 Studies**	**56-70 days**	**24-48 hr**	**16,794**	**97.4**

Source: Modified from Table 3, page 14-15, Chen-Creinin 2015 Review and submitted articles. All subjects had 200 mg oral mifepristone followed by 800 mcg buccal misoprostol.

Success percentages calculated by clinical reviewer.

[36] Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectivenesss and acceptability of medical abortion provided thorugh telemedicine. Obstet Gynecol 2011;118:296-303.

Table 4: Efficacy- Mifepristone 200 mg with Buccal Misoprostol 800 mcg 24-48 Hours Later- Non- US Studies

Study &Year/Country	Design, Location	Gestation (maximum)	M-M Interval (hrs)	Evaluable Subjects (N)	Success - no intervention (%)
Alam 2013[37] Bangladesh	**Prospective**	63	24	629	92.7
Blum 2012[70]	**Prospective**	63	24	210	92.9
Boersma 2011[22] Curacao	**Prospective**	70	24-48	307	97.7
Chai 2013[38] Hong Kong	**Prospective**	63	48	45	95.6
Dahiya 2012[39] India	**Prospective**	50	24	50	92
Chong 2012[40] Georgia, Vietnam	**Prospective**	63	36-48	560	96.4
Giri 2011[41] Nepal	**Prospective**	63	24	95	93.6
Goldstone 2012[20] Australia	**Retrospective**	63	24-48	11,155	96.5
Louie 2014[14] Azerbaijan	**Prospective**	63	24-48	863	97.3
Ngo 2012[42] China	**Retrospective**	63	36-48	167	91.0
Ngoc 2011[43] Vietnam	**Prospective**	63	24	201	96.5
Ngoc 2014[16] Vietnam	**Prospective**	63	24-48	1,371	94.7
Olavarietta 2015[85] Mexico	**Prospective**	70	24	884	98.2
Pena 2014[44] Mexico	**Prospective**	70	24-48	971	97.3

[37] Alam A, Bracken H et al. Acceptability and Feasibility of Mifepristone-Misoprostol for Menstrual Regulation in Bangladesh. Intnational Persp on Sexual and Reprod Health 2013;39(2):79-87.

[38] Chai J, Wong CY, Ho PC. A randomized clinical trial comparing the short-term side effects of sublingual and buccal routes of misoprostol administration for medical abortions up to 63 days' gestation. Contraception 2013;87:480-5.

[39] Dahiya K, Ahuja K, Dhingra A et al. Efficacy and safety of mifepristone and buccal misoprostol versus buccal misoprostol alone for medical abortion. Arch Gynecol Obstet 2012; 285: 1055-8

[40] Chong E, Tsereteli T, Nguyen NN, Winikoff B. A randomized controlled trial of different buccal misoprostol doses in mifepristone medical abortion. Contraception 2012;86:251-6.

[41] Giri A, Tuladhar H et al. Prospective study of medical abortion in Nepal Medical College- a one year experience. Nepal Medical Coll J 2011;13(3):213-15.

[42] Ngo TD, Park MH, Xiao Y. Comparing the WHO versus China recommended protocol for first trimester medical abortion: a retrospective analysis. Int J Womens Health 2012;4:123-7.

[43] Ngoc NTN, et al. Comparing two early medical abortion regimens: mifepristone+misoprostol vs. misoprostol alone. Contraception 2011;83:410-17.

[44] Pena M, Dzuba IG, Smith PS, et al. Efficacy and acceptability of a mifepristone-misoprostol combined

Sanhueza 2015[48] Mexico	**Prospective**	70	24-48	896	93.3
TOTALS	**15 Studies**	**56-70 days**	**24-48 hrs**	**18,425**	**96.1%**

Source: Modified from Table 3, page 14-15, Chen-Creinin 2015 Review and submitted articles. All subjects had 200 mg oral mifepristone followed by 800 mcg buccal misoprostol.

Success percentages calculated by clinical reviewer.

Reviewer's comments:

The data above in Table 3 and Table 4 from ~16,800 US women and ~18,400 non-US women in clinical studies of MAB through 70 days gestation with success rates of 97.4% (US) and 96.1% (non-US) strongly support the proposed new dosing regimen and the extension of the acceptable gestational age. The number of US and non-US studies, the number of evaluable women, and the overall complete abortion rates (termination with no surgical intervention) will be described in the efficacy table in Section 14 CLINICAL STUDIES in the new approved label. Additional discussion on increasing the gestational age through 70 days follows in the next major section.

Precise timing of the administration of misoprostol has not been shown to result in a higher success rate which is why the majority of the above studies allowed a range of hours between the mifepristone dose and misoprostol dose rather than one set time between the two drugs. The 2013 Raymond systematic review[18] of 87 studies that exclusively used a mifepristone 200 mg oral dose in over 45,000 women, followed by varying doses and routes of administration of misoprostol, concluded that if the mifepristone-misoprostol interval is < 24 hours, the procedure is less effective compared to an interval of 24-48 hours.

Another study[45] also looked at the question of the mifepristone-misoprostol interval. The authors conducted a systematic review of randomized controlled trials published from 1999 to 2008 to assess the evidence for a shorter mifepristone and misoprostol administration interval for first trimester medical termination. Searching strategy included MEDLINE, EMBASE, CLINAHL and Cochrane Library. The primary outcome measure was complete abortion without the need for a surgical procedure. "Five randomized controlled trials (RCTs) compared the efficacy of mifepristone-misoprostol administration intervals between 0 and 72 hours in 5,139 participants. The complete abortion rates varied between 90% and 98%. Although the meta-analysis of pooled data of all five RCTs showed no statistically significant difference in efficacy between

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regimen for early induced abortion among women in Mexico City. Int J Gynaecol Obstet 2014;127:82-5.

[45] Wedisinghe L and Elsandabesee D. Flexible mifepristone and misoprostol administration interval for first-trimester medical termination. Contraception 2010;81(4):269-74. doi: 10.1016/ j.contraception.2009.09.007. Epub Oct 29, 2009.

the shorter and longer dosing intervals, there was a trend toward slightly lower success rates with administration intervals < 8 hours." This study supports the finding that the proposed regimen is effective with the 24-48 hour flexible interval. Labeling will indicate that the regimen may not work as well if the misoprostol is taken earlier than 24 hours after Mifeprex.

Reviewer's Final Recommendation:

The new proposed regimen of 200 mg oral mifepristone followed in 24-48 hours with 800 mcg buccal misoprostol should be approved; there are sufficient data from the medical literature with over 35,000 women supporting the regimen's efficacy (termination without any additional surgical intervention) as being in the 91-98% range.

6.1.7 Increase in gestational age from 49 days to 70 days

Original NDA review:

The US clinical trial[31] was conducted from September 1994 to September 1995 and treated 2,121 women. A total of 2,015 women (95%) returned at the 14-day follow-up visit. The trial categorized women into three groups based on gestational age at the time of procedure, and evaluated the rates of "Success" (a complete pregnancy termination without use of any additional doses of misoprostol or surgical intervention), and the rates of "Failure" (with four sub-categories of incomplete abortion, ongoing pregnancy, intervention for medical reason, and intervention solely because of patient request). The success and failure data are shown in Table 5.

Table 5: Original NDA Efficacy Results

OUTCOME	≤ 49 Days N= 827 (%)	50-56 Days N= 678 (%)	57-63 Days N= 510 (%)
Success (mifepristone + misoprostol	**762 (92)**	**563 (83)**	**395 (77)*†**
Failure (any surgical intervention for any reason) N (%)			
Total failures	**8%**	**17%**	**23%*†**
Incomplete abortion	39 (5)	51 (8)‡	36 (7)
Ongoing pregnancy	8 (1)	25 (4)*	46 (9)* §
Medical indication for intervention	13 (2)	26 (4)‡	21 (4)‡
Patient's request for intervention	5 (0.6)	13 (2)	12 (2)‡

***P<0.001 for the comparison with the ≤ 49-days group.**

†P= 0.02 for the comparison with the 50 to 56-days group.

‡ 0.001 ≤ P<0.03 for the comparison with the ≤ 49-days group.

§ P<0.001 for the comparison with the 50 to 56-days group.

Source: Modified from Table 1, pg 1243 in the Spitz NEJM article (1998).

Reviewer's comments:

Looking at the results in the table above, it is reasonable that the approved use was only for women in the first 49 days' gestation, given the 8% "failure rate" in this subgroup, compared to 17% and 23% failure rates for the longer gestations. It is important to note that failure was defined as any case requiring surgical intervention for any of the following reasons:

- **incomplete abortion (incomplete expulsion)**
- **documented ongoing pregnancy**
- **medical reasons (usually heavy vaginal bleeding with or without retained products of conception)**
- **patient request (usually for bleeding)**

As has been pointed out, since the US trial data used for the FDA approval of Mifeprex, given the experience and data gained in the last 20 years from millions of women in the US and abroad, the success rates and overall outcomes are very different. Currently, when a "failure" occurs, using the original definition, options that are now commonly available include the following:

- **expectant management (wait and see) in the case of an incomplete abortion (i.e., pregnancy terminated but not fully expelled)***
- **medical treatment for bleeding, pain and other common symptoms**
- **clinical evaluation with the use of 1) office ultrasound and/or 2) hCG data determined by rapid, sensitive urine and/or serum testing***
- **additional doses of misoprostol for an incomplete abortion***
- **less invasive surgical intervention (vacuum aspiration) in the clinic/office instead of a D&C under anesthesia in an operating room**
- **continuing the pregnancy (although the medical recommendation is to proceed to a surgical abortion in such a case, we acknowledge that a woman could potentially decide to continue the pregnancy)**

*** per protocol, these options were NOT available in the original US trial**

It is also evident that the proposed new dosing regimen is considerably more effective for all gestations through 70 days [see data and discussion that follows for 57-63 and 64-70 days gestation], especially when compared to the original data using the FDA-approved regimen which had "success" rates of only 83% and 77% at 50-56 and 57-63 days gestation, respectively.

Current evidence for increasing the gestational age to 70 days

Current evidence demonstrates that the new proposed medical abortion regimen is effective for women in the range of 57-63 days and 64-70 days of gestation. A 2015

systematic review identified six published studies that recorded data on outcomes of medical abortions performed during gestational Days 64-70.[46]

The published studies were conducted in the United States, UK, Mexico, Curaçao, Vietnam, and the Republic of Georgia. All subjects were treated as outpatients between 2007 and 2015. The older UK study evaluated 127 women who were at 64-70 days gestation and treated with 200 mg oral mifepristone followed by 800 mcg vaginal misoprostol.[47]

Reviewer comment:

We evaluated the data separately for 57-63 and 64-70 days of gestation. The following two tables show the efficacy data for 57-63 and 64-70 days gestation (also known as Week 9 and Week 10).

[46] Abbas D, Chong E, Raymond EG. Outpatient medical abortion is safe and effective through 70days gestation. Contraception 2015;92:197-9.

[47] Gouk EV, et al. Medical termination of pregnancy at 63-83 days gestation. British J Obstet Gyn 1999;106:535-539.

Table 6: MAB Efficacy Outcome 57-63 Days Gestation

Study	Enrolled N	Followed N	Success N (%)	Ongoing Pregnancy N (%)	Lost to Follow up %	Comment
Winikoff [23] 2008 US-	132	115	109 (94.8)	2 (1.7)	13.0%	* Proposed Dosing
Winikoff [19] 2012 US	379	325	304 (93.5)	10 (3.1)	14.2%	* Proposed Dosing
Gatter[13] 2015 US	1527	1286	1228 (95.5)	21 (1.6)	15.8%	* Proposed Dosing
Sanhueza[48] 2015 Mexico City	196	190	171 (90.0)	6 (3.2)	3.1%	* Proposed dosing
Boersma[22] 2011** Curacao	105	95	91 (95.8)	2 (2.1)	9.5%	*Proposed dosing @ 24-36 hr @ home
Pena[44] 2014 Mexico City	177	171	164 (95.9)	2 (1.2)	3.4%	* Proposed dosing
Chong[40] 2012 Viet Nam, Georgia	86	85	79 (92.9)	2 (2.4)	1.2%	*Proposed dosing 36-48 hr
	81	81	77 (95.1)	2 (2.5)	0%	400 mcg buccal @ 36-48 hr
Bracken[49] 2014 4 countries-	389	382	362 (94.8)	7 (1.8)	1.3% (2 women withdrew)	400 mcg sublingual @ 24-48 hr
TOTAL	3,072	2,730	2,585 (94.7)	54 (2.0%)	11.1%	

***Mifepristone oral 200 mg followed in 24-48 hour range with misoprostol buccal 800 mcg.**

****Boersma study reported the interval from 50-63 days without further breakdown.**

Source: Data from published studies.

[48] Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. Reprod Health Matters 2015;22:75-82.

[49] Bracken H ,Dabash R, Tsertsvadze G et al. A two-pill sublingual misoprostol outpatient regimen following mifepristone for medical abortion through 70 days' LMP: a prospective comparative open-label trial. Contraception 2014;89(3):181-6.

Reviewer comments:

Although the Chong and Bracken studies do not use the exact proposed dosing regimen, it is felt that their efficacy results are relevant because both used a lower dose of misoprostol, which, if anything, would have been expected to provide lower efficacy.

After careful review of the above eight studies, we find the following results. A combined total of 3,072 women were treated at 57-63 days of gestation, with 2,730 (88.9%) providing outcome data. Of these women, 2,585 (94.7%) had a complete medical abortion (pregnancy termination without any surgical intervention), and 54 (2.0%) had ongoing pregnancies. This successful treatment rate is better (94.7% compared to 92.1%) than the rate in the data on which the 2000 FDA Mifeprex approval was based. The data are sufficient and acceptable for extending the approval of Mifeprex up to at least 63 days gestation.

The numbers here do not exactly match the results shown in the efficacy table for 57-63 gestational days that are in Section 14 CLINICAL STUDIES in the new approved label, which is limited to studies using the identical dosing regimen to that proposed in this supplement. The number of evaluable women here is higher because the Chong and Bracken data are included, as noted above in the comment. The label, however, states the same conclusion of a 94.7% complete medical abortion rate and a 2% ongoing pregnancy rate.

Data for 64-70 days gestation are found in the next table.

Table 7: MAB Efficacy Outcome 64-70 Days Gestation

Study	Enrolled N	Followed N	Success N (%)	Ongoing Pregnancy N (%)	Lost to Follow up %	Comment
Winikoff[19] 2012	350	304	282 (92.8)	9 (3.0)	13.1	*Proposed dosing
Sanhueza[48] 2015	150	147	134 (91.2)	5 (3.4)	2.0	* Proposed dosing
Boersma[22] 2011†	26	26	25 (96.2)	1 (3.8)	0	Proposed dosing @ 24-36 hr @ home
Pena[44] 2014	2	2	2 (100)	0 (0)	0	* Proposed dosing
Chong[40] 2012 RCT	1	1	1 (100)	0 (0)	0	* Proposed dosing @ 36-48 hr
	6	6	6 (100)	0 (0)	0	400 mcg buccal
[Y]Gouk[47] 1999 UK-misoprostol in hospital	127	127	120 (94.5)	7 (5.5)	0	800 mcg vaginal @ 36-48 hr
Bracken[49] 2014	325	321	295 (91.9)	7 (2.2)	1.2	400 mcg sublingual @ 24-48 hr
TOTAL	987	934	865 (92.6)	29/934 (3.1)	53/987 (5.4)	

*Mifepristone oral 200 mg followed in 24-48 hour range with misoprostol buccal 800 mcg.

[Y]The Gouk study in 1996-97 included 253 women at 63-83 days gestation (Weeks 10-12).

Source: Table modified with data from published studies. See Abbas D et al. Contraception [MAB through 70 days gestation] 92 (2015):197-199.

Reviewer comments:

Use of the Chong and Bracken data is discussed above. Although the Gouk regimen used a different route of administration for misoprostol, the effectiveness of the vaginal route appears to be similar to that of the buccal route; therefore, these data are considered relevant. Data on sublingual administration of misoprostol may be less generalizable due to the different pharmacokinetic (PK) profile and higher AE frequency compared to buccal

administration. Also, see Section 4.4.3 Pharmacokinetics and the Cross Discipline Team Leader review.

The abortion success rates shown above from seven studies are comparable to (and in several studies, greater than) the success rates for medical abortion in the initial 2000 decision for Mifeprex up to 49 days gestation. The proportion of subjects with complete success without any medical or surgical intervention in the US pivotal trial that supported the original approval was 92.1%, as shown in Table 5, in 827 women encompassing all gestational weeks up to 49 days. The data in the above two tables include 3,072 women treated at 57-63 days gestation and 987 women at 64-70 days gestation. We believe that this comprises a sufficient number of women in each gestational week upon which to make a clinical decision, and that the overall 94.7% and 92.6% success rates are acceptable for approval.

The data here clearly establish the efficacy of medical abortion with mifepristone and misoprostol through 70 days gestation. At least two Gynuity Health studies of outpatient medical abortion through 70 days are ongoing, so more information from clinical studies will be available in the future.

It is also worth noting that in November 2015, the National Medical Committee of PPFA approved medical abortion through 70 days, so this is currently their standard of care.

Reviewer's Final Recommendation:

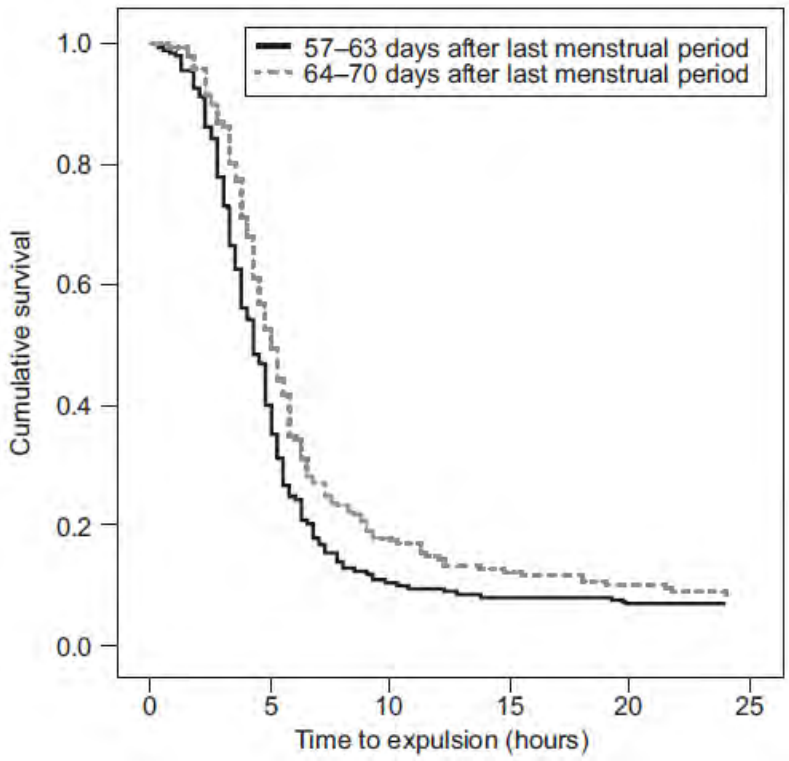
The new proposed regimen of 200 mg oral mifepristone followed in 24-48 hours with 800 mcg buccal misoprostol should be approved for use through 70 days gestation (10 weeks from the first day of the LMP).

6.1.8 At-home Administration of Misoprostol

For the majority of women, the most significant cramping and bleeding will occur within 2-24 hours after taking misoprostol. Requiring women to take misoprostol in the office necessitates another visit and can interfere with the woman's ability to make reasonable plans for the expected bleeding and cramping. With the option to take misoprostol at home the woman can:

- **Plan to experience cramping and bleeding at a safe and convenient time when support is available**
- **Minimize loss of income (for childcare or missed days of work)**
- **Experience improved comfort, satisfaction and privacy**

Data (graph below) from Winikoff (2012)[19] shows the time in hours to complete expulsion of the pregnancy after misoprostol administration for gestations at 57-63 and 64-70 days. Within about 5 hours after misoprostol dosing, 50-60% of the MABs are complete.



Many studies have recorded data on home use in the US and elsewhere and "demonstrated that 87-97% of women find home use of misoprostol acceptable. Home use of misoprostol is now standard in the US."[50] The 2009-10 Swica comparative study focused on the option to take both mifepristone and misoprostol at home after being counseled at the office/clinic. There was no significant difference in either efficacy or safety for the 139 women (46%) who took both medications at home compared to 161 women who took mifepristone in the office and misoprostol at home.

Table 8 that follows is a list of studies where data are available on home use of misoprostol and the specific efficacy findings.

[50] Swica Y, et al. Acceptability of home use of mifepristone for medical abortion. Contraception 2013;88:122-127.

Table 8: Misoprostol Self-administration at Home

Study	Evaluable N	Misoprostol at home	Success	Comment
US Studies				
Gatter 2015[13] US	**13,373**	**All subjects** at 24-48 hr	97.7%	Through 63 days; buccal miso 800 mcg
Winikoff 2008[23] US	421	**All subjects** at 24-36 hr	96.2%	Through 63 days; buccal miso 800 mcg
Winikoff 2012[19] US	629	**All subjects** at 24-48 hr	93.5% (Wk 9) 92.8% (Wk 10)	**Week 9 v Week 10;** buccal miso 800 mcg
Swica 2013[50] US	301	**All subjects** at 6-48 hr	96.7 %- home mife 95.6%- clinic mife	Through 63 days; 800 mcg miso
Foreign Studies				
Louie 2014[14] Azerbaijan	863	794 (92%) at home at 24-48 hr	97%	Through 63 days; buccal miso 800 mcg
Pena 2014[44] Mexico	**1,000**	**All subjects** at 24-48 hr	97.3%	Through 63 days; buccal miso 800 mcg
Bracken 2014[49] 4 countries	703 (382 v 321)	543 (**77%**) took miso at 24-48 hr	94.8% (Wk 9) v 91.9% (Wk 10)	**Week* 9 v Week 10** 400 mcg sublingual miso used
Boersma 2011[22] Curacao	307	**All subjects** at 24-36 hr	97.7%	Through **70 days (Wk 10);** **GP care**; buccal miso 800 mcg;
Chong 2012[40] 400 v 800 buccal	1115 (559 v 563 were enrolled)	851 **(76%)** at 36-48 hr	96.8% with home miso; 95.1% with clinic miso	Through 63 days; *DB, RCT in Vietnam and Georgia
Goldstone 2012[20] Australia:	**11,155**	**All subjects** at 24-48 hr	96.5%	Through 63 days; **buccal miso 800 mcg**
Sanhueza 2015[48]	**896**	**All subjects** at 24-48 hr	93.3	**Through 70 days (Wk 10)**
TOTAL	**30,763**	**30,210 (98.2%)**	**92%-97.7%**	**Different gestations, and regimens**

***DB, RCT: double-blind, randomized clinical trial.**

Source: FDA clinical reviewer table.

Reviewer comments:

The above table with data for home administration of misoprostol for 30,763 women in the US and other countries shows a success rate ranging from 91.9 to

97.7%. The two largest studies (Gatter and Goldstone) pooled showed 97% success using the new proposed dosing regimen with home use of buccal misoprostol. The lowest success rate above of 91.9% in the Bracken study is still supportive for approval and does not differ significantly from results with misoprostol taken in the clinic/office.

Of note is that 4 of the above studies provided data on home use of misoprostol through 70 days gestation.

Home use of misoprostol has been evaluated as part of the proposed protocol in studies including well over 30,000 patients, as well as in studies of home use of both mifepristone and misoprostol. The Raymond (2013) review[18] of early MAB with mifepristone 200 mg and misoprostol (different doses and routes of administration), analyzed 87 trials with 47,283 treated women up to 63 days gestation. The article concludes: "We found no evidence that allowing women to take the misoprostol at home increased the rate of abortion failure or serious complications." It is also notable that the NAF and ACOG guidances encourage home administration of misoprostol and it has been standard protocol for most PPFA clinics for since 2005.

While we do not have age-specific efficacy data for adolescents who took misoprostol at home, it is evident that many adolescents did take buccal misoprostol at home. In the Goldstone 2012 study, there were eight 14 year olds and 931 women ages 15-19 who took misoprostol at home. In the Gatter 2015 study, there were 24 adolescents age 11-14, 82 age 15, 216 age 16, and 435 age 17 who took misoprostol at home. The overall efficacy in these two large studies was excellent, as previously noted.

Reviewer's Final Recommendation:

There is no medical rationale against permitting the woman to be given the misoprostol on the day of the initial clinic/office visit and self-administer it at a convenient time in the next 24-48 hours at home. This would avoid another visit and the time, transportation, loss of work, inconvenience, etc. that such a visit would involve. Furthermore, given the fact that 22-38% of women abort within 3 hours and 50-60% within 5 hours of buccal misoprostol[19], it is preferable for the woman to be in a convenient, safe place (home or at a support person's location) for the expected uterine cramping and vaginal bleeding to occur. The new proposed regimen of 200 mg oral mifepristone followed in 24-48 hours with 800 mcg buccal misoprostol shows acceptable efficacy when misoprostol is self-administered at home.

6.1.9 Use of a Repeat Dose of Misoprostol if Needed

Several studies using buccal misoprostol allowed the option of repeat misoprostol at follow-up one week after mifepristone for persistent gestational sac; however, only a few

studies report specific outcomes. The Chen and Creinin 2015 review[12] of mifepristone with buccal misoprostol for MAB reported on four studies. Chong (2012)[40] provided additional information from 1,122 women. In the study protocols, women with an ongoing pregnancy at follow-up were recommended to undergo uterine suction curettage, whereas women who had retained products of conception were given the options of expectant management, suction curettage/aspiration, or a second dose of misoprostol. Limited additional data were provided by Gatter (2015)[13]: data on the use of a repeat dose of misoprostol were available from a subset of 7,335 women, of whom 87 (1.2%) received a repeat dose. Efficacy results, however, are not stated in the Gatter article, so this study is not included in Table 9, which highlights success rates after a repeat dose of misoprostol in seven published articles that included this specific outcome.

Table 9: Success with a Repeat Dose of Misoprostol - Incomplete MAB

Study/Country	Total N	Mife-Miso Interval (hrs)	Took 2nd Dose	Success with 2nd dose N (%)	Comment
***Raghavan 2010[51] Moldova**	277	24	2	2 (100)	Buccal Miso 400
***Winikoff 2008[23] US**	421	24-36	14	13 (93)	Buccal Miso 800
***Winikoff 2012[19] US**	629	24-48	[Y]20	[Y]Wk 9- 11 (91) Wk 10: 9 (67)	Week 9 v. Week 10: Buccal Miso 800
***Louie 2014[14] Azerbaijan**	863	24-48	16	16 (100)	Buccal Miso 800
Chong 2012[40] Georgia, Vietnam	1122	36-48	47	43 (92)	Buccal Miso 400 and 800 mcg
Boersma 2011[22] Curacao	307	24-36 hr	5	4 (80)	GP care; Buccal Miso 800 at home
Bracken 2014[49] 4 countries	703	24-48 hr	33	29 (88)	Sublingual Miso 400
TOTALS	**4,018**	**--**	**137 (3.4%)**	**123 (90%)**	

***These 4 studies are in Table 4 of the Chen and Creinin 2015 review article.**

[Y]These data are directly from the Winikoff article; the Chen and Creinin review had incorrect data.

Source: table modified by FDA reviewer from Chen and Creinin 2015 article and 3 other studies.

[51] Raghavan S, et al. Comparison of 400 mcg buccal and 400 mcg sublingual misoprostol after mifepristone medical abortion through 63 days' LMP: a randomized controlled trial. Contraception 2010; 82:513-9.

Reviewer's comment:

The completion success rates shown above are high. While only 3.4% of the women took a second misoprostol dose, 90% of these women avoided a surgical procedure to complete their termination. We believe the option of a repeat dose of misoprostol is acceptable and safe in the case that complete expulsion has not occurred after initial dosing (provided that the pregnancy is not still ongoing): it offers a choice for the healthcare provider and the patient on how to manage an incomplete expulsion (retained products of conception) following the initial treatment. As noted above, the other options are expectant management, suction aspiration in the office, or a surgical D&C in the operating room. It is also of note that it is standard protocol in many US clinics to offer the choice of a repeat misoprostol dose, especially for women with an incomplete termination (retained tissue/clots or a documented non-viable pregnancy). A second dose of misoprostol is generally not offered in the case of a documented ongoing pregnancy following use of mifepristone and misoprostol.

Reviewer's Final Recommendation:

Use of a repeat dose of misoprostol may be offered when using the new dosing regimen if the pregnancy has ended, but the expulsion is incomplete.

6.1.10 Physician v Other Healthcare Provider Treatment

The Applicant provided data on the efficacy of medical abortion provided by non-physician healthcare providers, including four studies with 3,200 women in randomized controlled clinical trials and 596 women in prospective cohorts. These studies took place in varying settings (urban, rural, international, low resource). The efficacy results are as follows:

- Olavarietta[85] demonstrated efficacy of 97.9% when the MAB was provided by nurses as compared with 98.4% with physicians
- Kopp Kallner[84] showed efficacy of 99% with certified nurse midwives versus 97.4% with physicians
- Warriner[52] demonstrated efficacy of 97.4% with nurses versus 96.3% with physicians
- Puri[83] showed efficacy of 96.8% compared with 97.4% in the "standard care" group

Reviewer comment:

The above findings for MAB efficacy from 5 studies clearly demonstrates that efficacy is the same with non-physician providers compared to physicians or the

[52] Warriner IK, Wang D, Huong NTM, Thapa K, Tamang A, Shah I et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. Lancet 2011; 377: 1155-61.

"standard care" treatment.

6.1.11 Follow-up Timing and Method

Concerning follow-up timing and method, follow-up within the 7-14 day interval after mifepristone administration is universally recommended; however, follow-up does not necessarily need to be done as currently labeled "in the clinic or healthcare provider's office 14 days after Mifeprex administration."

One strong argument for flexibility in follow-up timing, location and method after the administration of Mifeprex and misoprostol is to avoid placing an undue burden on either the provider or the patient, while maintaining the ability to identify incomplete terminations. The currently approved labeling specifies three visits (two for dosing, one for follow-up) at fairly rigid times that are often not practical, convenient or necessary.

Several articles were submitted by the Applicant to support flexible follow-up. The most noteworthy article is the 2013 Raymond review[18] of over 45,000 MABs using 200 mg oral mifepristone that concluded: "we observed no significant association between abortion failure rates and the timing of the follow-up evaluation." This topic is discussed thoroughly in the Section Submission-Specific Primary Safety Concerns.

Reviewer comment:

Follow-up during the 7-14 day window after the administration of mifepristone is necessary to determine that the termination was successful and the woman is in good health. If for some reason the follow-up contact is not made (the woman is "lost to follow-up"), the clinical guidelines of NAF state that "all attempts to contact the patient (phone calls and letters) must be documented in the patient's medical record." This guideline emphasizes the importance of follow-up but accepts the fact that women are sometimes lost to follow-up and there is no mechanism that can guarantee 100% follow-up in the normal clinical setting.

Reviewer's Final Recommendation:

Follow-up after taking Mifeprex and misoprostol is necessary. The exact timing and method should be flexible and determined jointly by the healthcare provider and the individual woman being treated, and should follow the standard guidelines for the office/clinic where the Mifeprex is being dispensed. Fortunately, there are several choices/methods of follow-up that can be used and it appears that no single option is superior to the others. The woman should always have the option to be seen at the office/clinic.

6.1.12 Subpopulations

Parity

The Raymond (2013) review article[18] had 74 trials with parity data for ~ 32,000 women. In 34 trials whose study populations comprised > 50% nulliparous women, the MAB success rate was 96.4%; in 40 trials with ≤ 50% nulliparous women, the success rate was 94.9%. This suggests that women who have not had a previous term pregnancy

delivery have a slightly higher early MAB success rate. These data are not definitive, however, because such factors as the dosing regimen, route of administration, and gestational age could also influence the success rates.

Previous abortion

One study[26] found that success rates are slightly better in women who have not had a previous abortion. Prior abortion, however, did not appear to be an important risk factor for abortion failure or success (Raymond[18].

Race

There does not appear to be any efficacy difference based on race. Results are reported in studies enrolling a large number of women. Gatter (2015)[13] had five racial/ethnicity groups among over 13,000 women at the PPFA centers in the Los Angeles area; the success rates ranged from a low of 97.2% (African-American) to a high of 97.8% (White, Asian and Other), which is not clinically or statistically significant.

Adolescents v. Older Women

There are at least three articles that support the efficacy of MAB in adolescents; each study used the same definition of success as the need for no further medical or surgical intervention:

- Phelps et al. 2001[53] conducted a pilot study in 28 adolescents aged 14-17, at ≤ 56 days gestation, using Mifeprex 200 mg followed 48 hours later by misoprostol 800 mcg vaginally. All 28 had complete medical terminations without complications or surgical intervention. Five adolescents did not require any misoprostol.
- Niinimaki et al. April 2011:[54] Finnish Registry from 2000-06 comparing rates of AEs in adolescents and adult women with MAB at ≤ 20 weeks gestation, which included 3,024 women < age 18 and 24,006 women age 18 or older. By gestational age, 2,424 adolescents were < 64 days gestation and 139 were within 64-84 days gestation. The specific dose regimens are not stated and may have varied according to the gestational ages. The odds ratio for an incomplete abortion for adolescents under age 18 compared to the women ≥ age 18 was 0.69, meaning that the younger women had a lower rate of incomplete abortions.
- Gatter, Cleland and Nucatola (2015):[13] US data using the proposed regimen of mifepristone 200 mg and misoprostol 800 mcg buccally through 63 days included 283 women aged 17 years and 322 under age 17 (see Table 10). The 605 women under age 18 had a 98.7% success rate while the 6,674 18-24 year olds had a 98.1% success rate. The four older age groups had success rates that ranged from 96.5 to 97.5% without any need for a surgical procedure and additional treatment. In

[53] Phelps RH, et al. Mifepristone abortion in minors. Contraception 2001;64:339-343.

[54] Niinimaki M, et al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. BJM 2011;342: d2111.

the pediatric population, there were no cases requiring transfusion, hospitalization or treatment for severe infection.

The table below shows the age distribution from the Gatter study. There were 24 adolescents between ages 11-14, 82 adolescents age 15, and 216 age 16 totaling 322 adolescents. As noted, 283 adolescents were age 17.

Table 10: MAB Success by Age Group

Age Group (years)	Total N Success (%)	Comment
< 18	**605 (98.7)**	**322 were age 11-16 283 were age 17**
18-24	6684 (98.1)	The age distribution here is representative of other US data on MAB - largest group is age 18-24 followed by age 25-29
25-29	3317 (97.5)	
30-34	1613 (96.5)	
35-39	855 (97.0)	
40+	299 (97.3)	
TOTAL	**13,373 97.7% overall success**	

Source: Data from Gatter 2015 review.

Reviewer comments:

Data from 3,657 adolescents under age 18 in the above three studies shows a MAB success rate that is consistently equal to or higher than that found in the women older than age 17. It is interesting that five (18%) of the adolescents in the Phelps study did not even need misoprostol. The percentage of women not needing any misoprostol is generally much lower, perhaps 1-3%, in other early MAB studies. From the articles reviewed, efficacy of early MAB in the adolescent population is not a concern.

Additional adolescent data were reported in the Goldstone 2012 study[20], where there were eight 14 year olds and 931 women ages 15-19 who took misoprostol at home for a MAB up to 63 days gestation. Efficacy and safety data by age groups were not reported in the article.

6.1.13 Analysis of Clinical Information Relevant to Dosing Recommendations

As noted in some of the reviewer comments and tables, there is evidence that lower doses of misoprostol (400 mcg), other ROAs (vaginal and sublingual), inclusion of more advanced gestational ages, and different dosing intervals between mifepristone and misoprostol have shown acceptable efficacy and safety results. However, for the purposes of this NDA review, our final recommendations are focused on the dosing regimen and other requests specifically made by the Applicant.

6.1.14 Discussion of Persistence of Efficacy and/or Tolerance Effects

There is no evidence that repeated medical or surgical abortion is unsafe or that there is a tolerance effect. Return to fertility is well-documented: in the Patient Counseling Information section, the labeling states "inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses" and "inform the patient that contraception can be initiated as soon as pregnancy expulsion has been confirmed, or before she resumes sexual intercourse."

6.1.15 Additional Efficacy Issues/Analyses

The Applicant has requested that revised labeling provide only for the new proposed regimen and that the original approved regimen be deleted.

Reviewer Final Recommendation:

While there are no safety or efficacy reasons that would lead us to withdraw approval of the currently labeled dosing regimen, we concur that it may be deleted from labeling because very few providers currently use it, and inclusion of two options for dosing could be confusing. Of note, PPFA and NAF guidelines have used mifepristone 200 mg oral and misoprostol 800 mcg (initially given vaginally and now buccally) since 2001.

7 Review of Safety

Safety Summary

- Medical abortion with the new proposed regimen of Mifeprex 200 mg followed 24-48 hours later by misoprostol 800 mcg buccally through 70 days gestation is safe. Major adverse events including death, hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy with the proposed regimen are reported rarely in the literature on over 30,000 patients. The rates, when noted, are exceedingly rare, generally far below 0.1% for any individual adverse event. The number of postmarketing deaths associated with Mifeprex pharmacovigilance is very low. Non-vaginal routes of administration of misoprostol have increased and since the *C. sordellii* deaths associated with vaginal misoprostol, there have been no *C. sordellii* deaths. Given that the numbers of these adverse events appear to be stable or decreased over time, it is likely that these serious adverse events will remain acceptably low.

- Common adverse events associated with medical abortion occur at varying but acceptable rates.

- There are scarce cases of uterine rupture associated with early medical abortion. Medical abortion using mifepristone with or without misoprostol in the first trimester is safe from this perspective.

- There does appear to be an association between angioedema and mifepristone administration. The risks of anaphylaxis and angioedema should be included in the labeling for Mifeprex and there should be continued pharmacovigilance for anaphylaxis.

- Home use of misoprostol has been evaluated as part of the proposed dosing regimen in studies including well over 30,000 patients, demonstrating an acceptable safety profile, with rates of adverse events equal to or lower than those with the approved regimen requiring in-office dispensing of misoprostol. Home use of misoprostol can increase patient convenience, autonomy and privacy without increased burden on the healthcare system.

- In the articles about repeat misoprostol after mifepristone administration, there is little information provided about safety. The need for a second dose is a relatively uncommon occurrence. In studies of medical abortion using misoprostol alone, using two or more doses as compared to one dose of misoprostol does increase the risk of the common adverse event of diarrhea. There are a very few reports of uterine rupture with multiple doses of misoprostol, in almost all cases in women with prior uterine surgery, such as a cesarean section.

- The Applicant demonstrates that alternatives to in-clinic follow-up, including standardized questions, telephone follow-up, and use of low and high sensitivity urine pregnancy tests, serum pregnancy tests, and ultrasound are effective and safe. Loss-to-follow-up rates do not exceed those of in-clinic follow-up. This option can increase flexibility and accessibility of medical abortion for women.

- Medical abortion in adolescents appears to be at least as safe, if not safer, as in adult women. These data support the safety of Mifeprex in adolescents and satisfy requirements for PREA. No information on safety or efficacy if used in premenarchal girls is required, as the medication is not indicated in that subset of the pediatric population.

- Midlevel providers in the United States, such as nurse practitioners, nurse midwives and physician assistants currently provide family planning services and abortion care, including medical abortion care, under the supervision of physicians. In light of the REMS requirements, midlevel providers who are currently practicing abortion care are doing so under the supervision of physicians. Therefore, facilities that employ midlevel providers already have an infrastructure in place for consultation and referral if, as required under the REMS, a prescriber is unable to provide additional care, including surgical management if needed.

- It is appropriate to modify the current adverse event reporting requirements under the REMS, which are currently outlined in the Prescriber's Agreement to include "hospitalization, transfusion or other serious event." FDA has received

such reports for 15 years, and it has determined that the safety profile of Mifeprex is well-characterized, that no new safety concerns have arisen in recent years, and that the known serious risks occur rarely. For this reason, FDA does not believe ongoing reporting of all of the specified adverse events is warranted. The proposed Prescriber's Agreement Form (to replace the Prescriber's Agreement) will continue to require that qualified healthcare providers report any deaths. The Applicant will still be required by law, as is every NDA holder, to report serious, unexpected adverse events as 15-day safety reports, and to submit non-expedited individual case safety reports, and periodic adverse drug experience.

- Upon review of historical documents and of current guidelines for REMS materials, the phrase "under Federal law" can be removed from the Prescribers' Agreement. We concur with (b) (6) review of the REMS document.

- The revised Indication Statement should read:

"Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation." Safe use of Mifeprex would be enhanced when other information necessary to describe appropriate use (i.e., the need to use Mifeprex in a combined regimen with misoprostol and the gestational age for use) is included in the Indication Statement. This would be consistent with current FDA thinking (e.g., the internal Label Review Tool) which states that the indication and use statement should include "Information if drug is to be used only in conjunction with another therapy."

7.1 Methods

The assessment of the clinical safety of Mifeprex through 70 days gestation is based on the Applicant's submission of numerous articles from the peer-reviewed medical literature. The various studies have different designs, inclusion criteria, dosing regimens and endpoints for safety and efficacy. For the evaluation of safety, this reviewer focused on the studies that evaluated the proposed dosing regimen . All the articles used for this review can be found in the extensive list of references in Section 9.6 at the end of this review.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The reviewer evaluated safety based on the studies that focused on the proposed dosing regimen, specifically Mifeprex 200 mg followed by misoprostol 800 mcg buccally 24-48 hours later, as listed in Table 11 below. Supportive data from studies that have less specific numerical data or studies that included other regimens, specifically with different routes of administration of misoprostol (vaginal, oral, sublingual) are not included in this portion of the review, but are discussed in Sections Major Safety Results and Supportive Safety Results. Table 11 lists the studies referenced in these discussions.

Table 11: Studies Used to Evaluate Safety

Study	
USA	**International**
Gatter 2015[13], retrospective	Ngoc 2014[16], Vietnam, prospective
Ireland 2015[15], retrospective	Goldstone 2012[20], Australia, retrospective
Chong 2015[17], prospective single-arm	Boersma 2011[22], Curacao, prospective
Winikoff 2012[19], prospective	
Grossman 2011[36], prospective	
Winikoff 2008[23], prospective RCT	
Creinin 2007[25], prospective	
Middleton 2005[24], prospective	

Source: NDA clinical reviewer table.

7.1.2 Categorization of Adverse Events

For the purposes of this review, adverse events categorized as serious include death; hospitalization; infection, including severe infection requiring hospitalization; bleeding requiring transfusion; and ectopic pregnancy. Other non-serious adverse events include: nausea, vomiting, diarrhea, fever, bleeding and cramping.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The data are not pooled across studies as the study designs are quite different. The incidence of individual adverse events is noted for each study, and can be used to provide an estimated range.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Per the Applicant, there have been approximately 2.5 million US uses of Mifeprex by US women since its approval in 2000. If evaluation is limited to the studies listed in Table 11 focusing specifically on the proposed new dosing regimen, exposure for this safety analysis is based on well over 30,000 patients. The exact number cannot be determined because two retrospective studies (Gatter[13] and Ireland[15]) are likely based on overlapping cohorts of patients from Planned Parenthood clinics in Los Angeles. There are likely some differences in the demographic data for the different studies; therefore, the descriptions are separated into US and international data. However, it is doubtful

that demographic differences such as race or ethnicity are clinically meaningful in relation to the safety and efficacy of medical abortion. The data do include adolescents exposed to Mifeprex; information on safety in this population is discussed in Section 7.4.5.

7.2.2 Explorations for Dose Response

NA for this review.

7.2.3 Special Animal and/or In Vitro Testing

NA for this review.

7.2.4 Routine Clinical Testing

From this reviewer's assessment of the literature, no routine clinical testing is needed to evaluate the proposed changes to the Mifeprex labeling.

7.2.5 Metabolic, Clearance, and Interaction Workup

NA for this review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Please see Important Safety Issues with Consideration to Related Drugs for discussion of potential adverse events for drugs in this class.

7.3 Major Safety Results

7.3.1 Deaths

Deaths are rare with medical abortion. Most of the articles provided did not specifically report on deaths with medical abortion. Among the seven US studies, only one reported on deaths (Grossman, 2011[36]) and noted zero deaths among 578 subjects. Among the three international studies, only one[20] reported on deaths. In this retrospective review of 13,345 medical abortions with the proposed regimen, the authors reported only one death, yielding a rate of 0.007%. More information on deaths associated with medical abortion is found in Section 8 Postmarket Experience.

7.3.2 Nonfatal Serious Adverse Events

The nonfatal serious adverse events typically discussed in the literature are hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy. See narratives below and Table 12, Table 13, and Table 14 for details.

Hospitalization data:

Most articles do not report hospitalization data. In the US studies, 19 patients were reported as being hospitalized out of a total of 16,696 subjects. The overall rates range

from 0.003-1.1%. Only three articles separated out hospitalizations by gestational age. In Gatter 2015[13], there were 3/8495 hospitalizations among women ≤ 49 days, 3/3142 among women at 50-56 days gestation and none among women at 57-63 days. In Winikoff 2012[19], there were only two hospitalizations, both among women at 57-63 days, and none in the 64-70 days gestation group. In Creinin[25] two of six total hospitalizations were in the 50-56 days group and two in the 57-63 days group. The two remaining hospitalizations in that study were unrelated to study drug and gestational age information was not provided for these two cases. There were none among women at 64-70 days gestation. See Table 12 below.

Among the international studies, only 3 of 15,109 women were hospitalized, with rates from 0.07-0.6%. These rates were not separated out by gestational age. See Table 12.

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Table 12: Hospitalizations by Gestational Age

Study	Design	Subjects (N)	Hospitalizations by gestational age [Total N in subgroup, rate (%)]				
			All Gestational Ages (Overall/not specified)	≤ 49 days	50-56 days	57-63 days	64-70 days
USA							
Gatter 2015[13]	retrospective	13,373	6‡ (0.04%)	N=8945 3/8945 (0.03%)	N=3142 (0.1%)	N=1286 0	N/A
Chong 2015[17]	prospective	400	2 (0.5%)	NR*	NR	NR	N/A
Winikoff 2012[19]	prospective	729	2 (0.27%)	N/A	N/A	N=325 2 (0.61%)^	N= 304 0%
Grossman 2011[36]	prospective	578	0	N=283 0%	N=103 0%	N=63 0%	N/A
Winikoff 2008[23]	prospective	421	3(0.71%)	N=213 NR	N=93 NR	N= 115 NR	N/A
Creinin 2007[25]	prospective	546	6 (1.1%)§	N=229 0%	N=172 2 (1.16%)§	N=145 2 (1.38%)§	NA
Middleton 2005[24]	prospective	223	NR	NR	NR	N/A	N/A
International							
Ngoc 2014[16] Vietnam	prospective	1433	1 (0.07%)	NR	NR	NR	N/A
Goldstone 2012[20] Australia	retrospective	13,345	NR	N=11,855 NR	N= 1441 NR	N=49 NR	N/A
Boersma 2011[22] Curacao	prospective	331	2/331 (0.6%)	N=199 NR	N=105 (50-63 d) NR	NR	N=26 NR

* NR= not reported

‡numbers of hospitalizations for Gatter study includes those for bleeding and infection in subsequent tables.

^ includes woman with sepsis noted in Table 13, and one woman with chronic pancreatitis, recurrent.

§includes subjects receiving transfusions noted in Table 14.

Source: NDA clinical reviewer table.

Serious infection:

Infections requiring hospitalization or IV antibiotics were rare in the studies. Only three US studies captured this information, with rates ranging from 0-0.015%. Two studies separated this information out by gestational age. In Gatter 2015[13], the two serious infections were in women ≤ 49 days gestation. There were no serious infections in

women at 50-56 or 57-63 days gestation. In Winikoff 2012[19], there was one serious infection in a woman at 57-63 days and none in women at 64-70 days. See Table 13.

Among the international studies, there were five women hospitalized with rates from 0.03-0.07%. This information was not broken down by gestational age. See Table 13.

Table 13: Serious Infection by Gestational Age

Study	Design	Subjects (N)	Serious Infection by gestational age {Total N in subgroup, rate (%)]				
			All Gestational Ages (Overall/ not specified)	≤ 49 days	50-56 days	57-63 days	64-70 days
USA							
Gatter 2015[13]	retrospective	13,373	2 (0.015%)	N= 8945 2 (0.022%)	N= 3142 0%	N=1286 0%	N/A
Chong 2015[17]	prospective	400	NR*	NR	NR	NR	N/A
Winikoff 2012[19]	prospective	729	1 (0.014%)	N/A	N/A	N=325 1 (0.31%)	N=304 0%
Grossman 2011[36]	prospective	578	NR	N=283 NR	N=103 NR	N=63 NR	N/A
Winikoff 2008[23]	prospective	421	NR	N=213 NR	N=93 NR	N=115 NR	N/A
Creinin 2007[25]	prospective	546	0	N=229 0%	N=172 0%	N=145 0%	N/A
Middleton 2005[24]	prospective	223	NR	NR	NR	N/A	N/A
International							
Ngoc 2014[16] Vietnam	prospective	1433	1 (0.07%)	NR	NR	NR	N/A
Goldstone 2012[20] Australia	retrospective	13,345	4 (0.03%)	N=11,855 NR	N=1441 NR	N=49 NR	N/A
Boersma 2011[22] Curacao	prospective	331	NR	N=199 NR	N=105 (50-63 d) NR	NR	N=26 NR

*** NR= not reported**

Source: NDA clinical reviewer table.

Transfusion data:

With regard to bleeding requiring transfusion, five of the seven US studies included this information as shown in Table 14. The rates of transfusion range from 0.03-0.7%. Three of the studies provided a breakdown by gestational age. In Gatter 2015[13], there were the following: one woman in the ≤ 49 days group, three in the 50-56 days and zero in the 57-63 days group. In Winikoff 2012[19], there were: two in the 57-63 days group

and 1 in the 64-70 days group. In Creinin 2007[25], there were two women transfused each in the 50-56 days and 57-63 days. Only one international study[20] (Goldstone 2012) reported on transfusions and 11/13,345 women or 0.08% required transfusion.

Table 14: Transfusion by Gestational Age

Study	Design	Subjects (N)	Bleeding Requiring Blood Transfusion by gestational age [Total N in subgroup, rate (%)]				
			All Gestational Ages (Overall/not specified)	≤ 49 days	50-56 days	57-63 days	64-70 days
USA							
Gatter 2015[13]	retrospective	13,373	4 (0.03%)	N=8945 1 (0.01%)	N=3142 3 (0.1%)	N=1286 0	N/A
Chong 2015[17]	prospective	400	NR	NR	NR	NR	N/A
Winikoff 2012[19]	prospective	729	3 (0.41%)	N/A	N/A	N=325 2 (0.53%)	N=304 1 (0.29%)
Grossman 2011[36]	prospective	578	1 (0.17%)	N=283 NR	N=103 NR	N=63 NR	N/A
Winikoff 2008[23]	prospective	421	NR	N=213 NR	N=93 NR	N=115 NR	N/A
Creinin 2007[25]	prospective	546	4(0.7%)	N=229 0	N=172 2 (0.36%)	N=145 2 (0.36%)	N/A
Middleton 2005[24]	prospective	223	1 (0.45%)	NR	NR	N/A	N/A
International							
Ngoc 2014[16] Vietnam	prospective	1433	NR	NR	NR	NR	N/A
Goldstone 2012[20] Australia	retrospective	13,345	11 (0.08%)	N=11,855 NR	N=1441 NR	N=49 NR	N/A
Boersma 2011[22] Curacao	prospective	331	NR	N=199 NR	N=105 (50-63 d) NR	NR	N=26 NR

***NR= not reported**

Source: NDA clinical reviewer table.

Ectopic pregnancy:

Ectopic pregnancies were rarely reported in the supporting literature submitted with this efficacy supplement. Only one ectopic pregnancy was reported among 847 patients (0.12%) in Winikoff 2008[23].

Several studies also included less detailed, though still useful, information on adverse events. Ireland et al[15] conducted a retrospective review of 30,146 women undergoing

medical or surgical abortion at ≤ 63 days gestation at Planned Parenthood clinics in Los Angeles between November 1, 2010 and August 31, 2013. The authors reported that 29 women of 13,221 (0.1%) undergoing medical abortion experienced a major complication, which was defined as including: emergency department presentation, hospitalization, infection, perforation and hemorrhage requiring transfusion. The article did not specify the rate of each event. No deaths or ectopic pregnancies were reported in this study. In 2011, Grossman[36] reported on a study of medical abortion provided through telemedicine, in which 578 women seeking abortion services at Planned Parenthood of the Heartland clinics in Iowa were offered in-person services or telemedicine services. The serious adverse event outcomes are reported in Table 12, Table 13 and Table 14 above, but in addition, he reported on adverse events among all medical abortion patients from July 1, 2008 through October 31, 2009 (a wider time frame than the study itself). Four of 1,172 telemedicine patients (0.3%) required a blood transfusion compared to 0.1% of 2,384 in-person patients. These figures were reported in the paper to support study findings of low rates of serious adverse events, including transfusion. Pena (2014)[44] reported on 1,000 women in Mexico who had a medical abortion up to 63 days gestation. Their paper reported that "there were no serious complications as defined by any occurrence that was unexpected, serious, and related to the induced abortion." Upadhyay et al[55] used 2009 through 2010 patient-level billing data from Medi-Cal, California's state Medicaid program, to evaluate the incidence of complications after abortion, including medical abortion. Major complications were defined as those which required hospitalization, surgery or blood transfusion. There were 11,319 medical abortions, with 35 women (0.31%) having a major complication.

Winikoff (2012)[19] provides data on other serious adverse events through 70 days. Regarding hospitalization, there were zero hospitalizations among 350 women receiving medical abortion at 64-70 days compared with 2/379 women at 57-63 days (0.5% rate). There were no serious infections in the 64-70 day group, compared with 1/379 (0.3% rate) in the 57-63 day group. There was one transfusion (1/350=0.3% rate) in the 64-70 day group, compared with 2/379 (0.5% rate) in the 57-63 day group.

Reviewer comments:

(b) (4) **. Serious adverse events including death, hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy with the proposed regimen are rarely reported in the literature. The rates, when noted are exceedingly rare, with rates generally far below 1.0% for any individual adverse event. This indicates that medical abortion with the proposed regimen up through 63 days is safe.**

[55] Upadhyay UD, Desai S, Lidar V, Waits TA, Grossman D, Anderson P, Taylor D. Incidence of emergency department visits and complications after abortion. Obstet Gynecol 2015;125(1):175-183.

Serious fatal or nonfatal adverse events in the 64-70 days gestation group, were evaluated in one US study (Winikoff 2012)[19]. This study with 379 women in the 64-70 day range is reassuring in that the rates of hospitalization, serious infection and transfusion are no higher than in the lower gestational age ranges. Based on the available safety data on medical abortion in totality, it appears that serious fatal or nonfatal adverse events are very rare through 70 days as well. This regimen should be approved for use through 70 days gestation.

Reviewer's Final Recommendation:

The regimen of mifepristone 200 mg followed by misoprostol 800 mcg buccally in 24-48 hours is safe to approve for use through 70 days gestation.

7.3.3 Dropouts and/or Discontinuations

The studies included in this safety review revealed a wide range of loss to follow-up, from 0.6% loss to follow-up in the study with telephone follow-up (Ngoc 2014[16]) to 22% in the Grossman[36] study using telemedicine to deliver medical abortion services. One study noted no differences in demographics between the subjects on whom follow-up was available, compared with those on whom no follow-up information was available. Only two studies evaluated other subgroups of women lost to follow-up. Gatter et al 2015[13] found a higher odds of loss to follow-up with age <18 and with income at or below the federal poverty level. Additionally they noted increased odds of loss to follow-up with increasing gestational age. As compared with women 43-49 days gestation, the Odds Ratio (OR) for loss to follow-up at 50-56 days was 1.17 (95% CI 1.05-1.31) and at 57-63 days was 1.28 (95% CI 1.10-1.48). The Boersma study[22] had a 7% loss to follow-up rate. The rate of loss to follow-up was 6.5% at ≤ 49 days, 7.6% at 50-63 days and 7.7% at 64-70 days. No tests for significance were applied to these numbers. Only one study reported on withdrawals: Winikoff 2012[19] reported that 0.27% of patients withdrew and noted this was similar to rates previously reported in the literature.

Reviewer comment:

There is a wide range of loss to follow-up in the studies submitted with the efficacy supplement. The loss to follow-up rate cannot be reliably linked to method of follow-up, though it is notable that the lowest rate of loss-to-follow-up occurred in the Ngoc trial with telephone follow-up (0.6%) and the highest with abortion services provided via telemedicine (22%). The range of loss to follow-up is well-within the range documented in literature covering real-world abortion practice.[1]

7.4 Significant Adverse Events

The label for misoprostol currently includes a boxed warning against the use past 8 weeks gestation, due to the risk of uterine rupture. The (b) (6) safety reviewer and

(b) (6) conducted separate literature searches on this topic. Chen et al 2008[56] evaluated 488 women with a mean gestational age of 7.8 weeks who received 800 mcg misoprostol as part of a randomized study of misoprostol vs. curettage for early pregnancy failure. They found that 78 (16%) of women in the misoprostol group had previous uterine surgery (>1 C-section or myomectomy). There were no uterine ruptures in that study. Gautam et al[57] reported in 2003 on 66 women up to 60 days' gestation and with previous Caesarean section scar, who received misoprostol 800 mcg for termination and found no uterine ruptures. The literature search also revealed five case reports of uterine rupture.[58, 59, 60 , 61, 62] Of these five cases, three occurred with combined mifepristone/misoprostol dosing. Four women had uterine scars, most commonly from at least one prior cesarean section, and one of them had had a prior uterine rupture in labor. Only one woman had no prior uterine scar (Willmott). In these case reports and studies, women received varying doses of misoprostol ranging from 400 mcg to 600 mcg to 800 mcg, and in two, the women received multiple doses of misoprostol (4 and 5 doses in the Wilmot and Bika reports respectively). The women required surgery to repair the uterus or hysterectomy and transfusion. See Table 15.

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56 Chen BA, Reeves MF, Creinin MD, Gilles JM, Barnhart K, Westhoff C, Zhang J. National Institute of Child Health and Human Development Management of Early Pregnancy Failure Trial. Am J Obstet Gynecol 2008;198(6):626. d1-5 doi: 10.1016/j.ajog.2007.11.045. Epub Feb 15, 2008.

57 Gautam R, Agrawal V. Early medical termination pregnancy with methotrexate and misoprostol in lower segment cesarean section cases. J Obstet Gynaecol Res 2003; 29(4):251-256.

58 Khan S, et al. Uterine rupture at 8 weeks' gestation following 600 µg of oral misoprostol for management of delayed miscarriage. J Obstet Gynaecol 2007;27(8):869-870.

59 Kim JO, et al. Oral misoprostol and uterine rupture in the first trimester of pregnancy: A case report. Reproductive Toxicology 2005;20:575–577.

60 Jwarah E, Greenhalf JO. Rupture of the uterus after 800 micrograms misoprostol given vaginally for termination of pregnancy. BJOG 2000;107:807.

61 Bika O, Huned D, Jha S, Selby K. Uterine rupture following termination of pregnancy in a scarred uterus J Obstet Gynaecol 2014;34(2):198-9. doi: 10.3109/01443615.2013.841132.

62 Willmott F, et al. Rupture of uterus in the first trimester during medical termination of pregnancy for exomphalos using mifepristone/misoprostol. BJOG 2008;115:1575-1577.

Table 15: Uterine Rupture with Misoprostol Case Reports

Study	GA (weeks)	Mifepristone used?	Dose of Misoprostol	Number of doses of misoprostol	Risk Factor for Rupture
Khan[58]	8	Yes; dose not specified	600 mcg	1	1 prior C-section, 1 prior uterine rupture at 32 weeks
Kim[59]	8	No	400 mcg	1	1 prior C-section
Jwarah[60]	8 2/7	No	800 mcg	1	1 prior C-section
Bika[61]	10 2/7	Yes; 200 mg	800 mcg x 2 doses then 400 mcg x 2 doses	4	2 prior C-sections
Willmott[62]	12 3/7	Yes; 200 mg	400 mcg	5	none

Source: NDA clinical reviewer table.

(b) (6) also conducted a review of FAERS cases from January 1,1965 through October 15, 2015 for reports of uterine rupture with mifepristone alone, misoprostol alone, or a combined regimen, with special interest in cases occurring in women ≤ 10 weeks pregnant (≤ 70 days). The FAERS search retrieved 80 cases of uterine rupture, with 77 citing misoprostol use alone and 3 citing both mifepristone and misoprostol use. No cases of uterine rupture were reported with mifepristone use alone. Vaginal administration of misoprostol was documented in the majority of the cases. The majority of the FAERS cases either occurred in the 3rd trimester of pregnancy, or did not report gestational age. In the cases where the gestational age was not reported, it is likely that most of these cases occurred during the 2nd or 3rd trimester, as many noted the induction of labor as the reason for misoprostol use. The majority of cases also noted at least one additional potential risk factor, with a history of at least one previous c-section, or the use of additional uterotonic drugs (e.g., oxytocin or dinoprostone) being the most commonly reported. The use of misoprostol during the 3rd trimester for the induction of labor, cervical ripening, or both, in women that had at least one previous c-section, was also documented in many cases.

There were only two cases (2.5% of all reports) that reported uterine rupture within the first 10 weeks of pregnancy. In both cases, misoprostol alone was utilized for termination of pregnancy. The first case provided minimal information other than documentation of a 5 week gestation, and an ultrasound noting “an important uterine separation” during an unspecified time after misoprostol (route not specified) administration. The remaining case was also a published case report in which uterine rupture was documented as occurring approximately 2.5 hours after 800 mcg of misoprostol was administered vaginally for cervical preparation prior to surgical termination of pregnancy. The patient was 8 weeks and 2 days pregnant, had a history of a prior c-section, and was of advanced maternal age. (b) (6) concluded that uterine

rupture associated with the use of mifepristone alone, misoprostol alone, or both, is likely a rare event in the 1st trimester.

Reviewer comment:

Based on the scarcity of reported cases in the first trimester of pregnancy, uterine rupture associated with early medical abortion using mifepristone with or without misoprostol is likely rare. There are a three reports of uterine rupture with mifepristone and misoprostol in the first trimester, most of which occurred in women with prior uterine surgery (e.g., a cesarean section).

7.4.1 Submission-Specific Primary Safety Concerns

Summary of requested dosing changes in the NDA Supplement that could affect safety:

1. **Proposing a new dosing regimen that uses mifepristone 200 mg oral and the buccal administration of 800 mcg misoprostol at 24-48 hours after Mifeprex and increasing the gestational age from 49 days to 70 days**

   The Applicant submitted several articles in support of the proposed dosing regimen as well as increasing the gestational age through 70 days using the proposed regimen, including the 24-48 hour interval. See Section 7.3 Major Safety Results for fatal and nonfatal serious adverse events reported with the proposed regimen and gestational age. The data submitted show these events to be exceedingly rare, indicating that the new dosing regimen and increasing the gestational age to 70 days is safe. Please see Section 7.3 Major Safety Results on Nonfatal Serious Adverse Events for a review of this information.

   In further support of changing the dosing interval for misoprostol to 24-48 hours after mifepristone is taken, the Applicant also provided a systematic review by Shaw et al.[63] In this study the authors searched Medline, ClinicalTrials.gov, Popline and the Cochrane Controlled Trials Register and included 20 randomized controlled trials and 9 observational studies. The majority of the studies used the proposed 200 mg dose of mifepristone, but three RCTs and two observational studies used 600 mg of mifepristone. The doses and route of misoprostol administration varied, including doses of 400 mcg, 600 mcg, and 800 mcg, some with repeat doses, and included vaginal, buccal, oral and sublingual routes. There was wide variation in time to administration of the misoprostol, ranging from <24 hours, 24-48 hours, 36-48 hours. Adverse events were not reported consistently. There was no statistically significant difference in nausea, vomiting or diarrhea.

[63] Shaw KA, Topp NJ, Shaw JG, Blumenthal PB. Mifepristone-misoprostol dosing interval and effect on induction abortion times. Obstet Gynecol 2013;121(6):1335-1347.

Reviewer comment:

Unlike the efficacy data, which is based on studies that look specifically at individual changes proposed by the Applicant, the adverse event data typically come from studies or reviews that include multiple changes (e.g., dose of each drug, dosing interval, gestational age) simultaneously. Therefore, it is not possible to provide safety data specific to each individual change.

The changing of the dosing interval to 24-48 hours does not appear to increase the risk of serious fatal or nonfatal adverse events or to increase the risk of common adverse events associated with medical abortion.

Reviewer's Final Recommendation:

Based on the available evidence, changing the dosing interval between mifepristone and misoprostol to 24-48 hours is safe to approve, including for use in gestations up through 70 days.

2. Home administration of misoprostol

Currently, the Dosage and Administration section of labeling for Mifeprex requires that patients return to the healthcare provider on Day 3 (two days after ingesting Mifeprex) for misoprostol. The Applicant proposes that the label be changed to allow for home administration of the misoprostol. The Applicant reasons that all published US trials after the initial trial by Spitz et al[26], as well as numerous international trials, included distribution of misoprostol for self-administration at home with evidence of safe and effective medical abortion. The Applicant also emphasizes that women usually start having bleeding within two hours of administration of the misoprostol and home administration gives the opportunity for more privacy in the process.

The Applicant submitted many articles to support this change. See Table 8 for US and foreign studies that enrolled over 30,000 women who administered misoprostol at home. None of the studies directly compare home versus clinic/office administration of misoprostol. Most of the studies include protocols where all of the subjects take misoprostol at home. Gatter[13] and Ireland[15] reported separately on large numbers of clients of Planned Parenthood Los Angeles (13,373 and 13,221 clients respectively, though likely with some overlap, in 2010-2011), while Winikoff (2012[19] and 2008[23]), Grossman[36], Creinin[25] and Middleton[24] reported on smaller numbers of US subjects. Internationally, Goldstone[20] reported on 13,345 medical abortions, while Kopp Kallner[64], Løkeland[65], Chong (2012)[40], Bracken[49], Pena[44],

[64] Kopp Kallner H, Fiala C, Stephansson O, Gemzell-Danielsson K. Home self-administration of vaginal misoprostol for medical abortion at 50-63 days compared with gestation of below 50 days. Human Reprod 2010;25(5):1153-1157.

[65] Løkeland M, Iversen OE, Engeland A, Økland I. Medical abortion with mifepristone and home administration of misoprostol up to 63 days' gestation. Acta Obstet Gynecol Scand 2014;93:647-653.

Ngoc[16], Louie[14], Sanhueza Smith[48], Boersma[22] and Lynd[66] report on smaller numbers of subjects. All of these studies have been reviewed above in Sections Deaths, Nonfatal Serious Adverse Events and Common Adverse Events. This information shows that home administration of misoprostol, as part of the proposed regimen, is associated with exceedingly low rates of serious adverse events, and with rates of common adverse events comparable to those in the original studies of clinic administration of misoprostol.

Swica et al[50] similarly conducted a non-randomized trial with 301 US women, 139 of whom chose home use of mifepristone and misoprostol and 162 of whom chose clinic administration of mifepristone followed by home use of misoprostol. The majority of women (74%) who chose home use took the mifepristone at the appointed 6-48 hour window; for those who took it at a different time than that planned with their provider, the median interval was 25 hours. Over 90% of women in both groups took the misoprostol at the scheduled time, and none waited past 72 hours to take the misoprostol. There were no significant differences in the mean number of days of work or school missed or dependent care needed. Most women made no additional calls (85% for home use group and 90% for office use group) or unscheduled visits to the doctor's office (96% for home use group and 99% for office use group).

The Applicant also submitted a commentary by Gold and Chong[67], in which they discuss benefits of home administration of Mifeprex and misoprostol. They cite the convenience of scheduling for women, the possibility of greater autonomy and privacy, the lack of burden on staff, and the safety.

Reviewer comment:

Home use of misoprostol has been evaluated as part of the proposed protocol in studies including well over 30,000 patients, as well as in dedicated studies of home use of mifepristone and misoprostol. The studies demonstrate that women take the misoprostol at the recommended time. The safety profile is acceptable, with rates of adverse events equal to or lower than those with the approved regimen requiring in-office dispensing of misoprostol. The studies, including those of home use of mifepristone and misoprostol, show increased convenience, autonomy and privacy for the woman, a smaller impact on their lifestyles, and no increased burden on the healthcare system. The safety data on the home use of misoprostol are adequate to support revision of labeling.

[66] Lynd K, Blum J, Ngoc NTN, Shochet T, Blumenthal PD, Winikoff B. Simplified medical abortion using a semi-quantitative pregnancy test for home-based follow-up. Int J Gynecol Obstet 2013;121:144-148.

[67] Gold M, Chong E. If we can do it for misoprostol, why not for mifepristone? The case for taking mifepristone out of the office in medical abortion. Contraception 2015;92:194-196.

Reviewer's Final Recommendation:
Based on the available data, home use of misoprostol is safe to approve.

3. Repeat dose of misoprostol if needed.

The Applicant reasoned that studies include an option for a repeat dose of misoprostol to allow women to avoid a surgical procedure if possible and that this is a safe way to treat an incomplete medical abortion. The Applicant submitted two articles on the repeat use of misoprostol, one randomized trial and one systematic review, that were relevant to this safety review (other articles[12, 17, 22] did not present safety data stratified by number of misoprostol doses). Only one randomized trial reviewed the safety of repeat misoprostol. Coyaji et al[68] conducted a randomized controlled trial of 300 women seeking medical abortion in India. After taking mifepristone, women in one group took 400 mcg misoprostol followed by placebo 3 hours later, while women in the other group took two doses of 400 mcg misoprostol 3 hours apart. As discussed in the efficacy portion of this review, there was no significant difference in the complete abortion rate between the groups; however, the repeat misoprostol reduced need for surgical intervention. Before discharge home, there was no significant difference in the adverse effects observed—similar percentages of women experienced cramping (87% in the single dose group, 89% in the repeat dose group), nausea (both groups 1%), vomiting (both groups 0%), and diarrhea (0% in the single dose group versus 2% in the repeat dose group). More women in the repeat dose arm experienced moderate to severe cramping than women in the single dose arm on Day 4 (24% versus 15%, p=0.032) and on Day 7 (10% versus 4%, p=0.006).

Gallo[69] performed a systematic review of data relating to the safety and efficacy of more than one dose of misoprostol after mifepristone for medical abortion. The search yielded three randomized controlled trials that studied medical abortion ≤ 63 days. The studies included doses of mifepristone ranging from 200 mg to 600 mg followed by misoprostol 6 to 48 hours later, in doses ranging from 400 mcg to 800 mcg via the oral, sublingual or vaginal routes. In two trials, all subjects received repeat misoprostol—in one, three hours later, while in the other study subjects received misoprostol twice a day for days 4-10. In the third trial, subjects only received repeat misoprostol if there was still a gestational sac present. The only side effects discussed in the trials were diarrhea, which was more common in those groups receiving misoprostol orally than in those receiving it exclusively vaginally (26-27% versus 9%). Rash was reported <1%.

There is a good deal of literature on the use of misoprostol alone for medical abortion and in those regimens, doses of up to 800 mcg repeated in three hours have been

[68] Coyaji K, Krishna U, Ambardekar S, Bracken H, Raote V, Mandlekar A, Winikoff B. Are two doses of misoprostol after mifepristone for early abortion better than one? BJOG 2007;114:271-278.

[69] Gallo MF, Cahill S, Castelman L, Mitchell EMH. A systematic review of more than one dose of misoprostol after mifepristone for abortion up to 10 weeks gestation. Contraception 2006;74:36-41.

used. In a study by Blum et al[70], misoprostol only, given as two doses of 800 mcg three hours apart, was compared to mifepristone-misoprostol medical abortion where only one dose of 800 mcg misoprostol was administered. The two groups had similar rates of nausea, vomiting, fever and chills. Subjects in the repeat misoprostol group had more diarrhea than in the mifepristone-misoprostol group (83.9% vs. 61.2%, p<0.001). Please see Section 7.4 Significant Adverse Events for additional discussion on safety concerns with repeat doses of misoprostol.

Reviewer comment:

There are few articles concerning the safety of repeat misoprostol after mifepristone administration. Generally, the success of mifepristone-misoprostol medical abortion renders the need for a second dose of misoprostol to be relatively uncommon. In studies of misoprostol alone given using a single repeat dose, there is an increased risk of the common adverse event of diarrhea. There have been rare reports of uterine rupture in women with a prior uterine scar who receive repeated doses of misoprostol.

Reviewer's Final Recommendation:

Based on the available data, the option for repeat misoprostol in women whose pregnancy has been terminated, but who have not completely expelled the pregnancy is safe and should be approved. For women whose pregnancy is ongoing at follow-up, surgical intervention is recommended, rather than repeated misoprostol. The rare reports of uterine rupture in women with a prior uterine scar who receive repeated doses of misoprostol is discussed in labeling.

4. Follow-up timing and method: follow-up is needed, but not necessarily in the clinic or licensed healthcare provider's office at 14 days after mifepristone administration

The Dosage and Administration section of the current approved label for Mifeprex stipulates that patients will return for a follow-up visit approximately 14 days after the administration of Mifeprex to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred. The Applicant acknowledges that follow-up is important to diagnose and treat complications, and to ensure complete abortion or identify ongoing pregnancies. However, the Applicant proposes to change the labeling to state that the provider should perform an assessment at 1-2 weeks, in order to broaden the timeframe and method used, to give patients and providers more flexibility and reduce loss to follow-up rates. Use of ultrasound, serum and urine pregnancy testing (semi-quantitative, and quantitative) and telephone calls have all been evaluated in the literature as options for follow-up of patients after medical

[70] Blum J, Raghavan S, Dabash R, Ngoc NTN, Chelli H, Hajri S, Conkling K, Winikoff B. comparison of misoprostol-only and combined mifepristone-misoprostol regimens for home-based early medical abortion in Tunisia and Vietnam. Int J Gynecol Obstet 2012;118:166-171.

abortion. Grossman and Grindlay[71] conducted a systematic review of the literature on alternatives to ultrasound for medical abortion follow-up. They identified eight studies, but found that outcomes of interest (ongoing pregnancy) were rare with medical abortion and not consistently defined across studies. Nonetheless, they found that serum hCG, a low sensitivity urine pregnancy test combined with a standardized assessment with multiple questions about women's symptoms, or standardized telephone follow-up, perhaps followed by high-sensitivity urine pregnancy test, all had sensitivities ≥90% and negative predictive values (NPVs) ≥99% and they resulted in a proportion of "screen positives (or women who had a self-assessment of ongoing pregnancy and had an unscheduled visit) ≤33%."

This reviewer analyzed relevant studies that were submitted by the Applicant and referenced in the Grossman and Grindlay assessment.[71] Perriera et al[21] conducted a prospective cohort study of 139 US women with ≤63 days gestation undergoing medical abortion at one center. Up to three attempts were made to phone subjects 7 days after taking mifepristone. The subjects were asked to confirm when they took misoprostol and generally to describe their experience. They were then asked a series of five standardized questions to assess for expulsion, including:

1 Did you have cramping and bleeding heavier than a period?
2 Did you pass clots or tissue?
3 What was the highest number of pads you soaked per hour?
4 Do you still feel pregnant now?
5 Do you think you passed the pregnancy?

If the clinician or the subject did not think the pregnancy had passed, the subject was asked to return to the center for an ultrasound within 7 days. If there was an ongoing pregnancy, women were offered additional misoprostol or a D&C. If the clinician and subject believed the pregnancy had passed, she was instructed to begin birth control or schedule a visit for injectable, implantable or intrauterine contraception. On Day 30, the subject was to perform a urine pregnancy test. Follow-up was obtained for 97.1% of subjects. Four subjects did not complete follow-up (2.9%)—one was never reached by phone, three were and two of them had positive pregnancy tests while one had an inconclusive test. These three never returned for an in-person visit and outcomes are not available on them. The sensitivity for correctly predicting an expelled pregnancy (completed abortion) was 95.9%, specificity was 50%, positive predictive value 97.5% and negative predictive value 37.5%. This study suggests that clinicians and subjects are almost always correct when they believe a pregnancy has passed. The loss to follow-up rate was not higher than for standard medical abortion follow-up.

Fiala et al[72] compared hCG with ultrasound for verification of completed abortion in 217 women ≤49 days with intrauterine pregnancy in Scotland. Successful expulsions were

[71] Grossman D, Grindlay K. Alternatives to ultrasound for follow-up after medication abortion: a systematic review. Contraception 2011;83:504-510.
[72] Fiala C, Safar P, Bygdeman M, Gemzell-Danielsson K. Verifying the effectiveness of medical abortion;

consistent with a marked decline in hCG values at follow-up. Using 20% of the initial value as cut-off at follow-up gave a high sensitivity. It allowed correct diagnosis in 98.5% of the patients with successful expulsion. When 20% of the initial hCG value was used as cut-off, a positive predictive value for successful expulsion was 99.5%. If the reduction of the hCG level was less than 80%, the negative predictive value was 50% and further evaluation was warranted. By contrast, the reliability of ultrasound examination in diagnosing successful expulsion was 89.8%.

Lynd et al[66] studied 300 women at ≤ 63 days gestation who underwent medical abortion in Vietnam. Women were given mifepristone and sent home with misoprostol and a semi-quantitative urine pregnancy test, a urine cup, instructions and a questionnaire. They were to take the urine test, record their impression of the results and complete the questionnaire on the morning of an in-person follow-up visit 2 weeks after mifepristone administration. Fifty-four women (18.5%) still felt pregnant at the follow-up visit, but only 11 of the semiquantitative urine tests indicated ongoing pregnancies. All 11 correctly identified ongoing pregnancies, with 100% sensitivity and 89.7% specificity. Ten of the 11 women with an ongoing pregnancy understood in-person follow-up was necessary.

Similarly, Cameron et al[73] reported on 1791 women undergoing medical abortion in Scotland, 1,726 (96%) of whom chose self-assessment with a low-sensitivity urine pregnancy test, instructions on how to interpret it, and signs/symptoms of ongoing pregnancy. The rest of the women chose in-clinic follow-up with an ultrasound or a phone call. Eight women in the self-assessment group had ongoing pregnancies, but only four of them had a positive low-sensitivity pregnancy test at the appointed time—within 4 weeks. Of the four who did not follow up in 4 weeks, two had a positive or invalid pregnancy test within two weeks after the medical abortion and should have presented for care, and two reported their pregnancy test was negative and did not present for care. All has successful termination either with repeat medical dosing or surgical aspiration. Most women presented within four weeks, but two women presented only after two missed menses. The delayed follow-up was not different from that for an in-person visit or an ultrasound.

Reviewer comments:

While the number of articles is not extensive, they include almost 2,400 subjects. The Applicant demonstrates that alternatives to in-clinic follow-up are effective and safe, detecting most of the ongoing pregnancies so that women can get needed treatment. It appears that, using standardized questionnaires or instructions or a telephone call along with a low or high sensitivity pregnancy test, ongoing pregnancies can be detected allowing for further treatment. There is some loss-to-follow-up, but the rates do not appear to exceed those associated

ultrasound versus hCG testing. Eur J Obstet Gynecol Reprod Biol 2003;109;190-195.
[73] Cameron ST, Glasier A, Johnstone A, Dewart H, Campbell A. Can women determine the success of early medical termination of pregnancy themselves? Contraception 2015;91:6-11.

with a planned in-clinic follow-up. Women should be allowed to have an in-person visit if desired, but also allowed the flexibility of other options if desired.

It is important to note that since 2005, Planned Parenthood Federation of America has waived the follow-up visit if it poses undue hardships owing to distances from abortion facilities or other reasons, and women manage their follow-up with serial hCG testing.[74] From the clinical reviewers' perspective, this is safe and acceptable. We further note that the NAF 2015 guidelines (page 23) state the following:

> **"Success of the medical abortion must be assessed by ultrasonography, hCG testing, or by clinical means in the office or by telephone. If the patient has failed to follow-up as planned, clinic staff must document attempts to reach the patient. All attempts to contact the patient (phone calls and letters) must be documented in the patient's medical record."**

The ACOG 2014 Practice Bulletin[1] on management of early MAB states "Follow-up after receiving mifepristone and misoprostol for medical abortion is important, although an in-clinic evaluation is not always necessary." Several options for follow up without an office/clinic visit are discussed and no specific method or algorithm is definitely recommended (i.e., it is left to the discretion of the provider and patient).

Reviewer's Final Recommendation:

Based on the available evidence, flexibility in the timing and method of follow-up is safe to approve.

7.5 Supportive Safety Results

7.5.1 Common Adverse Events

According to the currently approved Mifeprex label,[75] common adverse events include the following:

- Vaginal bleeding up to 16 days, with 8% of women experiencing bleeding up to 30 days. 4.8% of women in the original US trials and 4.3% in the original French trials required administration of uterotonic agents to control the bleeding. Only 1% of women required intravenous fluids and 1% required curettage. In the original French trials, 5.5% of women had a drop in hemoglobin of more than 2 g/dL.
- Abdominal pain in 96% of US women
- Uterine cramping in 83% of French women
- Nausea in 43-61%, vomiting in 18-26%

[74] Fjerstad M. Figuring out follow-up. Mife Matters. Planned Parenthood Federation of America/Coalition of Abortion Providers 2006;13:2–3.

[75] http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.htm

- Diarrhea in 12-20%
- Headache in 2-31%
- Dizziness in 1-12%

A review of the literature submitted in the efficacy supplement, which includes Mifeprex at the proposed dose but also includes misoprostol administered buccally, vaginally or orally, reveals the following. Table 16 addresses bleeding that did not require transfusion (which is covered inTable 14: Transfusion by Gestational Age above), but was still significant in terms of requiring another intervention or in terms of a decrease in measured hemoglobin. Most of the studies include subjects up to 63 days' gestation, with the exception of Middleton 2005[24], which includes subject to 56 days, and Sanhueza Smith 2015[48] and Winikoff 2012[19], which include subjects through 70 days.

Table 16: Bleeding and Cramping in Literature

Study	N	Maximal Gestational Age	Route of misoprostol administration	Adverse Event Rate (%)		
				Bleeding requiring intervention*	Bleeding with drop in hemoglobin > 2g/dL	Cramping/pain
Middleton 2005[24]	216	56 d	buccal	4.2	NR	NR
Coyaji 2007[68]					NR	87-89
Løkeland 2014[65]				4.9	NR	96.6
Kopp Kallner 2010[64]	395	63 d	vaginal	0.5	NR	NR
Pena 2014[44]	971	63 d	Buccal	1.7	NR*	NR
Ngoc 2014[16]	1433	63 d	buccal	0.07	NR	NR
Gatter 2015[13]	13,373	63 d	buccal	1.8	NR	NR
Ireland 2015[15]	13,221	63 d.	buccal	1.8	NR	NR
Winikoff 2012[19]	729	70 d	buccal	1.1	NR	NR
Sanhueza Smith 2015[48]	960	70 d	buccal	1.7	NR	NR

***Intervention includes aspiration or uterine evacuation, use of uterotonics, intravenous fluids**
***NR=not reported**

Source: NDA clinical reviewer table.

Reviewer Comments:

Given that Mifeprex and misoprostol are taken to terminate an intrauterine pregnancy, vaginal bleeding and cramping or abdominal pain are an expected

and necessary part of the process; therefore, these should only be considered adverse events if the amount of bleeding or pain exceeds what would be expected for such a process. The rate of bleeding requiring intervention is low and ranges from 0.5% to 4.2%, with the rates in the largest studies being around 1.8%. Two articles parsed the bleeding requiring intervention by gestational age. In Sanhueza Smith et al.[48] the rate was 1.1% (7/622) among women ≤ 56 days, 4.2% (8/190) in women 57-63 days and 1.4% (2/148) in women 64-70 days. In Gatter 2015[13], the rate was 0.65-1.43% up to 49 days, 2.04% in women 50-56 days, and 2.49% in women 57-63 days. These differing numbers from the two studies do not reveal a trend toward bleeding requiring intervention with increasing gestational age, specifically even through 70 days.

No articles submitted discussed a drop in hemoglobin of > 2 g/dL, most likely because routine laboratory studies are not obtained in medical abortion unless anemia or a medical illness is reported or suspected. Also not surprisingly, pain and cramping are an expected part of the medical abortion process, so most studies do not comment on the percentage of women who experience this.

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Table 17: Common Adverse Events in Literature

Study	N	Maximal GA (days)	Route of Misoprostol	Adverse Event Rate (%)							
				nausea	vomiting	diarrhea	fever	chills	headache	dizziness	weakness
Middleton 2005[24]	216	56 d	Buccal	70	37	36	42	NR	44	41	51
Blum 2012[70]			buccal	45.9	37.8	61.2	28.2	30.6			NR
Coyaji 2007[68]				1	0-2	NR*	NR	NR			NR
Kopp Kallner 2010[64]	395	63 d	vaginal	87.1	57.3	6.3	26.3	NR	4.1	3.6	2-3.1
Louie 2014[14]	860	63 d	buccal	38-53	13-25	1-3	15-23†				NR
Pena 2014[44]	971	63 d	buccal	NR	NR	7.8	8.9†	†	NR	NR	14.3
Creinin 2007[25]	544	63 d	vaginal	9.4	5.7	4.8	10.3†	†	6.6	6.8	NR
Chong 2012[40]	563	63 d	buccal	47	22	NR	33†	†	33	24	42
Winikoff 2012[19]	618	70 d	buccal	50.8	40.6	17.6	11.2	23.5	NR	NR	NR
Sanhueza Smith 2015[48]	960	70 d	buccal	27	23	44.6	46†	†	14.3	9.7	21

GA = gestational age; *NR= not reported. † includes fever and chills, which were grouped together

Source: NDA clinical reviewer table.

Reviewer comment:

The range of reported percentages for each adverse event is wide, with some studies reporting virtually no patients experiencing nausea, vomiting or diarrhea, while others report at least half of subjects suffering these side effects. Only the Winikoff 2012[19] article parses out these side effects by gestational age (57-63 days versus 64-70 days). There is no statistically significant difference in the rates of any side effect between gestational age group except for vomiting, where 35.8% of women 57-63 days had vomiting and 45.7% of women 64-70 days did (p=0.008). It is hard to determine a value that could be used in labeling based on these wide variations, but the adverse events are common, expected and well-known with the medical abortion regimen and the ranges should be reported in labeling.

7.5.2 Laboratory Findings

Mifepristone with misoprostol is a well-established regimen for termination of pregnancy. Few laboratory tests are necessary before use of the regimen. Those that are commonly performed include confirmation of pregnancy (urine or serum pregnancy testing) as well as Rh testing (unless it has been previously documented), such that RhD immunoglobulin can be administered as indicated. Pre-medical abortion assessment of hemoglobin or hematocrit is indicated when anemia is suspected. Routine follow-up laboratory testing is also not indicated unless dictated by the patient's clinical condition, for example, heavy bleeding or signs of infection. Lab results are not typically reported in the literature, except for when studies look at decreases in hemoglobin related to bleeding.

7.5.3 Vital Signs

Vital signs are not typically reported in the literature on medical abortion.

7.5.4 Electrocardiograms (ECGs)

Mifepristone used with a prostaglandin analogue has been approved for medical termination of pregnancy since 1988 in France and subsequently in many countries around the globe. It has been well-established that doing an ECG prior to MAB is not standard procedure. It can be done if individual circumstances warrant its use. Literature does not typically report on ECGs.

7.5.5 Special Safety Studies/Clinical Trials

The pediatric studies are addressed in Section 7.6.3.

7.5.6 Immunogenicity

NA to this review

7.6 Other Safety Explorations

This section is not relevant to this application.

7.6.1 Additional Safety Evaluations

7.6.2 Human Carcinogenicity

The Applicant submitted no new data on human carcinogenicity.

7.6.3 Human Reproduction and Pregnancy Data

As noted in the efficacy portion of this review, some women who use Mifeprex do have ongoing pregnancies. Most of these are treated with an aspiration or a surgical evacuation of the uterus; there is little information on outcomes of ongoing pregnancies not terminated by another method. At the time of approval of the drug, the Applicant agreed to two postmarketing commitments, including one to conduct a surveillance study of the outcomes of ongoing pregnancies. On January 11, 2008, the Applicant was released from this commitment due to the lack of an adequate number of women enrolled. The Applicant explained that the small number was due, in part, to the requirement that the patients consent to participation *[in the surveillance study]* after seeking a pregnancy termination.

A review of all of the articles submitted by the Applicant for outcomes of ongoing pregnancies after mifepristone administration yielded minimal information. There is one article reporting a case of a fetus with sirenomelia, a cleft palate and lip, micrognathia, and hygroma; this infant was born to a woman who had received mifepristone as RU 486 at 18 weeks and was reported to Roussel-Uclef in France in 1989.[76] A prospective observational study[77] from fifteen French pharmacovigilance centers followed women exposed to mifepristone in the first trimester between1997 and 2010. The study included pregnant women who sought counseling on mifepristone exposure from a pharmacovigilance center or Paris Teratology Information Service (TIS). A total of 105 pregnancies were exposed to mifepristone in the first trimester; 46 to mifepristone alone, and 59 to mifepristone and misoprostol. The mean gestational age at exposure was 7.9 weeks; 81% were exposed between weeks 5 and 9 of gestation. About 40% of patients received 200 mg of mifepristone while about 50% received 600 mg. Of the patients who received both mifepristone and misoprostol, 48 received repeat misoprostol with four receiving 1200–2000 mcg of misoprostol, a significantly higher dose than recommended. Among all exposed women, there were 94 live births (90.4%),10 (9.6%) miscarriages (including one with a major malformation of major hydrocephalus associated with adductus thumb and a normal karyotype) and one patient had an elective termination of pregnancy for the subsequent diagnosis of trisomy 21. Eight of the ten miscarriages occurred in the mifepristone-only group; however, after potential confounding factors such as maternal age, gestational age at inclusion,

[76] Pons JC, Papiernik E. Mifepristone teratogenicity. Lancet 1991;338(8778):1332-3.

[77] Bernard N, Elefant E, Carlier P.Tebacher M, Barjhoux CE, Bos-Thompson MA, Amar E, Descotes J, Vial T. Continuation of pregnancy after first-trimester exposure to mifepristone: an observational prospective study. BJOG 2013;120:568–575.

drug exposure, and mifepristone dose were controlled for by logistic regression, the rate of miscarriage did not differ across mifepristone only versus mifepristone-misoprostol groups (p= 0.08). Among the live births, the mean gestational age at delivery was 39.5 weeks and there was no difference in birth weights between groups. The overall rate of major congenital malformations among the 95 examinable cases was 4.2% (95% CI 1.2–10.4%), with two cases among 38 patients exposed to mifepristone alone, and two cases among 57 patients exposed to both mifepristone and misoprostol. Three of the four major congenital malformations occurred with exposure to 600 mg of mifepristone, while one occurred in exposure to 400 mg of mifepristone. The malformations included:

- Claude Bernard–Horner syndrome with stridor
- Hydrocephalus with triventricular dilatation and adductus thumb (miscarriage patient noted above)
- Möbius syndrome
- Retrognathism, slight cleft palate, trismus, swallowing disorder, club foot with four toes, incomplete genital development and mild hypoplasia of the cerebellar vermis

The authors posit that the cases of major malformations in patients exposed to mifepristone alone could be explained by associated medical conditions, for example, the case of congenital Claude Bernard Horner syndrome could have been related to traumatic vaginal delivery of a high birth weight newborn, a well-recognized cause of this syndrome, while the spontaneously aborted hydrocephalic fetus may have been caused by streptococcus B chorioamnionitis, which was subsequently confirmed on pathological examination, or be an X-linked hydrocephalus. The authors also note that the two cases of major malformations in patients exposed to both mifepristone and misoprostol were consistent with malformations described after exposure to misoprostol alone. The authors concluded that major malformations after first-trimester exposure to mifepristone is only slightly higher than the expected 2–3% rate in the general population, which was reassuring regarding the risk evaluation for continuation of pregnancy after mifepristone exposure.

There are reports that misoprostol can result in congenital anomalies when used during the first trimester, including defects in the frontal or temporal bones, limb abnormalities with or without Mobius syndrome.[1] The Korlym label notes in Important Safety Issues with Consideration to Related Drugs: “In a report of thirteen live births after single dose mifepristone exposure, no fetal abnormalities were noted.”

Reviewer Comment:

There are anomalies associated with the use of misoprostol in the first trimester. The risk of teratogenic effects with a continued pregnancy after a failed pregnancy termination with Mifeprex in a regimen with misoprostol is unknown. Birth defects have been reported with a continued pregnancy after a failed pregnancy termination with Mifeprex in a regimen with misoprostol, but it is not clear if this just represents the usual background rate of birth defects.

As discussed above, FDA requested at the time of initial approval that the Applicant conduct a surveillance study of the outcomes of ongoing pregnancies. The Applicant was subsequently released from this commitment because it had been unable to enroll a sufficient number of women with ongoing pregnancies after an attempted medical abortion in the surveillance study.

7.6.4 Pediatrics and Assessment of Effects on Growth

The Applicant submitted no new data on assessment of effects on growth in pediatric patients. The Applicant did submit data on efficacy and safety of medical abortion in adolescents, using the proposed regimen of 200 mg oral Mifeprex followed by 800 mcg buccal misoprostol 24-48 hours later at home, in order to satisfy requirements for PREA. Gatter et al (2015)[13] included data on 322 adolescents. (b) (6), (b) (4) The adolescent efficacy was similar to that of all older women; this implies that compliance in taking the misoprostol dose properly at home was also acceptable. The study included adolescents aged 11-16 per Table 18 below:

Table 18: Age of Adolescents Undergoing Medical Abortion

Age	# Subjects
11	1
12	1
13	2
14	20
15	82
16	216

Source: (b) (6), (b) (4) **NDA 20687s20**

(b) (4), (b) (6) As is evident in the table, no adolescents had a hospitalization, severe infection or hemorrhage which required a transfusion.

Table 19: Serious Adverse Events in Adolescents vs. Adults

	Under 17	17+	All
Transfusion	0.00% (0/251)	0.03% (4/13,122)	0.03% (4/13,373)
Hospitalization	0.00% (0/251)	0.05% (7/13,122)	0.05% (7/13,373)
Infection	0.00% (0/251)	0.02% (2/13,122)	0.01% (2/13,373)

Source: (b) (6), (b) (4) **NDA 20687s20**

In 2011, Niinimäki et al[54] published a retrospective cohort study of the Finnish abortion registry from 2000-2006, in which they evaluated the rates of adverse events in 3,024

adolescents and 24,006 adult women undergoing medical abortion (regimen unspecified). The study population included women ≤ 20 week's gestation; 84.6% of the adolescents were ≤ 12 weeks, while 86.6% of the adults were ≤ 12 weeks. Adolescents ranged in age from 13-17, with a mean age of 16.1 years. The study showed that after adjustment for parity, previous abortion, marital status, types of residence, duration of gestation and year of abortion, in adolescents, the adjusted ORs were significantly lower for hemorrhage (0.87, 95% CI 0.77 to 0.99), incomplete abortion (0.69, 95% CI 0.59 to 0.82) and surgical evacuation (0.78, 95% CI 0.67 to 0.90) compared to adults. There was no significant difference in the OR for infection (0.97, 95% CI 0.73 to 1.30).

Phelps[53] had previously conducted a pilot study in 28 adolescents aged 14-17, at ≤ 56 days gestation, using Mifeprex 200 mg followed 48 hours later by misoprostol 800 mcg vaginally. As reported in Section Subpopulations, 100% of study subjects had a complete abortion, with five not requiring misoprostol. There were no serious adverse events. Subjects noted common expected adverse events including bleeding (100%), cramping (95%), nausea (62%), and vomiting (43%).

It is also important to consider adherence to the proposed regimen (including taking misoprostol at a location other than the clinic) and adherence to follow-up among adolescents versus adults.

There are no data specifically comparing adherence to the regimen among adolescents <17 with women ≥17 years old. The Gatter[13] study clearly demonstrates the efficacy and safety is the same for both age groups, suggesting that there is no clinically significant difference in adherence to the regimen between age groups. The Goldstone[20] article included 8 subjects aged 14 and 931 subjects aged 15-19. The efficacy and safety are not separated out by age; however, all subjects did take the proposed regimen and overall efficacy and safety is reassuring, indicating that adolescents and adults alike likely did adhere to the mifepristone and misoprostol regimen in a safe and effective way.

Regarding adherence to follow-up, four articles included 346 subjects <17 years old. Ngoc[16] is based in Vietnam and Cameron[73] is based in Scotland, while Gatter[13] and Horning[78], are US-based studies. (b) (4), (b) (6) . The difference in the follow-up rate for the combined data is 6.5%. The Gatter study accounts for 85% of all patients being compared. The difference in follow-up adherence is not clinically relevant as there is no difference in efficacy between the two age groups.

Table 20: Adherence to Follow-Up Among Adolescents vs. Adults

	<17 years old			≥17 years old		
	N	# Adherent	Adherence %	N	# Adherent	Adherence %
Gatter[13]	322	251	78.0%	15,517	13,122	84.6%
Cameron[71]	5	4	80.0%	607	516	85.0%
Ngoc[16]	1	1	100.0%	1,406	1,345	95.7%
Horning[78]	18	16	88.9%	846	648	76.6%
TOTAL	346	272	78.6%	18,376	15,631	85.1%

Reviewer Comment:

Medical abortion in adolescents appears to be at least as safe, if not safer, as in adult women. Adolescents appear able to comply with the regimen, including use of misoprostol outside of the clinic setting, as well as with alternative follow-up methods. These data support the safety of Mifeprex in adolescents and satisfy requirements for PREA. No information on safety and efficacy of use in premenarchal girls is required, as the medication is not indicated in that subset of the pediatric population.

Reviewer's Final Recommendation:

The available evidence supports that Mifeprex and the new proposed dosing regimen are safe to use in adolescents.

7.6.5 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant submitted no new data on overdose, drug abuse potential withdrawal and rebound.

7.7 Additional Submissions / Issues

Summary of additional changes in labeling that may affect safety of Mifeprex

1. Change in labeled time for expulsion from 4-24 hours to 2-24 hours

The Applicant proposes to change the time to expulsion described in the labeling from 4-24 hours to 2-24 hours post misoprostol to more accurately reflect the data and real-life experiences with the drug. The Applicant reasons that in the large US trial upon

[78] Horning EL, Chen BA, Meyn LA, Creinin MD. Comparison of medical abortion follow-up with serum human chorionic gonadotropin testing and in-office assessment. Contraception 2012;85:402-407.

which labeling is based (Spitz, 1998[26]), the median time to expulsion was 4 hours. Indeed, in that study, women were observed for several hours after misoprostol administration, and during the four hours of observation, 49% of the women expelled the products of conception, and 60% had by the fifth hour. Several studies are provided to corroborate this. Only one uses buccal misoprostol; however, the misoprostol was administered within 5 minutes of the Mifeprex, not at the 24-48 hour interval as proposed in this supplement. Nonetheless, in this trial, Lohr[79] found the median time to onset of cramping to be 2 hours (range 10 minutes to 13 hours) and bleeding to be 3 hours (range 9 minutes to 11 hours). This shorter duration to expulsion is also seen in several other pilot studies submitted where subjects took vaginal misoprostol immediately or within 6-8 hours of mifepristone. If the focus is shifted to the randomized controlled studies that report times to onset of bleeding and cramping and include vaginal misoprostol, we find data confirming the timing of expulsion in the 2-24 hour window proposed by the Applicant. Creinin[25] noted a median time to onset of cramping of 1.7 hours and to onset of bleeding of 2 hours after misoprostol (administered 24 hours after Mifeprex). In a similar study[80] comparing misoprostol administered 24 vs. 6-8 hours after Mifeprex, the median time to onset of cramping was 1.5 hours and to bleeding was 2 hours in women with misoprostol given 24 hours after Mifeprex.

Reviewer comment:
The data from vaginal and buccal administration of misoprostol around 24 hours after mifepristone support the assertion that bleeding and cramping begin before the 4 hour mark that is currently labeled. Therefore the label should be revised to make this clearer. Median times seem to be around 1.5 to 2 hours. It is reasonable to label the time to expulsion 2-24 hours, but it could be labeled as beginning even earlier. A clearer label will help providers better counsel patients and patients can better select an appropriate time frame within the 24-48 hour window to take their misoprostol and can be prepared when the expulsion starts.

Reviewer's Final Recommendation:
Based on the available evidence, it is acceptable to revise the label so that it notes that the time to expulsion after misoprostol dosing is 2-24 hours.

2. Use of the term "(b) (4)

The Applicant proposes to use the term "(b) (4) in place of all other terms in labeling and in the REMS materials, for consistency and (b) (4) The Applicant

[79] Lohr PA, Reeves MF, Hayes JL, Harwood B, Creinin MD. Oral mifepristone and buccal misoprostol administered simultaneously for abortion: a pilot study. Contraception 2007;76:215-220.

[80] Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. MOD Study Trial Group: A randomized comparison of misoprostol 6-8 hours versus 24 hours after mifepristone for abortion. Obstet Gynecol 2004;103:851-859.

submitted an article demonstrating that nurse practitioners, certified nurse midwives and physician assistants can safely provide aspiration abortion.[81] The Division asked the Applicant to provide articles specifically addressing the provision of medical abortion services by non-physician practitioners, since that is the issue at hand.

The Applicant provided data on the efficacy of medical abortion provided by non-physician healthcare providers, including four studies with 3,200 women in randomized controlled clinical trials and 596 women in prospective cohorts. These studies took place in varying settings (urban, rural, international, low resource). The efficacy results are discussed in Section 6.1.10.

Regarding the safety of medical abortion provided by non-physician health care providers, a systematic review by Renner[82] identified five studies with a total of 8,908 subjects. A RCT in Nepal included 1,104 of those subjects, comparing medical abortions by nurses or auxiliary nurse midwives with those offered by physicians. Outcome data on 1,077 women showed no serious complications (hemorrhage requiring transfusion or condition necessitating hospitalization) and the rate of ongoing pregnancy or incomplete abortion did not vary by physician versus midlevel provider. Also in Nepal, Puri et al[83] described training female community health volunteers to provide education, and training auxiliary nurse midwives to provide medical abortion in intervention districts, and compared knowledge and medical abortion outcomes with those in neighboring districts where there were no interventions. Medical abortions were performed on 307 women in the intervention areas and 289 women in the comparison areas. There were five incomplete abortions (1.6%) in the intervention areas, treated with manual vacuum aspiration by the auxiliary nurse midwives, and 7 (2.4%) incomplete abortions in the comparison areas. The difference was not statistically significant. Kopp Kallner[84] conducted a randomized controlled equivalence trial of 1,068 women in Sweden who were randomized to receive medical abortion care from two nurse midwives experienced in medical terminations and trained in early pregnancy ultrasound versus a group of 34 physicians with varying training and experience. The trial showed fewer complications for the nurse midwife group, though this was not statistically significant (4.1% for nurse midwives, versus 6.1% for doctors, p=0.14).

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[81] Weitz TA, Taylor D, Desai S, Upadhyay UD, Waldman J, Battistelli MF, Drey EA. Safety of aspiration abortion performed by nurse practitioners, certified nurse midwives, and physician assistants under a California legal waiver. Am J Public Health 2013;103:454-461.

[82] Renner R-M, Brahmi D, Kapp N. Who can provide effective and safe termination of pregnancy care: a systematic review. BJOG 2013;10:23-31.

[83] Puri M, Tamang A, Shrestha P, Joshi D. The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal. Reproductive Health Matters 2015;Suppl(44):94-103.

[84] Kopp Kallner H, Gomperts R, Salomonsson E, Johansson M, Marions L, Gemzell-Danielsson K. The efficacy, safety and acceptability of medical termination of pregnancy provided by standard care by doctors or by nurse-midwives: a randomized controlled equivalence trial. BJOG 2015;122:510-517.

There were no serious complications and no blood transfusions in the study. There was no difference in unscheduled visits. Nurse midwives did call for more second opinions (26%) versus doctors (4%). Olavarrieta[85] conducted a randomized controlled non-inferiority trial in Mexico City abortion clinics. Eight physicians and seven nurses who had not previously independently provided medical abortion care received 1.5 weeks of training. A total of 1,088 women were randomized to two groups of providers. Nurses were not found to be inferior to physicians in the provision of abortion care. There was only one serious adverse event in the physician group, a woman requiring admission and surgical aspiration for heavy bleeding. Nurses requested consultation with an experienced obstetrician in 9 cases, whereas physicians requested consultation only twice.

Reviewer Comments:

The Applicant provided data from over 3,200 women in randomized controlled trials and data on 596 women in prospective cohorts comparing medical abortion care by physicians versus nurses or nurse midwives. The studies were conducted in varying settings (international, urban, rural, low-resource) and found no differences in efficacy, serious adverse events, ongoing pregnancy or incomplete abortion between the groups. Two studies did show that nurses or nurse midwives called for more second opinions than physicians, but these numbers were a small portion of the total subjects included.

Midlevel providers in the United States, such as nurse practitioners, nurse midwives and physician assistants currently provide family planning services and abortion care, including medical abortion care, under the supervision of physicians. The data here demonstrate that it would be safe to allow healthcare providers who are licensed to prescribe medications and who meet the criteria in the REMS to become certified to provide medical abortion care with Mifeprex and misoprostol. Midlevel providers are already practicing abortion care under the supervision of physicians, and the approved labeling and the REMS Prescriber's Agreement already stipulate that prescribers must be able to refer patients for additional care, including surgical management if needed. Therefore, facilities that employ midlevel prescribers already have an infrastructure in place for consultation and referral.

Reviewer's Final Recommendation:

Based on the available evidence, it is safe for midlevel providers to administer medical abortion. The term in the revised Prescriber Agreement Form will be "a healthcare provider who prescribes." Per the review by the (b) (6) ((b) (6) dated March 29, 2016, this term provides an accurate

[85] Olavarrieta CD, Ganatra B, Sorhaindo A, Karver TS, Seuc A, Villalobos A, Garcia SG, Pérez M, Bousieguez M, Sanhueza P. Nurse versus physician-provision of early medical abortion in Mexico: a randomized controlled non-inferiority trial. Bull World Health Organ 2015;93:249-258.

representation of the varied practitioners who are prescribers, while at the same time using language that is consistent with statute. We concur with the (b) (6) review.

3. Removal of references to "Under Federal Law" from the Prescriber's Agreement

The Applicant requests removal of the phrase "under Federal law" from the Prescriber's Agreement portion of the REMS materials. The phrase appears in two places:

- "Under Federal law, Mifeprex must be provided by or under the supervision of a licensed physician who meets the following qualifications:
  - Ability to assess the duration of pregnancy accurately.
  - Ability to diagnose ectopic pregnancies.
  - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary."
- "Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss them, obtain her signature on the Patient Agreement, and sign it yourself."

The Applicant rationalizes that all of the conditions of Mifeprex approval, including the REMS, are under Federal law and that the statement is redundant and are no more subject to Federal law than the other conditions of approval.

Reviewer comment:
A rationale for the original inclusion of the phrase "Under Federal law" cannot be discerned from available historical documents, nor is it consistent with REMS materials for other products. All the conditions of approval, including the REMS materials, are under Federal law; therefore, the phrase is unnecessary and can be removed from the Prescriber's Agreement.

Reviewer's Final Recommendation:
The term "under Federal law" can be removed from the Prescriber's Agreement.

4. Addition of misoprostol to the indication statement

The Indication and Usage section of the currently approved labeling is as follows:

> "Mifeprex is indicated for the medical termination of intrauterine pregnancy through 49 days' pregnancy. For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period in a presumed 28 day cycle with ovulation

occurring at mid-cycle. The duration of pregnancy may be determined from menstrual history and by clinical examination.

Ultrasonographic scan should be used if the duration of pregnancy is uncertain, or if ectopic pregnancy is suspected.

Any intrauterine device ("IUD") should be removed before treatment with Mifeprex begins.

Patients taking Mifeprex must take 400 mcg of misoprostol two days after taking mifepristone unless a complete abortion has already been confirmed before that time (see DOSAGE AND ADMINISTRATION).

Pregnancy termination by surgery is recommended in cases when Mifeprex and misoprostol fail to cause termination of intrauterine pregnancy (see PRECAUTIONS)."

The Applicant proposed two alternative indication statements, both of which include reference to misoprostol:

(b) (4)

Or

(b) (4)

The Applicant provides the rationale that:

- the two drugs are used in combination and placing misoprostol in the indication statement early on in labeling gives it greater prominence and highlights the importance of completing the full treatment regimen

- the mention of misoprostol enhances the goal of labeling, which is to give healthcare providers information necessary for safe and effective use of Mifeprex.

Subsequently on February 25, 2016, the Applicant proposed (b) (4) (b) (4) gestational age through 70 days, based on the literature already submitted.

Reviewer comment:

We recommend that the Indication Statement read:

> **"Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation."**

The rationale for this is that:

- **All supporting data are based on the combined regimen**
- **Inclusion of misoprostol in the Indication Statement would be consistent with the rest of Mifeprex labeling and with current medical practice**
- **It would be consistent with current FDA thinking (e.g., the internal Label Review Tool) which states that the indication and use statement should include "Information if drug is to be used only in conjunction with another therapy."**

Reviewer's Final Recommendation:

Misoprostol should be included in the Indication Statement for Mifeprex.

8 Postmarket Experience

A comprehensive review of the adverse events associated with Mifeprex from September 28, 2000 through November 17, 2015, performed by (b) (6) , (b) (6), yielded the following information on reported deaths. Regarding the US cases, there were 17 reported deaths. Deaths were associated with sepsis in eight of the 17 (seven cases tested positive for *Clostridium sordellii,* one case tested positive for *Clostridium perfringens).* Seven of the eight fatal sepsis cases reported vaginal misoprostol use; one case reported buccal misoprostol use. Seven of the nine remaining U.S. deaths involved two cases of ruptured ectopic pregnancy and one case each of the following: substance abuse/drug overdose; methadone overdose; suspected homicide; suicide; and a case of delayed onset toxic shock-like syndrome. In the eighth case, the cause of death could not be established despite performance of an autopsy; tissue samples were negative for *C. sordellii*. The autopsy report on the ninth death became available to the Agency and was reviewed on December 2, 2015. It showed the woman died of pulmonary emphysema.

There were 11 additional deaths in women in foreign countries who used mifepristone for medical termination of pregnancy. These fatal cases were associated with the

following: sepsis (*Clostridium sordellii* identified in tissue samples) in a foreign clinical trial; sepsis (Group A *Streptococcus pyogenes*); a ruptured gastric ulcer; severe hemorrhage; severe hemorrhage and possible sepsis; "multivisceral failure;" thrombotic thrombocytopenic purpura leading to intracranial hemorrhage; toxic shock syndrome (*Clostridium sordellii* was identified through uterine biopsy cultures); asthma attack with cardiac arrest; respiratory decompensation with secondary pulmonary infection 30 days after mifepristone in a patient on the lung transplant list with diabetes, a jejunostomy feeding tube, and severe cystic fibrosis; and a case of *Clostridium sordellii* sepsis (from a published literature report).

Reviewer Comments:

While an exact rate of death with use of mifepristone cannot be calculated from this information, given that there have been over 2.5 million uses of Mifeprex by US women since its marketing in 2000, the number of deaths is very low. Moreover, half of the deaths were associated with *C. sordellii* sepsis. Seven out of 8 of these cases occurred in women who used misoprostol via the vaginal route while one used buccal misoprostol. Since at least 2006, PPFA (comprising the majority of US medical abortion providers) switched its national guidelines to avoid vaginal administration of misoprostol (even though the data did not find a causal relationship).[23] Although the possibility that Mifeprex might increase the likelihood of infection by adversely affecting immune system function has been raised, the overall event rate of serious infections does not support this.

Since 2009, there have been no *C. sordellii* deaths associated with medical abortion in the US. This reviewer finds that the postmarketing data on deaths associated with medical abortion demonstrate low numbers and an improved safety profile with the buccal route of misoprostol administration as compared with the vaginal route.

The review by (b) (6) (b) (6) also yielded the following

Table 21 summarizing hospitalizations, blood loss requiring transfusions, and severe infections.

Table 21: US Postmarketing AEs- Mifepristone for Medical Abortion

Date ranges of reports received	09/28/00[†]-10/31/12	11/1/12 - 04/30/14[‡]
Cases with any adverse event	2740	504
Hospitalized, excluding deaths	768	110
*Experienced blood loss requiring transfusions[§]	416	66
Infections[‖] (*Severe infections[¶])	308 (57)	37 (5)

† U.S. approval date.
‡ FDA implemented FAERS on September 10, 2012, and migrated all of the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. As a result of this change, it is not recommended to calculate a cumulative number when reviewing the data provided in Table 5.
* The majority of these women are included in the hospitalized category in Table 5.
§ As stated in the approved Mifeprex (mifepristone) labeling, bleeding or spotting can be expected for an average of 9-16 days, and may last for up to 30 days. Excessive vaginal bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions.
‖ This category includes endometritis (inflammation resulting from an infection involving the lining of the womb), pelvic inflammatory disease (involving the nearby reproductive organs such as the fallopian tubes or ovaries), and pelvic infections with sepsis (a serious systemic infection that has spread beyond the reproductive organs). Not included are women with reported sexually transmitted infections such as chlamydia and gonorrhea, cystitis, and toxic shock syndrome not associated with a pelvic infection.
¶ This subset of infections includes cases that were determined to be severe based on medical review of the available case details. Severe infections generally result in death or hospitalization for at least 2-3 days, require intravenous antibiotics for at least 24 hours and total antibiotic usage for at least 3 days, or have other physical or clinical findings, laboratory data, or surgery that suggest a severe infection.

Source: Review by (b) (6) (b) (6) (b) (6) dated 08/27/2015.

The (b) (6) review also describes ectopic pregnancies:

Table 22: US Postmarketing Ectopic Cases- Mifepristone for Medical Abortion

Date Range of Cumulative Reports	9/28/2000-10/31/14*	11/1/14-4/30/2015
Ectopic Pregnancies†	79	10

* U.S. approval date

† Administration of mifepristone and misoprostol is contraindicated in patients with confirmed or suspected ectopic pregnancy (a pregnancy outside the uterus).

Source: (b) (6) (b) (6) (b) (6) Mifepristone U.S. Post-marketing Adverse Events 6 month Update Summary through 04/30/2015, dated 08/20/2015.

Reviewer comment:

While exact rates cannot be calculated, as these reports are spontaneously generated, a few conclusions can be drawn from the information provided:

- **Given that there have been over 2.5 million uses of Mifeprex by US women since its marketing in 2000, including the use of the proposed dosing regimen and extended gestational age at many clinic/office sites, the numbers of hospitalizations, severe infections, blood loss requiring transfusion and ectopic pregnancy will likely remain acceptably low.**
- **The numbers of each of these adverse events appears to have remained steady over time, with a possible decrease in severe infections.**

A discussion of a (b) (6) review of uterine rupture is found in the Section Significant Adverse Events.

(b) (6) identified another safety signal in a review dated January 27, 2016. A FAERS search retrieved one case of anaphylaxis and six cases of angioedema with mifepristone administration. A literature search did not reveal any case reports of either adverse event with mifepristone. Six of the seven cases were seen in women using mifepristone for termination of pregnancy. Six of the seven cases noted some type of medical intervention, such as treatment with an antihistamine, a histamine H2 antagonist, a corticosteroid, or a combination of the various medications. Hospitalization was noted in three of the seven total cases; all three hospitalization cases occurred in patients who experienced angioedema.

In the case of anaphylaxis, it was reported that the patient experienced an anaphylactic reaction three hours after mifepristone administration; however, co-administration of doxycycline was also documented. Because both mifepristone and doxycycline were discontinued simultaneously, the exact cause of the anaphylactic reaction cannot be determined.

Regarding angioedema, five of the six cases noted a time-to-onset within 24 hours of mifepristone administration for the termination of pregnancy, with no additional suspect medications reported. The remaining case of angioedema with mifepristone reported a time-to-onset of approximately one week in a Cushing's syndrome patient with a complex medical history and multiple concomitant medications; however, this case noted both a positive dechallenge and rechallenge upon sole re-introduction of mifepristone therapy. Evaluation of these FAERS cases provides supportive evidence of a drug-event association between angioedema and mifepristone. The (b) (6) reviewer recommends the inclusion of anaphylaxis and angioedema within the Mifeprex labeling, specifically to the Contraindications and Adverse Reactions Postmarketing Experience sections.

Reviewer Comment:

There does appear to be an association with angioedema and mifepristone administration. The reviewers agree with inclusion of anaphylaxis and angioedema in the labeling for Mifeprex and with continued pharmacovigilance for anaphylaxis.

9 Appendices

9.1 Literature Review/References

This NDA review obviously involved an extensive review of resources and the peer-reviewed medical literature that was pertinent to the requested changes of the Applicant. Such sources are noted throughout the review in footnotes. A detailed Reference List is found in Appendix 9.6.

9.2 Labeling Recommendations

The package insert (PI) for this product was submitted in the Physician Labeling Rule (PLR) format. Although not required for this supplement, Section 8 was revised in accord with the Pregnancy and Lactation Labeling Rule (PLLR). Section 17 Patient Counseling Information was also revised to be compatible with the new dosing regimen and follow-up. Major changes were made that updated the labeling with new safety and efficacy information, especially in two areas:

1) 6.1 Clinical Trials Experience in the section 6 Adverse Reactions
2) 14 Clinical Studies

Changes were also made in the patient package insert (PPI) and Medication Guide for the product. These format and content updates marked a significant improvement in the label. Agreement on the Final Approved label was reached with the Applicant on March 29, 2016.

Reviewer comment:

The new dosing regimen was based on the extensive number of articles submitted by the Applicant from the peer reviewed medical literature. The revised label used the new PLR format which is a complete change from the previous style. This meant that the newly approved label was extensively rewritten and much improved from the old format.

9.3 Advisory Committee Meeting

An Advisory Committee met in 1996 to discuss the approval of mifepristone plus misoprostol for medical termination of early pregnancy. There has been extensive US (15+ years with over 2.5 million uses) and global use (27+ years) of mifepristone and misoprostol for the medical termination of early pregnancy. No special external consultations were requested by the review Divisions. The FDA determined that the efficacy supplement did not raise complex scientific or other issues that would warrant holding an advisory committee meeting before approval of the supplement.

9.4 (b) (6) ((b) (6) Meeting

As noted in Product Regulatory Information, Mifeprex was originally approved under 21 CFR part 314, subpart H, “Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses” (subpart H). Specifically, in accordance with § 314.520 of subpart H, FDA restricted the distribution of Mifeprex and required that Mifeprex be provided by or under the supervision of a physician who met certain qualifications. Further, practitioners had to complete a Prescriber’s Agreement, provide patients with a Medication Guide and have patients sign a Patient Agreement. Mifeprex was included on the list of products deemed to have in effect an approved REMS[86] under section

86 Federal Register / Vol. 73, No. 60 | Issued: March 27, 2008

505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of FDA Amendments Act (FDAAA) of 2007. A formal REMS proposal was submitted by Danco and approved on June 8, 2011, with the essential elements unchanged. The REMS included:

- Medication Guide
- Elements to Assure Safe Use (ETASU):
  - Prescribed only by certified prescribers (ETASU A; includes a Prescriber's Agreement)
  - Dispensed only in certain healthcare settings (ETASU C)
  - Dispensed with documentation of safe use conditions (ETASU D; includes a Patient Agreement)
- Implementation System
  - Distributed only by certified distributors

Following this approval, two REMS assessment reports were completed. The Year 1 assessment was completed on June 1, 2012 and the Years 2-4 assessment was completed on June 2, 2015. Agency review of these reports determined that the REMS goals were being met and that no modifications were required to the REMS at that time.

On July 16, 2015, the Applicant submitted a revised REMS as part of the efficacy supplement. The proposed modifications included:

- Prescriber's Agreement Form
  - Remove "Under Federal law"
  - Replace "physician" with "(b) (4)

The Agency determined that broader review of the REMS was warranted concurrently with the efficacy supplement because some proposed changes in labeling dovetail with proposed changes to the REMS, and the documents should remain consistent with each other. Further, extensive review of the postmarketing experience based on the literature submitted to support the efficacy supplement, and pharmacovigilance, suggested that certain components of the REMS may no longer be necessary to assure safe use of Mifeprex.

In light of the efficacy review, upon assessment of the proposed modifications, (b) (6) concurs with (b) (6) recommendations that:

- Removal of "under Federal law" from the Prescribers' Agreement was acceptable (see discussion in Additional Submissions / Issues)
- The term "healthcare providers who prescribe" is preferable to (b) (4) (see discussion in Additional Submissions / Issues)

(b) (6) and (b) (6) also proposed the following modifications:

- Removal of the Medication Guide from the REMS (will remain a part of labeling and must be distributed by the prescriber as required under 21 CFR part 208)
- Removal of the Patient Agreement form - Documentation of Safe Use (ETASU D)

- Revision of the Prescriber's Agreement form
- Revision of the REMS goal to reflect above changes

FDA considered the need for the current adverse event reporting requirements under the REMS, which are currently outlined in the Prescriber's Agreement to include "hospitalization, transfusion or other serious event." FDA has received such reports for 15 years; the safety profile of Mifeprex is well-characterized, no new safety concerns have arisen in recent years, and the known serious risks occur rarely. For this reason, the reviewers do not believe ongoing reporting of all of the specified adverse events is warranted. The Applicant will still be required by law, as is every NDA holder, to report serious, unexpected adverse events as 15-day safety reports, and to submit non-expedited individual case safety reports, and periodic adverse drug experience.

(b) (6) and (b) (6) met with the (b) (6) ((b) (6) on January 15, 2015, to discuss the proposed modifications. The (b) (6) concurred with the removal of the term "under Federal law" and with use of the term "healthcare providers who prescribe." The (b) (6) also concurred with the removal of the Medication Guide (MG) from the REMS, though the document would remain a part of labeling. FDA has been maintaining MGs as labeling but removing them from REMS when, as here, inclusion in REMS is not necessary to ensure that the benefits of a drug outweigh the risks, such as when the MG is redundant and not providing additional use or information to the patient about the risk(s) the REMS is intended to mitigate. This is consistent with ongoing efforts to streamline REMS by allowing for updates to the MG without need for a REMS modification. (b) (6) and the (b) (6) had subsequent interactions and on February 23, 2016, the (b) (6) concurred with the decision to remove the Patient Agreement (ETASU D) from the REMS. This decision was based on the following rationale:

- The safety profile of Mifeprex is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance
- Established clinical practice includes patient counseling and documentation of Informed Consent, and, more specifically with Mifeprex, includes counseling an all options for termination of pregnancy, access to pain management and emergency services if needed. The National Abortion Federation (NAF) provides clinical practice guidelines**Error! Bookmark not defined.** and evidence shows that practitioners are providing appropriate patient counseling and education; a survey published in 2009 demonstrated that 99% of facilities surveyed provided pre-abortion counseling with patient education.[87] This indicates that the Patient Agreement form is duplicative and no longer necessary to ensure that the benefits of the drug outweigh the risks.

APPEARS THIS WAY ON ORIGINAL

[87] O'Connell K, Jones HE, Simon M, Saporta V, Paul M, Lichtenberg ES. First-trimester surgical abortion practices: a survey of National Abortion Federation members. Contraception 2009; 79: 385–392.

- Medical abortion with Mifeprex is provided by a small group of organizations and their associated providers. Their documents and guidelines cover the safety information that is duplicated in the Patient Agreement.
- ETASUs A and C remain in place: The Prescriber's Agreement under ETASU A requires that providers "explain the procedure, follow-up, and risks to each patient and give her an opportunity to discuss them." The REMS will continue to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals. This ensures that Mifeprex can only be dispensed under the supervision of a certified prescriber at the time the patient receives treatment with Mifeprex.
- Labeling mitigates risk: The Medication Guide, which will remain a part of labeling, contains the same risk information covered under the Patient Agreement.

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9.4 Abbreviations

List of Abbreviations

Abbreviation	Term
ACOG	American College of Obstetrics and Gynecology
APHA	American Public Health Association
CDER	Center for Drug Evaluable and Research
CDRH	Center for Devices and Radiological Health
(b) (6)	(b) (6)
FU	follow up
GA	gestational age
IRB	Institutional Review Board
LFU	lost to follow up
LMP	last menstrual period
MAB	medical abortion
MG	Medication Guide
Miso	misoprostol
NA	not applicable
NAF	National Abortion Federation
NDA	New drug application
NR	not reported
NSAID	non-steroidal anti-inflammatory drug
PPFA	Planned Parenthood Federation of America
PREA	Pediatric Research Equity Act
REMS	Risk Evaluation and Mitigation Strategies
ROA	route of administration
(b) (6)	(b) (6)
SAB	surgical abortion
WHO	World Health Organization

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9.6 Mifepristone Approvals Globally

1988
- China
- France

1991-
- UK

1992
- Sweden

1999
- Austria
- Belgium
- Denmark
- Finland
- Germany
- Greece
- Iceland
- Israel
- Luxembourg
- Netherlands
- Russia
- Spain
- Switzerland

2000
- Norway
- Taiwan
- Tunisia
- US

2001
- New Zealand
- South Africa
- Ukraine

2002
- Belarus
- Georgia
- India
- Latvia
- Serbia
- Vietnam

2003
- **Estonia**

2004
- Guyana
- Moldova

2005
- Albania
- Hungary
- Mongolia
- Uzbekistan

2006
- Kazakhstan

2007
- Armenia
- Kyrgyzstan
- Portugal
- Tajikistan

2008
- Nepal
- Romania

2009
- Cambodia
- Italy

2010
- Zambia

2011
- Ghana
- Mexico
- Mozambique

2012
- Australia
- Bangladesh
- Ethiopia
- Kenya

2013
- Azerbaijan
- Bulgaria
- Czech Republic
- Slovenia
- Uganda
- Uruguay

2014
- Thailand

2015
- Canada

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

03/29/2016

(b) (6)

03/29/2016

(b) (6)

03/29/2016

I concur with (b) (6) conclusions and recommendations for approval of this efficacy supplement.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 020687 **Applicant: Danco Labs** **Stamp Date: May 29, 2015**

Drug Name: Mifeprex (Mifepristone) **NDA/BLA Type: supplement #020**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			Paper submission.
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?			x	
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?		x		The applicant has not provided module 2 summaries as this is an NDA based on published literature. The applicant has provided a justification summarizing the evidence of safety and efficacy for the proposed changes.
9.	Has the applicant submitted the integrated summary of safety (ISS)?		x		See comment for 8.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		x		See comment for 8.
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			Scientific justification-30 pg document
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	x			(b) (2)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	x			The sponsor provides a bridge from the approved product to the proposed changes, with literature based

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					on both the approved product and the proposed regimen.
15.	Describe the scientific bridge (e.g., BA/BE studies)	x			See #14.
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Many articles from the published medical literature. Study Title: Sample Size: Arms: Location in submission:	x			
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:	x			The applicant provides 54 articles total, with 32 specifically on efficacy of the proposed regimen. These include controlled trials, meta-analyses, observational and retrospective studies.
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	The applicant provides 54 articles total. 46 are studies (trials, retrospective, observational studies) and of these 17 are foreign. There are also 3 metanalyses which include foreign studies.
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			The applicant provides 21 articles with information on safety, specifically on the serious adverse events of interest (hospitalization,

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					transfusion, infection requiring IV antibiotics, death). There are another 5 articles with limited safety information and 6 articles with safety information, but using different dosing regimens (e.g. not the approved or proposed new regimen).
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			x	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			x	There is no mapping of investigator terms to preferred terms. AE's were variably ascertained; 21 studies include data on SAE's of interest, 7 have limited safety information, 6 have safety information on the approved dosing regimen. Some 7 studies report no safety information.
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			x	As of 7/16/15, there is one reported death; a complete report will be forthcoming. This

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					is not part of the presently submitted application.
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			The applicant requested a partial waiver for patients <12 and a waiver for patients 12-17, based on data from one study which included 322 subjects <17 years old.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	29/46 studies are US data, 17 are based on foreign data.
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			x	NDA relies upon published studies; datasets were not provided.
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			x	
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	
37.	Are all datasets to support the critical safety analyses available and complete?			x	
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			x	NDA relies upon published studies; CRFs were not provided.
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?			X	
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an			x	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	IRB and with adequate informed consent procedures?				

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There is one review issue which will need to be addressed.
The proposed label contains information from the original studies and not from the studies supporting the new dosing regimen and the other proposed changes (e.g., including healthcare providers prescribing Mifeprex and home use of misoprostol). The Sponsor will need to update the proposed label.

(b) (6)

Reviewing Medical Officers — Date: 7/16/15

(b) (6)

Date: 7/16/15

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

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07/17/2015

(b) (6)

07/17/2015

TTT # 2022-2468
NDA 020687
ANDA 091178
Mifepristone U.S. Post-Marketing Adverse Events Summary through 12/31/2024

The following information is from United States (U.S.) post-marketing reports received by FDA of adverse events that occurred among patients who had taken mifepristone for medical termination of pregnancy. Because FDA has eliminated duplicate reports, and in some cases, reclassified the adverse event terms for individual cases after reviewing the narrative details, the numbers provided here may differ from the numbers of the reports that may be obtained through Freedom of Information Act requests. These events cannot with certainty be causally attributed to mifepristone because of information gaps about patient health status, clinical management of the patient, concurrent drug use, and other possible medical or surgical treatments and conditions. The estimated number of women who have used mifepristone in the U.S. for medical termination of pregnancy through the end of December 2024 is approximately 7.5 million women.

For informational purposes, fatal foreign cases that were reported after U.S. approval of mifepristone for medical termination of pregnancy are also included in a footnote in Table 1.

Table 1. Cumulative Post-Marketing Fatal and Ectopic Pregnancy Reports in U.S. Women Who Used Mifepristone for Medical Termination of Pregnancy

Date range of cumulative reports	09/28/00[†] - 12/31/24
Died [‡]	36
*Ectopic pregnancies [||]	97

[†] U.S. approval date

[‡] The fatal cases are included regardless of causal attribution to mifepristone. Deaths were associated with sepsis in 13 of the 36 reported fatalities (9 cases tested positive for *Clostridium sordellii*, 1 case tested positive for *Clostridium perfringens*, 2 cases had negative blood cultures, and 1 case did not have blood culture data). Ten of the 13 fatal sepsis cases reported vaginal misoprostol use; 2 cases reported buccal misoprostol use; 1 case did not report the route of misoprostol use. Twenty-two of the 23 remaining U.S. deaths involved 2 cases of homicide, 2 cases of combined drug intoxication/overdose, 2 cases of ruptured ectopic pregnancy, 2 cases of drug intoxication, 2 cases of suicide, and 1 case each of the following: substance abuse/drug overdose; methadone overdose; suspected homicide; delayed onset toxic shock-like syndrome; hemorrhage; bilateral pulmonary thromboemboli; unintentional overdose resulting in liver failure; probable anaphylactic medication reaction; septic shock due to necrotizing fasciitis; sepsis with multiple complications possibly secondary to toxic shock syndrome 82 days after mifepristone; sudden death of undetermined etiology despite performance of an autopsy; and a case of natural death due to severe pulmonary emphysema. In the 23rd case, the cause of death could not be established despite performance of an autopsy; tissue samples were negative for *Clostridium sordellii*. There were 13 additional reported deaths in women in foreign countries who used mifepristone for medical termination of pregnancy. These fatal cases were associated with the following: sepsis (*Clostridium sordellii* identified in tissue samples) in a foreign clinical trial; sepsis (Group A *Streptococcus pyogenes*); a ruptured gastric ulcer; severe hemorrhage; severe hemorrhage and possible sepsis; "multivisceral failure;" thrombotic thrombocytopenic purpura leading to intracranial hemorrhage; toxic shock syndrome (*Clostridium sordellii* was identified through uterine biopsy cultures); sepsis (*Enterococcus faecalis* and *Escherichia coli* were identified in blood culture); asthma attack with cardiac arrest; thromboembolism; respiratory decompensation with secondary pulmonary infection 30 days after mifepristone in a patient on the lung transplant list with diabetes, a jejunostomy feeding tube, and severe cystic fibrosis; and a case of *Clostridium septicum* sepsis (from a published literature report).

* The majority of these women are included in the hospitalized category in Table 2.

[||] Administration of mifepristone and misoprostol is contraindicated in patients with confirmed or suspected ectopic pregnancy (a pregnancy outside the uterus).

Table 2. Post-Marketing Adverse Events in U.S. Women Who Used Mifepristone for Medical Termination of Pregnancy		
Date ranges of reports received	09/28/00[†] - 10/31/12	11/01/12 - 12/31/24[‡]
Cases with any adverse event	2740	1512
Hospitalized, excluding deaths	768	288
*Experienced blood loss requiring transfusions [§]	416	190
Infections [||] (*Severe infections [¶])	308 (57)	114 (22)

[†] U.S. approval date

[‡] FDA implemented the FDA Adverse Event Reporting System (FAERS) on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. As a result of this change, it is not recommended to calculate a cumulative number when reviewing the data provided in Table 2.

* The majority of these women are included in the hospitalized category in Table 2.

[§] As stated in the approved labeling for Mifeprex (mifepristone) and its approved generic version, bleeding or spotting can be expected for an average of 9-16 days, and may last for up to 30 days. Excessive vaginal bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions.

[||] This category includes endometritis (inflammation resulting from an infection involving the lining of the womb), pelvic inflammatory disease (involving the nearby reproductive organs such as the fallopian tubes or ovaries), and pelvic infections with sepsis (a serious systemic infection that has spread beyond the reproductive organs). Not included are women with reported sexually transmitted infections such as chlamydia and gonorrhea, cystitis, and toxic shock syndrome not associated with a pelvic infection.

[¶] This subset of infections includes cases that were determined to be severe based on medical review of the available case details. Severe infections generally result in death or hospitalization for at least 2-3 days, require intravenous antibiotics for at least 24 hours and total antibiotic usage for at least 3 days, or have other physical or clinical findings, laboratory data, or surgery that suggest a severe infection.

Center for Drug Evaluation and Research (CDER)

(b) (6)

Application Type	NDA and ANDA
Application Number	020687 and 91178
Reviewer Names	(b) (6)
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	(b) (6)
	(b) (6)
Review Completion Date	December 16, 2021

Subject	REMS Modification Rationale Review
Established Name	Mifepristone REMS
Name of Applicants	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablets

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EXECUTIVE SUMMARY

This review provides the [redacted] rationale and conclusions regarding modifications to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178.

ANDA 91178 was approved with the approval of the Mifepristone REMS Program on April 11, 2019 to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021. The REMS consists of elements to assure safe use (ETASU) under ETASU A, C and D, an implementation system, and a timetable for submission of assessments. To determine whether a modification to the REMS was warranted, FDA undertook a comprehensive review of the published literature; safety information collected during the COVID-19 public health emergency (PHE); the one-year REMS assessment report of the Mifepristone REMS Program; adverse event data; and information provided by advocacy groups, individuals and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation discussed below.

The modifications to the REMS will consist of:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to here as the "in-person dispensing requirement" for brevity)
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified

A REMS Modification Notification letter will be sent to both Applicants in the Single Shared System.

1. Introduction

In connection with the *Chelius v. Becerra* litigation, FDA agreed to undertake a full review of the Mifepristone REMS Program, in accordance with the REMS assessment provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[a] This review provides the analysis of the (b) (6) ((b) (6) and the (b) (6) ((b) (6) regarding whether any changes are warranted to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone (hereafter referred to as the Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178. The Mifeprex REMS was initially approved in 2011; the single, shared system REMS for mifepristone 200 mg, known as the Mifepristone REMS Program, was approved in 2019.

The last time the existing REMS elements to assure safe use (under ETASU A, C and D) were reviewed was in the context of our review of supplement S-020 to NDA 20687; these ETASU were updated following review and approval of supplement S-020 on March 29, 2016. The key changes approved in 2016 are summarized below.

Changes to labeling included:

- Changing the dosing of Mifeprex to 200 mg orally x 1
- Extension of maximum gestational age through 70 days
- Inclusion of misoprostol in the indication statement
- Replacing the term “physician” with “licensed healthcare provider”
- Removal of the phrase “Under Federal Law”

The Mifeprex REMS and REMS materials were updated to reflect the changes above, and additional changes were made including:

- Removing the Medication Guide as part of the REMS but retaining it as part of labeling.

2. Background

2.1. PRODUCT AND REMS INFORMATION

[a] Section 505-1(g)(2) of the FD&C Act (21 U.S.C. § 355-1(g)(2)).

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifepristone is available as 200 mg tablets for oral use.

Mifeprex (mifepristone) was approved on September 28, 2000 with a restricted distribution program under 21 CFR 314.520 (subpart H)[b] to ensure that the benefits of the drug outweighed the risk of serious complications associated with mifepristone when used for medical abortion. Mifeprex was deemed to have a REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007, and the Mifeprex REMS was approved on June 8, 2011. On March 29, 2016, as noted above, a supplemental application and REMS modification was approved for Mifeprex. On April 11, 2019, ANDA 091178 was approved, and the Mifepristone REMS Program was approved. The Mifepristone REMS Program is a single, shared system REMS that includes NDA 020687 and ANDA 91178.

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

a. Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program (under ETASU A).
b. Ensuring that mifepristone is only dispensed in certain healthcare settings, by or under the supervision of a certified prescriber (under ETASU C).
c. Informing patients about the risk of serious complications associated with mifepristone (under ETASU D).

Under ETASU A, to become specially certified to prescribe mifepristone, a healthcare provider must review the prescribing information, complete and sign the *Prescriber Agreement Form,* and follow the guidelines for use of mifepristone. Under ETASU C, mifepristone must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. Under ETASU D, mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions (i.e., the patient must sign a *Patient Agreement Form*). The Mifepristone REMS Program also includes an implementation system, and a timetable for assessments (one year from the date of the initial approval of the REMS on April 11, 2019, and every three years thereafter).

[b] NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

2.2. REGULATORY HISTORY AND EVENTS RELEVANT TO THIS REMS MODIFICATION RATIONALE REVIEW

The following is a summary of significant regulatory history since approval of the REMS modification on March 29, 2016:

- 03/29/2016: FDA approved an efficacy supplement (S-020) that, among other things, provided a new dosing regimen (200 mg mifepristone, followed in 24 to 48 hours by 800 mcg buccal misoprostol), increased the gestational age (GA) to which mifepristone may be used (through 70 days gestation), and modified the REMS.

- 03/29/2019: A Citizen Petition was received requesting that FDA revise the product labeling to reflect pre-2016 provisions (including limiting GA to 49 days and requiring patients to make 3 office visits) and that FDA maintain the REMS.

- 04/11/2019: ANDA 91178 was approved along with the Single Shared System REMS for Mifepristone 200 mg (Mifepristone REMS Program) for NDA 20687 and ANDA 91178.

- 01/31/2020: the COVID-19 public health emergency (PHE) was declared by the Secretary of Health and Human Services (HHS) as having existed since January 27, 2020.[c]

- 7/13/2020: The United States (US) District Court of Maryland granted a preliminary injunction in the *ACOG v. FDA* litigation to temporarily bar enforcement of the Mifepristone REMS Program in-person dispensing requirement during the COVID-19 PHE.

- 1/12/2021: US Supreme Court granted a stay of that injunction.

- 04/12/2021: FDA issued a General Advice Letter to both the NDA and ANDA Applicants, stating that provided that all other requirements of the Mifepristone REMS Program are met, and given that in-person dispensing of mifepristone for medical termination of early pregnancy may present additional COVID-related risks to patients and healthcare

[c] *See* Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued January 31, 2020, and subsequently renewed), available at https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx

personnel because it may involve a clinical visit solely for this purpose, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement in the Mifepristone REMS Program, including any in-person requirements that may be related to the *Patient Agreement Form.* FDA further stated that to the extent all of the other requirements of the Mifepristone REMS Program are met, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of mifepristone through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

- 05/07/2021: FDA stated that it would be reviewing the elements of the Mifepristone REMS Program in accordance with the REMS assessment provisions of section 505-1 of the FD&C Act.

- 05/14/2021: A modification was approved for the Mifepristone REMS Program. This modification was to revise the *Patient Agreement Form* to include gender-neutral language.

- 06/30/2021: An Information Request (IR) was sent to the Applicants for additional information on shipments and any program deviations, adverse events, or noncompliance with the REMS that occurred during the period from April 1, 2021 through September 30, 2021.

- 7/15/2021: An IR was sent to the Applicants to provide the total number of shipments during the period from April 1, 2021 to September 30, 2021 and details on whether any of those shipments were involved in any program deviation or non-compliance.

- 8/5/2021: An IR was sent to the Applicants for additional clinical and other information (e.g., adverse events and units of mifepristone shipped) for the period of March 29, 2016 through June 30, 2021, to be provided by August 31, 2021. This IR also requested information covering the period of July 1, 2021 through September 30, 2021 and an

aggregate summary (for the period of March 29, 2016 through September 30, 2021), to be provided by October 12, 2021.[d]

- 8/26/2021: The ANDA Applicant submitted a response to the IR issued on 8/5/2021.
- 08/27/2021: The NDA Applicant submitted a response to the IR issued on 8/5/2021.
- 10/08/2021: The NDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR. The NDA Applicant also included a follow-up to their initial response provided on August 27, 2021 to the August 5, 2021 IR.
- 10/12/2021: The ANDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR.
- 10/16/2021: The ANDA Applicant revised their Oct 12, 2012 response to provide a correction to the number of mifepristone tablets.
- (b) (4) .
- 11/02/2021: A (b) (6) ((b) (6) meeting was convened to obtain CDER concurrence on the removal of the in-person dispensing requirement and the addition of a certification requirement for pharmacies. The (b) (6) (b) (6) and senior CDER leadership concurred with removing the in-person dispensing and adding pharmacy certification.

3. Rationale for Proposed REMS Modification

[d] Multiple Information Requests were issued to obtain additional information on drug shipments, any program deviations or noncompliance, and use of alternative methods for drug distribution during the COVID-19 PHE. These IRs are referenced as appropriate in this document and the one-year REMS Assessment Review of the Mifepristone REMS Program, December 16, 2021.

3.1. CURRENT REQUIREMENTS FOR THE APPROVED REMS

The Mifepristone REMS Program includes elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. Elements to assure safe use in the current REMS include a prescriber certification requirement (ETASU A), a requirement that mifepristone be dispensed only in certain healthcare settings by or under the supervision of a certified prescriber (ETASU C), and a requirement that mifepristone be dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions under ETASU D consists of a *Patient Agreement Form* between the prescriber and the patient indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with mifepristone 200 mg for medical termination of early pregnancy.

3.2. EVALUATION OF THE EVIDENCE

We reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation. Below is an overview of how information relevant to the current Mifepristone REMS Program was retrieved, analyzed, and applied to each of the individual ETASUs to determine if further changes should be considered.

Methods for the literature search

(b) (6) conducted a literature search in PubMed and Embase to retrieve publications relevant to this review. The time period used for this literature search was between March 29, 2016 (when the Mifeprex labeling and REMS were last substantially revised) through July 26, 2021. The search terms used were “medical abortion” and “mifepristone” and “pregnancy termination and mifepristone.”

The search retrieved 306 publications from PubMed and 613 from Embase, respectively; the search yielded 646 unique publications after eliminating duplications between the two databases. The result of our literature search was also supplemented by an examination of literature references provided by advocacy groups, individuals, plaintiffs in the *Chelius* litigation, and the Applicants, as well as letters from healthcare providers and researchers.

References included in these letters were considered for inclusion in this review using identical selection criteria to the (b) (6) literature search (outlined below).

For this review of the REMS, (b) (6) focused on publications containing safety data related to outcomes of medical abortion (objective safety data) obtained from our literature search and from the references provided to us relevant to the REMS ETASUs. We excluded systematic reviews and meta-analyses because these publications did not include original safety data related to the outcomes of medical abortion. The following are examples of materials that were excluded from our literature search:

- Information from survey studies or qualitative studies that evaluated perspectives on and/or satisfaction with medical abortion procedures from patients, pharmacists, clinic staff, or providers, even if the study assessed REMS ETASUs. These surveys or qualitative studies did not include objective safety data related to outcomes of medical abortion.

- Opinions, commentaries, or policy/advocacy statements. These publications did not include objective safety data related to outcomes of medical abortion.

- Safety data related to mifepristone use for second trimester medical abortion. These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.

- Safety data related to mifepristone use for spontaneous first trimester abortion (i.e., miscarriages). These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.

- Safety data that pertained only to surgical abortion or did not separate out medical abortion from surgical abortion.

- Other safety information unrelated to the REMS elements (e.g., articles limited to case reports or those discussing unrelated gynecologic or medical issues)

- Publications for which it was not possible to conduct a full review of the methods or results, i.e., the references were limited to an abstract of the study methods and results.

- Publications that provided only general statistics on abortion care in the United States.

- Information pertinent to molecular or other basic science aspects of mifepristone.

- Data on the logistics of accessing abortion care in general, such as time to appointment or the distance traveled to obtain care.

- Publications that provided data not related specifically to abortion care or the REMS (e.g., references focused on federal poverty guidelines, poverty data, or the financial impact of the COVID-19 pandemic).

One exception to the above literature search criteria was the inclusion in Section 3.2.2 of this review, which discusses the *Patient Agreement Form*, of publications that discussed changes in provider volume. The data discussed in relation to provider volume was obtained from surveys. This data was included because changes in provider volume could only be obtained from well-conducted survey studies.

Regarding medical/scientific references submitted with letters from the plaintiffs in the *Chelius* litigation, we applied the same criteria as for the literature search, as described above.

Letters from the plaintiffs in the *Chelius* litigation included several references that preceded our 2016 review of the REMS. Two of those pre-2016 studies were not captured in our 2016 literature search. These two studies were assessed as part of our current review; their results are consistent with the existing safety profile of the approved medical abortion regimen, and therefore, support our current conclusions regarding the REMS. See Appendix A.

3.2.1. Evaluation of the requirement for healthcare providers who prescribe the drug to be specially certified (ETASU A)

In order to become specially certified, prescribers must: 1) review the prescribing information for mifepristone and 2) complete the *Prescriber Agreement Form*. In signing the *Prescriber Agreement Form*, prescribers agree they meet the qualifications listed below:

- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to

ensure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of mifepristone (which the provider can access by phone or online).

In addition to meeting these qualifications, as a condition of certification the healthcare provider also agrees to follow the guidelines for use below:

- Review the *Patient Agreement Form* with the patient and fully explain the risks of the mifepristone treatment regimen. Answer any questions the patient may have prior to receiving mifepristone.
- Sign and obtain the patient's signature on the *Patient Agreement Form*.
- Provide the patient with a copy of the *Patient Agreement Form* and the Medication Guide.
- Place the signed *Patient Agreement Form* in the patient's medical record.
- Record the serial number from each package of mifepristone in each patient's record.
- Report deaths to the Applicant, identifying the patient by a non-identifiable patient reference and the serial number from each package of mifepristone.

The literature review was the primary source of information that contributed to our reassessment of ETASU A.

We continue to be concerned that absent these provider qualifications, serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed. Our review of the literature did not identify any studies comparing providers who met these qualifications with providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention or arrange for such care through others if needed, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol. Therefore, our review continues to support the conclusion that a healthcare provider who prescribes mifepristone should meet the above qualifications. We conclude it is reasonable to maintain the requirement for a one-time prescriber certification where prescribers attest to having the ability to diagnose an intrauterine

pregnancy, to diagnose an ectopic pregnancy,[e] and to either manage serious complications themselves or arrange for other providers to provide the needed care in a timely manner.

In addition, in signing the *Prescriber Agreement Form* and placing it in the patient's medical record, the prescribers acknowledge the requirement to report patient deaths associated with mifepristone to the manufacturer. Such a requirement ensures that the manufacturer receives all reports of patient deaths and, in turn, fulfills its regulatory obligations to report those deaths to the FDA.

As discussed in Section 3.2.2 below, there is a potential for doubling of the number of prescribers of mifepristone if the in-person dispensing requirement in ETASU C is removed from the Mifepristone REMS Program. Given the potential addition of new prescribers, in addition to the considerations described above, we conclude that we should maintain the requirement for prescriber certification, to ensure that providers meet the necessary qualifications and adhere to the guidelines for use. Our literature review supports that these requirements are still necessary, and the potential increase in new prescribers under the REMS is a further reason to maintain prescriber certification. Healthcare provider certification continues to be a necessary component of the REMS to ensure the benefits of mifepristone for medical abortion outweigh the risks. The burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one time for each applicant.

3.2.2. Evaluation of the requirement for the drug to be dispensed with evidence or other documentation of safe-use conditions (ETASU D)

In order to receive mifepristone for medical termination of pregnancy through 70 days gestation, the patient must sign a *Patient Agreement Form* indicating that the patient has received, read, and been provided a copy of the *Patient Agreement Form* and received counseling from the prescriber regarding the risk of serious complications associated with mifepristone for this indication. The *Patient Agreement Form* ensures that patients are informed of the risks of serious complications associated with mifepristone for this indication.

[e] American College of Obstetricians and Gynecologists (ACOG) Practice Bulleting Number 191, February 2018. Tubal Ectopic Pregnancy. https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/03/tubal-ectopic-pregnancy. Mifepristone is not effective for terminating ectopic pregnancy. Some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. A missed ectopic pregnancy that ruptures is a medical emergency that requires immediate surgical intervention.

In a number of approved REMS, *Patient Agreement Forms* or *Patient Enrollment Forms* ensure that patients are counseled about the risks of the product and/or informed of appropriate safe use conditions.[f]

As a condition of certification under the Mifepristone REMS Program, healthcare providers must follow the guidelines for use of mifepristone, including reviewing the *Patient Agreement Form* with the patient, fully explaining the risks of the treatment regimen, and answering any questions the patient may have before receiving the medication. With this form, the patient acknowledges that they have received and read the form, and that they have received the counseling regarding when to take mifepristone, the risk of serious complications associated with mifepristone and what to do if they experience adverse events (e.g., fever, heavy bleeding). Both the healthcare provider and patient must sign the document and the patient must receive a copy of the signed form. In addition to the counseling described in the *Patient Agreement Form*, patients also receive a copy of the Medication Guide for mifepristone. Ultimately, the *Patient Agreement Form* serves as an important counseling component, and documentation that the safe use conditions of the Mifepristone REMS Program have been satisfied, as the prescriber is required to place the signed *Patient Agreement Form* in the patient's medical record.

Prior to the March 29, 2016 approval of the S-020 efficacy supplement for Mifeprex, FDA undertook a review of all elements of the REMS. At that time, the (b) (6) ((b) (6)), along with the (b) (6) ((b) (6)), recommended removal of the *Patient Agreement Form* (ETASU D). This recommendation received concurrence from the (b) (6) on February 23, 2016. The rationale for this recommendation in the 2016 review[g] is summarized here as follows:

- The safety profile of Mifeprex is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance.
- Established clinical practice includes patient counseling and documentation of informed consent and evidence shows that practitioners are providing appropriate patient

[f] REMS@FDA, https://www.accessdata fda.gov/scripts/cder/rems/index.cfm, Accessed November 15, 2021.
[g] (b) (6) Clinical Review, NDA 020687/S20, dated March 29, 2016. https://darrts fda.gov/darrts/faces/ViewDocument?documentId=090140af803dc7bd&_afrRedirect=386175573203745

counseling and education; the *Patient Agreement Form* is duplicative of these established practices.

- Medical abortion with Mifeprex is provided by a small group of organizations and their associated providers. Their documents and guidelines are duplicated in the *Patient Agreement Form*.
- ETASUs A and C remain in place: The *Prescriber Agreement Form* and the requirement that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals under the supervision of a certified prescriber, remain in place.

In light of a memorandum from the Director of the Center for Drug Evaluation and Research, an addendum to the (b) (6) March 29, 2016 review and a memorandum from the signatory authority in (b) (6) indicated that the *Patient Agreement Form* would be retained in the REMS.[h,i]

The current review of literature from March 29, 2016 to July 26, 2021, is relevant to our assessment of the necessity of the *Patient Agreement Form* as part of the REMS. While our literature search yielded no publications which directly addressed this element of the REMS, we identified the following literature that focused on the informed consent process. These studies were reviewed for their potential relevance on this topic, though the articles do not directly assess the need for the *Patient Agreement Form* as a condition necessary to assure safe use of Mifepristone under ETASU D.

- Two studies[1,2] (both authored by Dr. Grossman in 2021) used the *Patient Agreement Form* and additional clinic-specific written informed consent forms as part of the study methodology. One study evaluated medical abortion with pharmacist dispensing of mifepristone and another evaluated mail-order pharmacy dispensing. Safety and efficacy outcomes were not assessed regarding the element of consent in isolation or the *Patient Agreement Form*.
- Several studies included use of electronic or verbal consent. Two studies were conducted using signed electronic consent (Chong[3], Kerestes[4]). Aiken[5] reported that patients had the option of providing consent verbally and the discussion had to be recorded in the notes. Rocca[6] described obtaining verbal informed consent from patients seeking medical abortion provided in pharmacies or government-certified

h (b) (6) Review of proposed REMS modifications to Mifeprex. March 29, 2106.
i (b) (6) Summary of Regulatory Action for Mifeprex. March 29, 2016.

public health facilities by auxiliary nurse midwives (ANMs) in Nepal. Outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

- A retrospective chart review (Wiebe[7]) was conducted in Canada. This study included telemedicine abortions between January 31, 2017 and January 31, 2019 and a similar group of controls seen in the clinic during the same time frame, matched by date of initial appointment. As part of the telemedicine process, patients read a consent form (not specified whether they could view an electronic version) and gave verbal consent "witnessed by the counselor". Again, outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

After review, we conclude that there are no outcome data from these studies that address the need for the *Patient Agreement Form* as a condition necessary to assure safe use of mifepristone. Nor do any of these studies provide evidence of whether the patient's informed consent has been adequately documented under the process set out in the study protocol. Therefore, these studies do not provide evidence that would support removing ETASU D.

Although (b) (6) agrees that informed consent in medicine is an established practice, the National Abortion Federation's 2020 Clinical Policy Guidelines for Abortion Care[8] continue to include a detailed section on patient education, counseling, and informed consent. The guidelines state that these steps are essential parts of the abortion process; that they should be conducted by appropriate personnel, with accurate information, including about alternatives and potential risks and benefits; and that the patients must have an opportunity to have any questions answered to their satisfaction prior to any intervention. Under these guidelines, documentation must show that the patient affirms that they understand all the information provided and that the decision to undergo an abortion is voluntary. The guidelines specifically list the risks that must be addressed at a minimum, including those pertinent to medical abortion: hemorrhage, infection, continuing pregnancy, and death. Additionally, Practice Bulletins from ACOG[9] and the Society of Family Planning also support detailed patient counseling.

In addition, trends in US clinical practice are developing which could negatively impact adequate patient counseling about the risks of medical abortion. One survey by Jones 2017[10] of abortion providers in the United States and Canada prior to the COVID-19 pandemic did reveal strong adherence to evidence-based guidelines. However, this same survey noted continued increasing uptake of medical abortion by US providers. Grossman[11] conducted a US survey in

2019 which suggested that the number of obstetrician/gynecologists providing medical abortion care may be increasing and that uptake might increase if mifepristone were dispensed by pharmacies instead of being dispensed in-person. A subsequent survey of US obstetricians/ gynecologists by Daniel in 2021[12] evaluated a subsample (n = 868) from a prior national survey of providers and found that 164 (19%) reported providing medical abortion in the previous year. Of those obstetrician/gynecologists not providing medical abortion, 171 (24%) said they would offer the method to their patients if the in-person dispensing requirement for mifepristone were removed. This indicates a potential doubling of providers (+ 104%, 95% confidence interval (CI): 97% −112%). There were geographical variations, with the largest potential increases being in the Midwest (+ 189%, 95% CI: 172% −207%) and the South (+ 118%, 95% CI: 103% −134%).

Based on the articles discussed above, removal of the in-person dispensing requirement from the Mifepristone REMS Program (as discussed below in section 3.2.3) could significantly increase the number of providers to a larger group of practitioners. The *Patient Agreement Form* is an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients, and also provides the information in a brief and understandable format for patients. The requirement to counsel the patient, to provide the patient with the *Patient Agreement Form*, and to have the healthcare provider and patient sign the *Patient Agreement Form*, ensures that each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care. The single-page *Patient Agreement Form* is in line with other elements of this REMS, in that it supports the requirement that certified prescribers be able to accurately assess a patient, counsel a patient appropriately and recognize and manage potential complications. The form is placed in the patient's medical record to document the patient's acknowledgment of receiving the information from the prescriber and a copy is provided to the patient. We determined, consistent with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients, and that the *Patient Agreement Form* remains necessary to assure the safe use of Mifepristone.

After considering potential burden on healthcare providers and patients and considering the available data discussed above, including the potential for increased prescribing of mifepristone if in-patient dispensing is removed from the REMS, we conclude that the *Patient Agreement Form* should remain a safe use condition in the REMS.

3.2.3. Evaluation of the requirement for drug to be dispensed only in certain healthcare settings (ETASU C)

Mifepristone applicants must ensure that mifepristone is available to be dispensed to patients only in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber. This creates what we refer to in this document as an in-person dispensing requirement under the REMS; i.e., the patient must be present in person in the clinic, medical office or hospital when the drug is dispensed. The mifepristone REMS document states that mifepristone may not be distributed to or dispensed through retail pharmacies or settings other than these.

The following information contributed to our analysis of this requirement: Mifepristone REMS Program year-one assessment data, postmarketing safety information and literature review.

REMS Assessment Data

Reporting period for the Mifepristone REMS Program - April 11, 2019 through February 29, 2020

We evaluated information included in the one-year (1st)[j] REMS assessment reports for the Mifepristone REMS Program, which included healthcare provider certification data, program utilization data, compliance data, audit results and patient exposure data.[13] The assessment reports were submitted on April 10, 2020 by the NDA Applicant and April 15, 2020 by the ANDA Applicant and cover a reporting period from April 11, 2019 through February 29, 2020. During this reporting period, the NDA Applicant reported (b) (4) newly certified healthcare providers, and the ANDA Applicant reported (b) (4) newly certified healthcare providers in the Mifepristone REMS Program. The NDA Applicant reported a total of (b) (4) certified healthcare providers (includes new and previously certified) ordered mifepristone during the assessment reporting period, and the ANDA Applicant reported a total of (b) (4) certified healthcare providers ordered mifepristone during the assessment reporting period. The NDA Applicant estimated that a total of (b) (4) patients were exposed to mifepristone during the assessment reporting period. The ANDA Applicant reported an estimated total of (b) (4) patients were exposed to mifepristone during the reporting period.

During the reporting period, a small number of non-compliance events were reported. The authorized distributor for the NDA applicant reported to the NDA Applicant that they experienced deviations with scanning of the product serial numbers which were confirmed during the February 2020 audit. The authorized distributor conducted a root cause analysis and developed a corrective and preventive action (CAPA) on February 12, 2020. The CAPA was

[j] This REMS assessment report was the first to be submitted following the approval of the single, shared system REMS for mifepristone.

validated and deployed with monitoring of the system through April 10, 2020. The corrective action will prevent similar events from occurring in the future.

January 27, 2020 through September 30, 2021

During the timeframe from January 27, 2020 through September 30, 2021, there were periods when the in-person dispensing requirement was not being enforced.

- On July 13, 2020, the United States District Court for the District of Maryland granted a preliminary injunction in the *ACOG* case to temporarily bar enforcement of the in-person dispensing requirement during the COVID-19 PHE.
- On January 12, 2021, the United States Supreme Court issued a stay of the injunction.
- On April 12, 2021, the FDA issued a General Advice Letter informing the applicants of the Agency's intent to exercise enforcement discretion during the COVID-19 public health emergency regarding the in-person dispensing requirement in the Mifepristone REMS Program.[k,l]

To better understand whether there was any impact on safety or noncompliance during the periods when the in-person dispensing requirement was not being enforced, we requested additional information from the Applicants to provide for more comprehensive assessment of the REMS for the time period from January 27, 2020 (the effective date of the COVID-19 PHE) to September 30, 2021. We requested the Applicants provide a summary and analysis of any program deviation or noncompliance events from the REMS requirements and any adverse events that occurred during this time period that had not already been submitted to FDA. As part of an additional request for information for the REMS assessment report, the Applicants were also asked to submit the adverse events to FAERS and to notify FDA that the reports were submitted.

Between January 27, 2020 and September 30, 2021, the NDA Applicant distributed (b) (4) shipments representing (b) (4) tablets. The NDA Applicant reported that there were (b) (4) shipments representing a total of (b) (4) tablets sent to (b) (4) non-certified healthcare providers.[m,n] (b) (4) of these healthcare providers subsequently became certified while (b) (4) did not. Of the (b) (4) healthcare providers who were not subsequently certified, (b) (4) returned a total of (b) (4)

[k] FDA General Advice Letter for NDA 20687, April 12, 2021.
[l] FDA General Advice Letter for ANDA 091178, April 12, 2021.

[m] NDA 020687 September 9, 2021 response to the FDA's September 2, 2021 Information Request.
[n] NDA 020687 October 8, 2021 response to the FDA's June 30, 2021 Information Request.

Mifeprex tablets to the distributor. (b) (4) non-certified healthcare provider dispensed (b) (4) to a patient; no adverse events were reported. The NDA Applicant attributed the non-compliance observed to the authorized distributor's transition to a new platform. The NDA Applicant implemented a corrective and preventative action to address this issue, which we found to be acceptable.

The ANDA Applicant distributed (b) (4) shipments representing (b) (4) tablets of mifepristone from January 27, 2020 to September 30, 2021 and reported no instances of shipments to non-certified healthcare providers during this timeframe.

The NDA and the ANDA applicants reported a total of eight cases reporting adverse events between January 27, 2020 and September 30, 2021. These eight cases were also identified in the FAERS database and are described in the section below.

The number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use for medical termination of pregnancy is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these reported adverse events. Further analysis of the adverse events is included below in the section on Pharmacovigilance Data.

Pharmacovigilance Data

The (b) (6) ((b) (6) conducted a search of the FAERS database and the published medical literature to identify U.S. postmarketing adverse events that reportedly occurred from January 27, 2020 through September 30, 2021 with mifepristone use for medical termination of pregnancy.[o,p]

The data for this time period were then further divided into date ranges when the in-person dispensing requirement was being enforced per the REMS (January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021) versus when the in-person dispensing requirement was not being enforced (July 13, 2020 - January 12, 2021 (in-person dispensing requirement was temporarily enjoined) & April 13, 2021 - September 30, 2021 (in-person dispensing requirement was not being enforced because of the COVID-19 PHE)).

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[o] (b) (6). Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. (b) (6) # 2007-525. Finalized April 12, 2021.

[p] (b) (6) Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. (b) (6) # 2007-525. Finalized December 16, 2021.

A total of eight cases that met the search criteria were identified in FAERS and no additional case reports were identified in the medical literature. Two of the eight cases reported adverse events that occurred when the in-person dispensing requirement in the REMS was being enforced (i.e., January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021). These two cases reported the occurrence of uterine/vaginal bleeding (case 1) and uterine/vaginal bleeding and sepsis (case 2). Of note, uterine/vaginal bleeding and sepsis are labeled adverse events. Five of the eight cases reported adverse events that occurred when the in-person dispensing requirement was not being enforced (i.e., July 13, 2020 - January 12, 2021 & April 13, 2021 - September 30, 2021). These five cases reported the occurrence of ongoing pregnancy (case 3), drug intoxication and death approximately 5 months after ingestion of mifepristone (case 4), death [cause of death is currently unknown] (case 5), sepsis and death (case 6), and pulmonary embolism (case 7). Although these adverse events occurred during the period when the in-person dispensing requirement was not being enforced, the narratives provided in the FAERS reports for cases 5, 6, and 7 explicitly stated that mifepristone was dispensed in-person. Of note, ongoing pregnancy, and sepsis, including the possibility of fatal septic shock, are labeled adverse events. The remaining case from July 2021 reported the occurrence of oral pain/soreness (case 8) but did not provide sufficient information to determine the exact date of the adverse event. Based upon the U.S. postmarketing data reviewed, no new safety concerns were identified by (b) (6)

In addition to the FAERS data provided above, (b) (6) routinely monitors adverse events reported to FAERS and published in the medical literature for mifepristone for medical termination of pregnancy. (b) (6) has not identified any new safety concerns with the use of mifepristone for medical termination of pregnancy.

To enable additional review of adverse events, the Applicants were requested[q] to provide a summary and analysis of adverse events reported with incomplete medical abortion requiring surgical intervention to complete abortion, blood transfusion following heavy bleeding or hemorrhage, ectopic pregnancies, sepsis, infection without sepsis, hospitalization related to medical abortion, and emergency department (ED)/urgent care encounter related to medical abortion. The Applicant for Mifeprex provided a summary of postmarketing safety information from March 29, 2016, when S-020 was approved, through September 30, 2021, on August 27 and October 8, 2021. During the time period in question, (b) (4) tablets were shipped, and

[q] On August 5, 2021, an IR was sent to the Applicants requesting a summary and analysis of adverse events from March 29, 2016 through June 30, 2021 and from July 1, 2021 through September 30, 2021.

48 adverse events were received. The 48 adverse events included 4 deaths (one of which occurred in 2010 but was reported in 2017), 25 incomplete abortions requiring surgical intervention, 17 blood transfusions following heavy vaginal bleeding, 2 ectopic pregnancies, 7 infections (1 sepsis and 6 infection without sepsis), 13 hospitalizations, and 43 ED or urgent care visits related to medical abortion. For the period between January 27, 2020 and September 30, 2021, a time frame that includes the entire period when the COVID-19 public health emergency (PHE) has been in effect, there were three adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 1 (uterine/vaginal bleeding), case 2 (uterine/vaginal bleeding and sepsis), and case 4 (drug intoxication and death).

The ANDA Applicant provided a summary of postmarketing safety information from April 11, 2019 (date of ANDA approval) through September 30, 2021. On August 26, 2021, the Applicant provided distribution and adverse event information from April 11, 2019 through June 30, 2021. During this time period, a total of (b) (4) tablets were shipped. There were 7 adverse events including 3 deaths (1 from sepsis, 1 from bilateral pulmonary artery thromboemboli, 1 in a patient who complained of not being able to breathe), 1 ongoing pregnancy treated with uterine aspiration, 2 blood transfusions, 1 sepsis (with death), 1 hospitalization, and 3 ED or urgent care visits related to medical abortion. On October 12, 2021 the Applicant provided information from July 1, 2021 to September 30, 2021; there were no additional adverse events. For the period between January 27, 2020 and September 30, 2021, there were four adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 3 (ongoing pregnancy), case 5 (death unknown cause), case 6 (sepsis and death), and case 7 (pulmonary embolism).[r]

The postmarketing data from FAERS were analyzed by (b) (6) to determine if there was a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. Based on this review, we conclude that there does not appear to be a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. This suggests that mifepristone may be safely used without an in-person dispensing requirement.

[r] The eighth FAERS case, oral pain/soreness, was not within the scope of the August 5, 2021 IR and was not considered for this review of postmarketing safety information submitted by the Applicants in response to the IRs.

(b) (6) review of the Applicants' IR responses, which included the same cases identified by (b) (6) from FAERS, did not change our conclusion.[s]

Literature Review

Published studies have described alternatives in location and method for dispensing mifepristone by a certified prescriber (or an equivalent healthcare provider in countries other than the US). Some studies have examined replacing in-person dispensing in certain health care settings with dispensing at retail pharmacies (Grossman[2], Wiebe[7], Rocca[6]) and dispensing mifepristone from pharmacies by mail (Grossman[1], Upadhyay[14], Hyland[15]). Other studies have evaluated two modes of dispensing by prescribers: (1) prescribers mailing the medications to women (Gynuity study [Raymond[16], Chong[3], Anger[17]], Kerestes[4], Aiken[5] (2021)) and (2) prescribers using couriered delivery of medications (Reynolds-Wright[18]). Other studies have evaluated dispensing mifepristone by mail by an entity described as "a partner organization" (Aiken[19] (2017), Norton[20], Endler[21]). For ease of review, in the sections below that describe these studies, we have separated relevant references by the methodology used to dispense mifepristone.

Retail pharmacy dispensing

Three studies report medical abortion outcomes for retail pharmacy dispensing of mifepristone after clinical evaluation. Grossman[2] conducted a US-based study in which mifepristone and misoprostol were dispensed from a pharmacy partnered with the clinic where the participant had an evaluation by ultrasound and counseling. Of the 266 participants enrolled, 260 had known abortion outcomes. Complete abortion without additional procedure occurred in 243 participants (93.5% of those with known outcomes). Seventeen participants (6.5% of those with known outcomes) were diagnosed with incomplete abortion and underwent uterine aspiration. The reported proportion of complete abortion is within the range described in the approved mifepristone labeling. However, the finding represents a lower-than-expected efficacy based on the cohort's GA (84% of participants were at ≤ 56 days GA, a cohort for which the labeled success rate is 96.8%). No participants experienced a serious adverse event, were hospitalized, or required transfusion. Three participants had ED visits with treatment (intravenous hydration, pain medication, pelvic infection after uterine aspiration for incomplete abortion). The study's

[s] The reporting period of (b) (6) assessment of the adverse events in FAERS is not identical to the time period for summaries of adverse events in the IRs to the Applicants. Therefore, the numbers of cases and adverse events summarized in (b) (6) assessment may differ from the numbers of cases and adverse events summarized by the Applicants in their responses to IRs (note that each case report may include more than one adverse event).

safety and efficacy outcomes are consistent with labeled frequencies. The majority of participants (65%) were very satisfied with the experience. There were some complaints from participants about not receiving all prescribed medications at the initial pharmacy visit, privacy not being adequately maintained, and perceived negative pharmacist attitude.

Overall, we conclude that this study has limited generalizability because it was conducted in two US states and involved partnered pharmacies, some of which were in the same building as the clinic. Additionally, all participating pharmacies in this study were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. The study conditions may not be generalizable to US retail pharmacies; there is insufficient information to assess this. Rocca[6] conducted an observational study evaluating 605 participants at ≤63 days GA who obtained medical abortions in Nepal by comparing the provision of medical abortion service by newly trained nurse midwives in pharmacies to medical abortion provided in government-certified clinics. Participants who presented to pharmacy study sites underwent clinical screening including a pelvic exam by trained nurse midwives at the pharmacy (which was equipped with an examination room) and if eligible for medical abortion, were dispensed mifepristone and misoprostol in the pharmacy at the time of their visit. Participants who presented to public health facilities underwent clinical screening including pelvic examination by abortion providers including trained nurse midwives and if eligible for medical abortion were dispensed mifepristone and misoprostol in the clinic at the time of their visit. The authors reported that, with respect to complete abortion (>97%) and complications (no hospitalizations or transfusions), evaluation and dispensing in pharmacy was non-inferior to in-clinic evaluation and dispensing.

Wiebe,[7] in a retrospective, chart review study conducted in Canada, compared abortion outcomes of 182 women at ≤ 70 days GA who underwent medical abortion with telemedicine consult, and either received medications by courier or picked them up at a local pharmacy, with outcomes of a matched control cohort of 199 women who received the medications at a pharmacy after an in-clinic visit. The groups had similar documented complete medical abortion outcomes (90%, calculated maintaining subjects with unknown outcomes in the denominator; ≥ 95% calculated with known outcomes only). The telemedicine group had one case of hemorrhage (0.5%) and one case of infection requiring antibiotics (0.5%) compared with no cases of hemorrhage or infection requiring antibiotics in the in-clinic cohort. The telemedicine group had more ED visits (3.3% compared to 1.5% in-clinic cohort). Both models of dispensing mifepristone resulted in efficacy and safety outcomes within labeled frequency.

None of the three studies described above allow a determination regarding differences in safety between in-person dispensing by a certified prescriber in a health care setting and dispensing through a retail pharmacy, due to limitations on the generalizability of the studies to the current retail pharmacy environment in the US. The outcome findings from the one US study (Grossman[2]), in which the pharmacies were partnered with prescribers, may not be generalizable to much of the US as they do not reflect typical prescription medication availability with use of retail pharmacy dispensing. Although retail pharmacy dispensing of mifepristone and misoprostol in Canada has been described in the literature, there are important differences in healthcare systems between Canada and the US that render the findings from studies in Canada (Wiebe[7]) not generalizable to the US. In the Wiebe study, timely provision of medication from the retail pharmacy was accomplished by either courier to the woman or faxed prescription to the woman's pharmacy. It is unknown whether conditions that allow timely access to medications for medical abortion would occur in retail pharmacies throughout the US. Canada's federal government has reaffirmed that abortion is an essential health service[t] which may have implications affecting access to medical abortion from retail pharmacies in Canada. The Rocca[6] study evaluated medical abortion provided in Nepali pharmacies and essentially moved the abortion provider and clinical examination into the pharmacy, a scenario that is not, at this time, applicable to the US retail setting.

Mail order pharmacy

Grossman[1] published an interim analysis of an ongoing prospective cohort study evaluating medical abortion with mifepristone and misoprostol dispensed by mail-order pharmacy after in-person clinical assessment. All participants were evaluated for eligibility during a clinic visit with GA up to 63 days confirmed with either an ultrasound or examination; instead of receiving medication at the clinic visit, participants received medications from a mail-order pharmacy. A total of 240 participants have been enrolled; three participants did not take either medication. A total of 227 (94.6%) provided some outcome information, of whom 224 provided abortion outcome information. Complete abortion without additional procedures occurred in 217 participants (96.9% of those with known outcomes). Two (0.9%) participants experienced serious adverse events (SAE); one received a blood transfusion, and one was hospitalized overnight. Nine (4%) participants attended 10 ED visits. In this interim analysis, the outcomes are consistent with labeled frequencies. With respect to the time interval between a

[t] As noted in Mark[23] and Martin[24], most provincial and federal health insurance programs in Canada cover medical abortion, and covered services are free at the point of care.

participant's clinic visit and receipt of medications, of the 224 participants with known abortion outcomes, 184 (82.1%) received medication within 3 days. However, 17% received between 4-7 days and one participant waited over 7 days for receipt. Seven of 216 (3.2%) participants who completed the day-3 survey reported compromised confidentiality (e.g., someone found their medication, privacy concerns).

Upadhyay[14] reports findings from a retrospective cohort study of 141 women undergoing medical abortion in the US without a consultation or visit. Eligibility was assessed based on a participant-completed online form collecting pregnancy and medical history. Participants who were considered eligible received medication delivered by a mail-order pharmacy. Three interactions via text, messaging or telephone occurred to confirm medication administration, assessment of expulsion and pregnancy symptoms, and results of a 4-week home pregnancy test. Abortion outcome was determined by either the day 3 assessment or the 4-week pregnancy test. The investigators reported a complete abortion rate without additional procedures of 95% (105 participants out of 110 for whom outcomes were known) and stated that no participants had any major adverse events. The proportion of abortion outcomes assessed at 3 days versus 4 weeks is not reported. Regardless, determining outcomes at 3 days is insufficient to determine outcome rates or safety findings because a 3-day follow-up period is too short. Additionally, a substantial number of participants (31) provided no outcomes information. Among the 141 participants enrolled, 128 had any follow-up contact with the study staff, and 110 provided outcomes information. Excluding outcomes of 22% of the cohort is a limitation of this study. This study used a model with numerous deviations from standard provision of medical abortion in the US, such as no synchronous interaction with the prescriber during informed consent or prior to prescribing medication, no confirmation of self-reported medical, surgical, and menstrual history. Further, follow-up information based on a 3-day period is insufficient to determine outcome rates or safety findings. These deviations, limited follow-up information, and small sample size limit the usefulness of this study.

Hyland[15] describes findings from a cohort study in Australia evaluating medical abortion outcomes utilizing telemedicine and a central mail order pharmacy. All participants obtained screening tests including ultrasound confirmation of GA. A total of 1010 participants completed the screening process and were provided mifepristone and misoprostol. Abortion outcomes were determined for 754 (75%) of the 1010. Outcomes for the remaining 256 participants (25%) were not included because 31 provided no relevant information after shipment, 14 reported not taking misoprostol, and 211 did not have "full follow up" (i.e., known outcome of either complete medical abortion, uterine evacuation, or ongoing pregnancy with plan to continue).

Complete abortions without additional procedures occurred in 727 participants (96% of those with definitively documented outcomes) and is consistent with labeled efficacy. Of the 754 participants included in the analysis 717 (95%) had no face-to-face clinical encounters after medications were mailed while 21 (3%) were admitted to the hospital and 16 (2%) had an outpatient encounter. One participant who was hospitalized and underwent a surgical uterine evacuation received a transfusion. Not included in the findings are 7 hospitalizations occurring in 7 participants who did not have "full follow up". The authors do not report any other adverse events and conclude use of the telemedicine medical abortion service is safe. The reasons for hospitalization are not discussed by the authors; therefore, it is unknown why the patients were hospitalized. Although the reported number of hospitalizations (3%) is higher than the less than 1% in the FDA-approved mifepristone labeling, conclusions regarding the safety findings in this study cannot be made in the absence of information about the reasons for hospitalization. Other limitations of this study include incomplete information about outcomes with face-to-face encounters, and not reporting outcomes of 25% of the enrolled cohort.

Overall, the three studies evaluating mail order pharmacy dispensing suggest that the efficacy of medical abortion is maintained with mail order pharmacy dispensing. In the Grossman[1] study, the interim analysis, although small, does not raise serious safety concerns. We note that 18% of participants did not receive medications within 3 days; the potential for delay in receiving medication by mail could limit the GA eligible for medical abortion through mail order pharmacy dispensing, because women at GA closer to 70 days might not receive medication in time. A small proportion (3%) of participants raised concerns regarding the issues of confidentiality and privacy. Safety findings from the Hyland[15] study are difficult to interpret. Although only one transfusion is reported, and the authors state the findings demonstrate safety, the higher hospitalization rates, and lack of information on the reasons for hospitalization do not allow any conclusions about safety findings. Lastly, the Upadhyay[14] study had no reported adverse events, but the findings are less useful because of the limited follow-up, and because medical abortions were provided using a model with numerous deviations from standard provision of medical abortion in the US.

Clinic dispensing by mail

A total of five studies evaluated clinic dispensing by mail.[3,4,5,16,17] Gynuity Health Projects conducted a prospective cohort study (the "TelAbortion" study) evaluating use of telemedicine for remote visits and mifepristone being dispensed from clinics via overnight or regular tracked mail. Three publications reviewed have reported outcomes for the Gynuity population

exclusively: Raymond[16] from May 2016 to December 2018, Chong[3] from May 2016 to September 2020 and Anger[17] from March 2020 to September 2020. Due to the pandemic, the Gynuity study deviated from the protocol requirement of confirmation of GA by examination or ultrasound for many participants treated from March 2020 onward (although none of the three publications reported on the single element of dispensing mifepristone from the healthcare setting by mail). A fourth study, Kerestes,[4] reports outcomes of medical abortion at the University of Hawai'i from April 2020 to November 2020: seventy-five (of whom 71 were enrolled in the Gynuity study) of the 334 participants in Kerestes were dispensed mifepristone by mail after a telemedicine consult. The section below discusses these four studies from the US as well as a large UK study by Aiken[5] (2021).

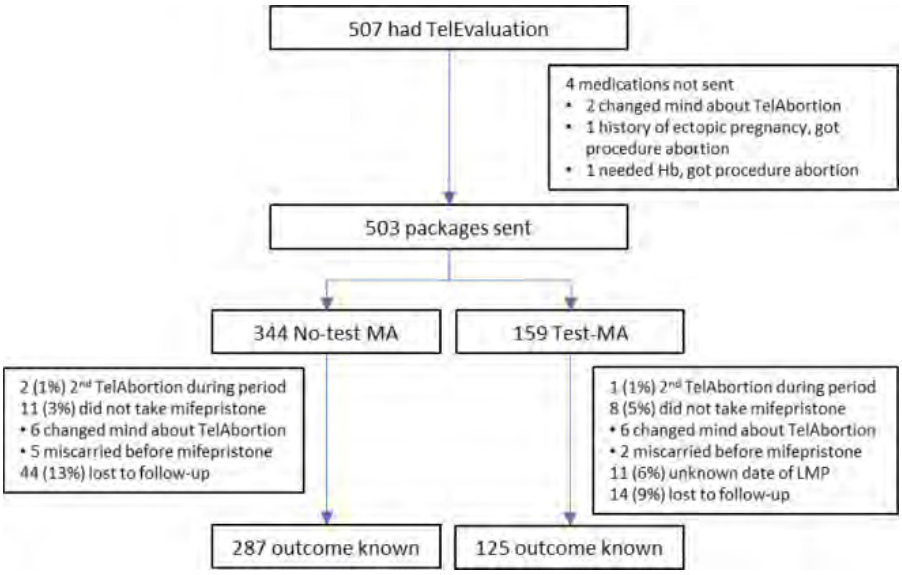
Raymond [16] (2019) reported outcomes from the Gynuity study prior to the pandemic. In the TelAbortion study, participants were not required to have an in-person clinic visit; rather, they obtained screening tests at laboratories and radiology offices and then communicated with the abortion provider by videoconference. If the participant was eligible for treatment, the provider dispensed the medications by mail. Of 433 women screened, 165 (38%) either declined to schedule the videoconference or did not keep the videoconference appointment. Among the 268 participants evaluated via videoconference, medication packages were sent to 248. Abortion outcomes were determined for 190 (77%) of the 248; outcomes for 58 (23%) participants were unknown. Complete abortion without additional procedures occurred in 177 participants (93% of those with known outcomes). The investigators obtained follow-up information from 217 participants after package shipment; there were two hospitalizations (one received a transfusion for severe anemia despite having had a complete abortion), and 16 other participants (7%) had clinical encounters in ED and urgent care centers. The reported outcomes in Raymond[16] (2019) are similar to outcomes described in approved labeling except the combined ED/urgent care center encounters (7%) exceeded the ED visits in approved labeling (2.9-4.6%). The authors note that half of the ED/urgent care visits did not entail any medical treatment and opine that the increased number of visits may have been due to the study participants living farther from the abortion providers.[16] All participants received medications within 8 days.

Chong[3] updated the findings from the Gynuity study described in Raymond[16] and reported on 1157 medical abortion outcomes, of which approximately 50% occurred during the period of the COVID-19 PHE. Although a screening ultrasound was required per the protocol, sites determined in 52% (346/669) of abortions that occurred during the period of the COVID-19 PHE that, in order to avoid potential exposure to COVID-19 at a health care facility, those

participants were not required to obtain a screening ultrasound. Use of urine pregnancy test to confirm abortion completion also increased from 67% (144/214) in the 6 months prior to the pandemic to 90% (602/669) in the 6 months during the pandemic. Of the 1390 participants to whom medicine packages (containing both mifepristone and misoprostol) were mailed, 1157 (83.2%) had known abortion outcomes. Complete abortion without a procedure occurred in 1103 participants (95% of the those with a known outcome). Ten women experienced an SAE (5 transfusions (0.4%) and 7 hospitalizations (0.7%)) and 70 (6%) participants had unplanned clinical encounters in ED/urgent care. Surgical interventions were required in 47 participants (4.1% of 1390) to complete abortion. The reported outcomes in this study are similar to outcomes described in approved labeling, except that the combined ED/urgent care center encounters (6%) exceeded the ED visits in approved labeling (2.9-4.6%).

Anger[17] compared outcomes among participants enrolled in the Gynuity study who did versus did not have confirmation of GA/intrauterine location with an examination or ultrasound from 10 jurisdictions across the US. These participants were screened for enrollment from March 25 through September 15, 2020. All participants had a telemedicine consultation and received mifepristone and misoprostol by mail from the healthcare facility. Determination of which participants did not require confirmation of GA by examination or ultrasound to be eligible depended on the study clinician's assessment of eligibility for "no-test medication abortion"[u] based on a sample protocol published by Raymond[22] (2020). There were two key differences between the two groups. Participants for whom the study clinician determined a pre-abortion ultrasound was required were more likely than the participants who had no ultrasound or examination to live further than 150 miles from the clinic (51.2% vs. 31.7%) and were more likely to have a GA above 63 days (12.0% vs. 1.7%). The study sites shipped 503 medication packages during the analysis period; 344 packages went to the "no test" group while 159 went to the "test" medical abortion cohort (see figure below). However, because the two cohorts were not randomized in this study, they had different baseline characteristics. Consequently, findings based on the comparisons between the two cohorts should be interpreted carefully.

[u] "No-test medication abortion" refers to medical abortion provided without a pretreatment ultrasound, pelvic examination, or laboratory tests when, in the judgment of the provider, doing so is medically appropriate (appropriateness based on history and symptoms); "no-test medication abortion" does include post-abortion follow up. A sample protocol is described by Raymond et al.[22]



Source: Figure 1 in this publication. MA= medical abortion.

The investigators' analyses excluded 91 (18% of 503; 57 in the no-test group and 34 in the test group) participants because they did not provide a date of the last menstrual period (LMP), did not take mifepristone, or did not have a recorded abortion outcome. Overall, 410 participants (81.5% of 503) provided outcomes data. There were no reported ectopic pregnancies in either group. The number of ED/urgent care visits and the proportion of unplanned clinical encounters that led to medical treatment were not reported. In the no-test group, complete medical abortion was confirmed in 271 participants who took medications (94% among those with known outcome). In the no-test cohort, two participants were "hospitalized and/or blood transfusion," and 36 (12.5%) had an unplanned clinical encounter (participant sought in-person medical care related to abortion and the visit was not planned prior to abortion).

In the test medical abortion group, complete abortion was confirmed in 123 participants (of 125 with known outcomes); the completion rate was 98% among those with known outcomes. In the test medical abortion group, one participant was "hospitalized and/or blood transfusion," and 10 (8.0%) had an unplanned clinical encounter. The authors concluded that, compared to participants who had an ultrasound prior to medical abortion, those without an examination prior to medical abortion were more likely to require procedural interventions and had more unplanned clinical encounters.

Kerestes[4] was the only publication that linked outcomes of medical abortion with different delivery models. Participants included in the report had GA up to 77 days and received

medications in Hawaii between April 2020 and January 2020. A total of 334 medication packages (to 330 unique participants) were dispensed containing mifepristone and misoprostol; three different delivery models were used concurrently: 110 (32.9%) had traditional in-person visits, 149 (44.6%) had telemedicine consultation with in-person pick-up of medications, and 75 (22.5%) were sent medications by mail (71 of these were enrolled through Gynuity's TelAbortion study). Seven participants of the 330 participants who received 334 medication packages reported that they did not take them and were excluded from analysis of the outcomes. Among participants with follow-up data, the rates of successful medical abortion without surgery were 93.6%, 96.8%, and 97.1% in the in-clinic group, telemedicine + in-person pickup group, and telemedicine + mail group, respectively; these were consistent with outcomes in approved labeling. Blood transfusion was given to two participants (both in the telemedicine + in-person pickup group). Eleven participants went to an ED. Although ED visits occurred the most frequently in the telemedicine + mail group (four participants or 5.8%) and the least in the in-person group (two participants or 2.1%), the study reported no increases in other serious adverse events.

Taken together, the three Gynuity study reports[3,16,17] and Kerestes[4] support dispensing mifepristone and misoprostol by mail after a telemedicine visit. Efficacy was maintained in all four studies. All of the studies reported SAEs frequencies comparable to labeled rates, except two of the Gynuity study reports (Raymond[16], Chong[3]) and Kerestes[4] report a higher frequency of ED/urgent care visits than the labeled frequency of ED visits. We do not know whether the reporting of combined ED and urgent care visits represents an increased rate of ED visits compared to the labeled rate of ED visits (2.9-4.6%). Other labeled SAEs (e.g., transfusion) occur infrequently (< 1%).

Aiken[5] (2021) reports outcomes of medical abortion up to 70 days GA in the UK before and during the pandemic in a retrospective cohort study. In the UK, prior to the COVID-19 pandemic, all patients attended an in-clinic visit where they received an ultrasound, were administered mifepristone in the clinic, and given misoprostol in-clinic for use at home (traditional model). During the pandemic, medical abortion consultations were performed remotely by telephone or video. Based on the consultation and questionnaire (including date of last menstrual period; menstrual, contraceptive and medical history; symptoms; risk for ectopic pregnancy), an assessment of eligibility for treatment via telemedicine was made. If eligible, medications were delivered to participants via mail or were made available for collection from the clinic for use at home. If the participant was assessed to be ineligible for treatment via

telemedicine, an in-person assessment with ultrasound was performed and medications were provided from the clinic for home use (hybrid model).

The study compared the two cohorts: 22,158 obtained medical abortion before the pandemic and had in-person visits and dispensing (traditional model) and 29,984 obtained medical abortion during the pandemic with either in-person visit and in-person dispensing, or a telemedicine visit and dispensing by mail or picked up from the clinic (hybrid model). Outcomes were obtained from electronic records and incident databases. Outcomes of all hospitalizations related to abortion, ED visits, infection without sepsis, and hemorrhage without transfusion were not reported. The investigators' analysis for non-inferiority determined the efficacy and safety were comparable between both cohorts. Complete abortion occurred in > 98% in both cohorts. Hemorrhage requiring transfusion was reported in 0.04% and 0.02% of the traditional and hybrid cohorts, respectively; this is lower than the labeled 0.5% transfusion rate. There were no severe infections requiring hospitalization, major surgery or deaths reported.

A secondary analysis of the hybrid cohort was reported. Within the 29,984-person hybrid model cohort, 11,549 (39%) abortions were conducted in-person (in-person assessment with ultrasound was performed and medications provided from the clinic for home use) and 18,435 (61%) abortions were provided by telemedicine visit, without tests or confirmation of GA/intrauterine position by ultrasound, and medications either mailed or picked up from the clinic. Outcomes stratified by type of mifepristone dispensing were not reported. The rate of complete abortion was slightly higher in the telemedicine group (99.2%) than that in the in-person group (98.1%). There were no significant differences in the rates of reported SAEs. Adjustments for clinical and demographic characteristics were made because the two groups differed in baseline characteristics, including a higher proportion of pregnancies with GA over 6 weeks in the in-person group (68.2% compared with 55.1%). The authors conclude a hybrid model for medical abortion that includes no-test medical abortion[u] (no ultrasound, no pelvic exam, no pregnancy test) is effective and safe.

We conclude that although the Aiken[5] (2021) study has a large sample size and includes 85% of all medical abortions performed in England and Wales during the study period, the study has limitations. The authors acknowledge the main limitation of their study was that analysis was based on deidentified information in the NHS database and the investigators were unable to verify the outcomes extracted. Other limitations included that their search only captured

outcomes in electronic records and incident databases that met the authors' defined threshold for SAE reporting, and that the labeled abortion outcomes considered serious, such as hospitalizations related to abortion, infection without sepsis, hemorrhage without transfusion, or ED/urgent care visits, were not all included in the authors' definition of serious adverse event.

Data from the mail order dispensing studies with telemedicine visits from Gynuity (Raymond, Chong and Anger),[3,16,17] Kerestes[4], and Aiken[5] (2021) support that efficacy of medical abortion was maintained. The Aiken[5] study appears to be of sufficient sample size to determine whether safety outcomes with mail dispensing differ from in-person dispensing; however, the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings. Study reports of Raymond[16] Chong[3], and Kerestes[4] all suggest there may be an increase in ED/urgent care visits with telemedicine visits and dispensing by mail without increases in other adverse events. Anger's[17] comparative analysis suggests a pre-abortion examination may decrease the occurrence of procedural intervention and decrease the number of unplanned visits for postabortion care. Overall, despite the limitations noted, these studies support that dispensing by mail is safe and effective. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other SAEs related to mifepristone use. One reason for the increase in frequent ED/urgent care visits in the Raymond[16] publication, according to its authors, may have been that a substantial proportion of participants lived significant distances from their providers and increased distances have been associated with higher use of ED following treatment. Raymond[16] reported that half of the participants who had an ED/urgent care visit did not require medical treatment.

Clinic dispensing by courier

Reynolds-Wright[18] reported findings from a prospective cohort study of 663 women at less than 12 weeks' GA in Scotland undergoing medical abortion at home with use of telemedicine during the pandemic (from April 1 to July 9, 2020). The majority of medical abortions (78.7%) used telemedicine visits, eliminated pre-abortion ultrasound, and provided mifepristone for pick up at the service or by couriered delivery to woman's home. The number of couriered deliveries was not reported; thus, this study does not provide abortion outcomes separately for couriered delivery of mifepristone and misoprostol. With access to NHS regional hospital databases, the investigators were able to verify pregnancy outcomes and complications. Of the 663 participants, 642 (98.2%) were under 10 weeks GA, 21 (1.8%) were between 10 and 12 weeks

GA, and one participant was never pregnant. A total of 650 participants had complete abortion without requiring surgical intervention (98%), 5 (0.8%) an ongoing pregnancy and 4 (0.6%) an incomplete abortion. The outcomes from this study in Scotland are consistent with labeled mifepristone outcomes. The study shares the same limitations as the Aiken[5] (2021) study.

Partner organization dispensing by mail

Women on Web (WoW), an internet group, connects patients and providers outside of the US and provides medical abortion globally, dispensing mifepristone through "a partner organization" by mail.[v] Medical abortion eligibility is determined using an online questionnaire with asynchronous physician review. If eligible, medications are mailed to the women. WoW provides help and support by email or instant messaging.

Aiken[19] (2017) conducted a population-based study analyzing findings from 1,636 women in the Republic of Ireland and Northern Ireland who were sent medications between 2010 and 2012. Receipt of medications was confirmed for 1,181 women, among whom 1,023 confirmed use of mifepristone and misoprostol; outcome information was available for 1,000 (61% of women sent medications). Of the 1,000 women, the majority (781, 78%) were less than 7 weeks GA and 219 (22%) were at 7-9 weeks. Complete abortion without surgical intervention occurred in 947 (94.7% of 1,000 with known outcome); 7 (0.7%) women received a blood transfusion, 26 (2.6%) received antibiotics (route of administration undetermined) and 87 (8.7%) sought medical care at a hospital or clinic for symptoms related to medical abortion. Hospitalizations related to abortion were not reported. The reported proportion of complete abortion is within the range labeled for medical abortion up to 70 days (92.7-98.1%). However, the finding of 94.7% complete abortion represents a lower-than-expected efficacy based on the cohort's GA (almost 80% less than 7 weeks, labeled success for medical abortion ≤ 49 days is 98.1%). This study has limitations, including outcomes based on self-report without validation of completed abortion by examination or laboratory testing, and no known outcomes for 39% of study cohort. Additionally, the authors noted medical abortion was provided in a legally-restrictive setting, where the law provided a maximum penalty of life imprisonment for the woman undergoing the abortion, which may affect participants' self-reporting.

[v] In March 2019, FDA sent a WL to Aidaccess.org, a group affiliated with WoW. Aidaccess.org received this WL because it was introducing misbranded and unapproved new drugs into the U.S. In the context of this REMS review, studies involving WoW are included solely for purposes of evaluating of data regarding the methods of dispensing mifepristone.

Endler[21] and Norten[20] have reported outcomes from WoW cohorts but do not provide relevant information on mifepristone dispensing by mail, because neither provide meaningful outcomes data for consideration. Endler[21] compared the outcomes of self-reported heavy bleeding and clinical visits occurring during the "first or second day of abortion" that occurred in women undergoing medical abortion at 9 weeks GA or less, with outcomes from women at more than 9 weeks GA. Outcome data from day 1 or 2 is of limited usefulness. Norten[20] describes findings from a survey of women who were sent medical abortion medication through WoW and provided self-reported outcomes. Results were based on surveys returned from only 37% of participants, a return rate that is too low for the study to be considered valid.

WoW uses a model with numerous deviations from the standard provision of medical abortion in the US. For example, this model has no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history or confirmed pregnancy testing. Further, although Aiken[19] (2017) is a large cohort study, the outcomes are self-reported with no verification of complete abortion by laboratory or clinical evaluation and 39% of outcomes are unaccounted for. These limitations in the Aiken study result in the data being insufficient to determine the safety of dispensing mifepristone by mail through a partner organization.

4. Discussion

After review of the published literature, safety information collected during the COVID-19 PHE, postmarketing data, information from the first Mifepristone REMS Program assessment report, responses to information requests to the Applicants, and information provided by advocacy groups, individuals and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that the REMS can be modified to reduce burden without compromising patient safety.

Prescriber Certification

None of the publications we reviewed would support a conclusion that a healthcare provider who prescribes mifepristone does not need to meet the qualifications included in the Mifepristone REMS Program as described above in section 3.2.1. Absent these provider qualifications, serious complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed.

We conclude that prescriber certification (ETASU A) should be maintained. The current process requires the prescriber to agree to the requirements of the Mifepristone REMS Program and to attest that they meet the qualifications described in section 3.2.1 above. The REMS has been structured to minimize burden to prescribers by requiring only a one-time certification by the prescriber for each Applicant. We have determined that healthcare provider certification continues to be necessary to ensure the benefits outweigh the risks, especially considering that, if the in-person dispensing requirement is removed from the Mifepristone REMS Program, the number of new providers may increase (see discussion in section 3.2.2 above).

Drug to be dispensed with evidence or other documentation of safe use conditions

The requirement to counsel the patient and provide them with the *Patient Agreement Form* ensures that each patient is informed of the appropriate use of mifepristone, the risks associated with treatment, and what to do if they experience symptoms that may require emergency care.

In 2016, we initially recommended eliminating the *Patient Agreement Form* (see section 3.2.2), though the form was ultimately maintained as part of the REMS. As discussed above, our current literature review has indicated that there is no basis to remove the *Patient Agreement Form* from the REMS. In addition, surveys we reviewed suggest that if the in-person dispensing requirement for mifepristone is removed, there could be a potential doubling of medical abortion providers. This potential doubling of medical abortion providers supports the continued need to ensure that patients are consistently provided patient education under the Mifepristone REMS Program regarding the use and risks of mifepristone. The *Patient Agreement Form* is an important part of standardizing the medication information that prescribers communicate to their patients, including new prescribers, and also provides the information in a brief and understandable format to patients. We determined, in accordance with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients.[w]

Given the likelihood of a potential increase in new prescribers if the in-person dispensing requirement is removed from the Mifepristone REMS Program, we conclude that maintaining the *Patient Agreement Form* remains necessary to assure safe use at this time.

[w] *The Patient Agreement Form* can be signed in person or through other means.

Drug to be dispensed only in certain healthcare settings

As discussed above in section 3.2.3, our evaluation of information submitted by the applicants in the one-year (1st) REMS assessment report for the Mifepristone REMS Program and in response to follow-up requests from the Agency indicates that the number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these adverse events. We further conclude, based our review of the postmarketing safety data from FAERS during the COVID-19 PHE and information submitted by the applicants for the timeframe of January 27, 2020 through September 30, 2021, that there does not appear to be a difference in adverse events between periods during the COVID-19 PHE when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced; nor have we identified any new safety concerns with the use of mifepristone for medical termination of early pregnancy.

Alternatives to in-person dispensing of mifepristone have been investigated in several studies and countries. The literature review identified 15 publications[x] that assessed safety outcomes from various medication delivery models (US, UK, Canada, Ireland, Australia, Nepal), including dispensing by retail and mail order pharmacies, prescribers mailing medications or using couriered service to deliver medications, and dispensing by "partner organizations". The ability to generalize the results of these studies to the US population is hampered by differences in pre-abortion care (e.g., telemedicine versus in-person, testing), and the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy.

In addition, there are factors which complicate the analysis of the dispensing element alone. Some of these factors are: (1) only a few studies have evaluated alternatives for in-person dispensing of mifepristone in isolation; for example, most studies on mail dispensing of mifepristone also include telemedicine consultation, and (2) because most SAEs with medical abortion are infrequent, though they can be life threatening, further evaluation of changes in dispensing would require studies with larger numbers of participants. We did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the US.

[x] The 15 publications correspond to endnote numbers: 1-7, 14-21.

Based on the literature identified by our review, dispensing mifepristone by mail from the clinic or from a mail order pharmacy does not appear to jeopardize the efficacy of medical abortion. The studies we reviewed are not adequate on their own to establish the safety of the model of dispensing mifepristone by mail, although the safety and efficacy outcomes reported in these studies remain within the ranges described in mifepristone labeling except for increased numbers of ED/urgent care visits and hospitalizations.

Four publications (Raymond[16], Chong[3], Anger[17] and Kerestes[4]), describe a relevant US cohort where dispensing mifepristone from the clinic by mail was paired with telemedicine visits. These studies showed that efficacy was maintained and there was no increased frequency of SAEs except for higher ED/urgent care visits. The increased ED/urgent care visits were not associated with increases of other SAEs, and in the view of one study's authors (Raymond[16]), may be associated with participants being located significant distances from their providers. The Aiken[5] (2021) study of a large UK cohort where the clinics mailed mifepristone report small (lower than labeled) occurrences of transfusion and no significant infections requiring hospitalization. In Grossman[1] and Hyland[15], where the pharmacies mailed mifepristone after prescribers confirmed GA, efficacy is maintained. Grossman's[1] interim analysis found no increases in SAEs. Hyland[15] reported higher numbers of hospitalizations but did not report increases of other SAEs. Overall, while the studies assessing mifepristone dispensing by mail suggest more frequent encounters with healthcare providers, they generally support a conclusion that dispensing by mail is safe. Despite the limitations of the studies we reviewed, we conclude that overall, the outcomes of these studies are not inconsistent with our conclusion that, based on the 1st year REMS assessment report and postmarketing safety data, mifepristone will remain safe, and efficacy will be maintained if the in-person dispensing requirement is removed from the Mifepristone REMS Program.

Based on the REMS assessment data, FAERS data from the time period when the in-person dispensing requirement was not being enforced, our review of the literature, and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that mifepristone will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met, and pharmacy certification is added as described below.

Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to

ensure that the benefits of mifepristone for medical abortion outweigh the risks. Therefore, to reduce the burden imposed by the REMS, the Mifepristone REMS Program should be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies, in addition to in-person dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C.

New requirement to be added for pharmacy certification

The current distribution model requires the certified prescriber to dispense mifepristone directly to the patient in a clinic, medical office, or hospital. During the periods when the in-person dispensing requirement was not being enforced, both applicants used mail order pharmacies to receive and hold mifepristone on behalf of the certified healthcare providers who had purchased the product.[j,y,z] Pursuant to a prescription for mifepristone, the mail order pharmacy would ship the product to a named patient.

The Mifepristone REMS Program continues to require that mifepristone be prescribed only by certified prescribers. With the removal of the in-person dispensing requirement, however, the drug is no longer required to be dispensed only in a clinic, medical office or hospital. Under the REMS as modified, mifepristone can be dispensed through a pharmacy, provided the product is prescribed by a certified prescriber and all other requirements of the REMS are met. Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies under ETASU B. Adding the pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Without pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber. Adding pharmacy certification ensures that ETASU A is met prior to dispensing the product to a patient; certified prescribers, in turn, have agreed to meet all the conditions of the REMS, including ensuring that the *Patient Agreement Form* (ETASU D) is completed. In addition, wholesalers and distributors can only ship to certified pharmacies. Based on our review of the safety data and our consideration of the distribution model implemented by the Applicants during the periods

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y ANDA 091178: September 23, 2021 response to the September 15, 2021 information request; October 11 and 16, 2021 responses to the June 30, 2021 and July 15, 2021 information requests; October 26, 2021 response to the October 22, 2021 information request; October 29, 2021 response to the October 27 information request.
z NDA 020687: September 20, 2021 response to the September 15, 2021 information request; October 26, 2021 response to the October 22 information request.

when the in-person dispensing requirement was not being enforced, as well as REMS assessment data and published literature, we conclude that provided all other requirements of the REMS are met, the REMS program, with the removal of the in-person dispensing requirement and the addition of a requirement for pharmacy certification, will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients. As modified, the REMS would allow, for example, dispensing by mail order or specialty pharmacies, similar to the distribution model used by applicants during the periods when the in-person dispensing requirement was not being enforced.[aa]

The above recommendations were discussed with the (b) (6) ((b) (6) and senior leadership from CDER on November 2, 2021. The (b) (6) (b) (4) along with senior CDER leadership, concurred with removing the in-person dispensing requirement provided that all of the remaining REMS requirements are met, including but not limited to prescriber certification where prescribers need to attest to having certain qualifications, and maintaining the *Patient Agreement Form*. The (b) (6) (b) (4) and senior leadership from CDER were also in favor of adding pharmacy certification to assure the safe use of mifepristone.

5. Conclusions and Recommendations

Based on the results of REMS assessments; our review of safety data collected during the PHE as well as data from FAERS; our literature search; and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, (b) (6) and (b) (6) have concluded that a REMS modification is necessary and should include the following changes:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified.

[aa] Our current conclusion that the REMS would allow dispensing by mail order or specialty pharmacies is based on data received from Applicants relating to the periods when the in-person dispensing requirement was not enforced and mail-order pharmacies were used to dispense the product, as well as our analysis of postmarketing safety data and available literature. At this time we do not have data (from the Applicants or from other sources) to assess the certification of retail pharmacies under the REMS. We have not yet determined the details of pharmacy certification requirements, including whether any limitations on the types of pharmacies that may dispense the product are necessary.

(b) (6) and (b) (6) recommend the Applicants be issued a REMS Modification Notification Letter that requests submission within 120 days from the date of the letter.

6. References

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[3] Chong E, Shochet T, et al. Expansion of a direct-to-patient telemedicine abortion service in the United States and experience during the COVID-19 pandemic. Contraception 2021;104:43-48.

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7. Appendix A

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References cited in letter from *Chelius v. Becerra* Plaintiffs (September 29, 2021)	
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Aiken A et al. BJOG 2021: 128 (9): 1464-1474	
Chong, et al. Contraception 2021; 104(1) 43-48	
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References excluded from the REMS review	**Rationale for Exclusion**
Am. Coll. of Obstetricians & Gynecologists, *Position Statement: Improving Access to Mifepristone for Reproductive Health Indications* (June 2018), https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications	Policy/advocacy statement
House of Delegates, Am. Med. Ass'n., *Memorial Resolutions Adopted Unanimously No. 504 (2018)* https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/hod/a18-resolutions.pdf	Policy/advocacy statement
Cong. Of Delegates, Am. Acad. Of Fam. Physicians, *Resolution No. 506 (CoSponsored C) Removing Risk Evaluation and Mitigation Strategy (REMS) Categorization of Mifepristone* (May 24, 2018) https://www.reproductiveaccess.org/wp-content/uploads/2019/02/Resolution-No.-506-REMS.pdf	Policy/advocacy statement
Schummers L et al, Contraception 2020; 102(4): 273	Abstract
Upadhyay UD et al.) Obstet & Gynecol 2015; 125: 175	Published prior to March 29, 2016-July 26, 2021 timeframe for current literature review. We note that the extensive literature review conducted as part of the 2016 review, which was consistent with the division's standard approach for reviewing an efficacy supplement

Reference ID: 4905882

	and encompassed 90 references, did not capture this publication. However, the authors' conclusion in this publication is consistent with our review of the safety data in 2016.
Kapp N et al. Best Pract Clin Obstet Gynaecol. 2020;63:37-44	Abstract. Also outside the scope of first trimester medical abortion.
Fuentes L et al. J Women's Health 2019; 28 (12): 1623, 1625 Bearak JM, Lancet Pub Health 2017 Nov;2(11): e493, e495-96 Cartwright A et al 20 J Med Internet Res 2018 20(5):e10235 Barr-Walker J, et al PLoS One 2019;14(4): e0209991 Grossman et al JAMA Network 2017;317(4):437, 437-438 Dobie S et al 31 Fam Plan Persp 1999; 31(5): 241-244 Shelton JD 8 Fam Plan Persp 1976; 8(6):260, 260-262 Norris AH et al Am J Pub Health 2020; 110 (8): 1228,1232 Upadhyay UD et al Am J Pub Health 2014; 104(9):1687, 1689	Focused on the logistics of accessing abortion care.
CDC MMWR Abortion Surveillance – United States, 2018 https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T5_down	Contains primarily general statistics on abortion care by state.

References cited in appendix from *Chelius v. Becerra* Plaintiffs (September 29, 2021)
References included in the REMS review
None

References excluded from the REMS review	Rationale for Exclusion
Jones RK et al Guttmacher Institute Abortion Incidence and Service Availability in the United States, 2017 (2019) Guttmacher Inst, Induced Abortion in the United States (2019)	Contains primarily general statistics on abortion care and logistics of accessing abortion care.
University of Minnesota Healthy Youth Dev. Prevention Rsch Ctr, 2019 Minnesota Adolescent Sexual Health Report 3 (2019)	Not related specifically to abortion care.
Jerman J et al Guttmacher Inst, Characteristics of U.S. Abortion Patients in 2014 and Changes since 2008 (2016)	Contains figures on patient characteristics from 2008-2014.
Roberts CM et al Women's Health Issues 2014; 24:e211, e215	Focused on cost of abortion.
CDC MMWR Abortion Surveillance 2018 https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T7 down (last updated Nov. 7, 2020)	Contains primarily statistics on number of abortions in the US.
Jones RK Persp on Sexual & Reprod Health 2017; 49:17, 20	Focused on abortion incidence and service availability.
Fuentes L et al (as above) Bearak JM et al (as above) Cartwright A et al (as above) Johns NE et al. BMC Health Serv Res 2017; 17: 287, 294	Focused on logistics of accessing abortion care.

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Chong et al. Contraception 2021;104(1): 43-48	
Aiken A et al. BJOG 2021; 128 (9): 1464 -1474	
Hyland 2018 et al. Aust New Zeal J Obstet Gynaecol 2018; 58 (3): 335-340	
References excluded from the REMS review	**Rationale for Exclusion**
Schummers L et al. BMJ Sex Reprod Heal 2021;47(e1)	Abstract
Kapp et al. 2020 (as above)	Abstract
Upadhyay et al. 2015 (as above)	(See rationale above)
Srinivasulu et al. Contraception 2021; 104(1):92-97	Survey on clinician perspectives on access to mifepristone.
Calloway D et al. Contraception 2021; 104(1): 24-28	Primarily addresses provider stigma around abortion care.
Rasmussen et al. Contraception; 104(1): 98-103	Opinion/commentary
Cleland et al. Obstet Gynecol 2013;121(1):166-171	Published prior to March 29, 2016 - July 26, 2021 timeframe for current literature review. We note that the extensive literature search conducted as part of the 2016 clinical review, which was consistent with the division's standard approach for reviewing an efficacy supplement and encompassed 90 references, did not capture this publication. However, the authors' conclusion in this publication is consistent with our review of the safety data in 2016.
National Academy of Sciences, Engineering, and Medicine. Safety and Quality of Abortion Care in the US 2018	General information about abortion care in the US. Did not provide safety data relevant to the elements of the REMS
Raymond EG. Obstet Gynecol 2012: 119(2): 215-219	Does not separate out medical and surgical abortion.

Bartlett LA et al. Obstet Gynecol 2004; 103(4): 729-737	Focused on surgical abortion.
Jones RK, Jerman J. Time to appointment and delays in accessing care among U.S. abortion patients, Guttmacher 2016	Focused on logistics of accessing abortion care.
Foster DG et al. Perspect Sex Reprod Health 2013; 45(4):210-218	Focused on second trimester abortion.
Ely G et al. Heal Soc Work 2019;44(1):13-21	Focused on logistics of accessing abortion care.
Munro S et al. Ann Fam Med 2020; 18(5):413-421.	Survey on physician perspectives on implementing medical abortion with mifepristone.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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Questions and Answers on Mifepristone for Medical Termination of Pregnancy Through Ten Weeks Gestation

On this page:

- General Information
- The Mifepristone REMS Program
- Additional Information
- The January 2023 REMS Modification
- Litigation and Other Legal Issues

General Information

1. **What is mifepristone and how does it work?**

   Mifepristone is a drug that blocks a hormone called progesterone that is needed for a pregnancy to continue. Mifepristone, when used together with another medicine called misoprostol, is used to end an intrauterine pregnancy through ten weeks gestation (70 days or less since the first day of the last menstrual period). The approved mifepristone dosing regimen is:

   - On day one: 200 mg of mifepristone taken by mouth
   - 24 to 48 hours after taking mifepristone: 800 mcg of misoprostol taken buccally (in the cheek pouch), at a location appropriate for the patient
   - About seven to fourteen days after taking mifepristone: follow-up with the health care provider

2. **When did the FDA approve mifepristone for medical termination of pregnancy?**

   The FDA first approved Mifeprex (mifepristone) in September 2000 for medical termination of pregnancy through seven weeks gestation, and this was extended to ten weeks gestation in 2016. FDA approved a generic version of Mifeprex, Mifepristone Tablets, 200 mg, in April 2019. The agency's approval of this generic reflects the FDA's determination that Mifepristone Tablets, 200 mg, is therapeutically equivalent to Mifeprex and can be safely

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substituted for Mifeprex. Like Mifeprex, the approved generic product is indicated for the medical termination of an intrauterine pregnancy through 70 days gestation. The labeling for the approved generic version of Mifeprex is consistent with the labeling for Mifeprex.

3. **Who should not take mifepristone, in a regimen with misoprostol, for medical termination of pregnancy?**

   An individual should not take mifepristone, in a regimen with misoprostol, for medical termination of pregnancy if it has been more than 70 days since the first day of their last menstrual period, or if they:

   - have an ectopic pregnancy (a pregnancy outside of the uterus)
   - have problems with the adrenal glands (the glands near the kidneys)
   - are currently being treated with long-term corticosteroid therapy
   - have had an allergic reaction to mifepristone, misoprostol or similar drugs
   - have bleeding problems or are taking anticoagulant (blood thinning) drug products
   - have inherited porphyria (a rare disorder that can affect the liver and other organs)
   - have an intrauterine device (IUD) in place (it must be removed before taking mifepristone)

4. **Is it safe to use mifepristone?**

   Yes. Mifepristone is safe when used as indicated and directed and consistent with the Mifepristone Risk Evaluation and Mitigation Strategy (REMS) Program. The FDA approved Mifeprex more than 20 years ago based on a thorough and comprehensive review of the scientific evidence presented and determined that it was safe and effective for its indicated use. As of 2016, it is approved for use for medical termination of pregnancy up to 70 days of gestation. The FDA's periodic reviews of the postmarketing data for Mifeprex and its approved generic have not identified any new safety concerns with the use of mifepristone for medical termination of pregnancy through 70 days gestation. As with all drugs, the FDA continues to closely monitor the postmarketing safety data on mifepristone for the medical termination of pregnancy.

5. **What are the possible side effects of using mifepristone for medical termination of pregnancy through ten weeks gestation?**

   The possible side effects are described in the labeling (https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s025Lbl.pdf) and in the Medication Guide (https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s025Lbl.pdf#page=16) for mifepristone.

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6. **What serious adverse events have been reported after the use of mifepristone for medical termination of pregnancy through ten weeks gestation?**

   As with all approved drugs, when the FDA receives new information regarding adverse events, the agency reviews the new information and, as appropriate, takes necessary action. This could include, for example, providing updates to health care providers and their patients so that they have information on how to use a drug safely.

   It is common for the FDA to receive reports of serious adverse events for prescription drugs after they are approved. Many drugs are associated with serious adverse events that are known at the time of approval and considered when the FDA makes its approval decision. The FDA continuously reviews reports of adverse events to, among other things, determine whether they are known risks or whether they are signals of emerging safety concerns.

   The FDA has received reports of serious adverse events in patients who took mifepristone. As of December 31, 2024, there were 36 reports of deaths in patients associated with mifepristone since the product was approved in September 2000, including two cases of ectopic pregnancy (a pregnancy located outside the womb, such as in the fallopian tubes) resulting in death, and several fatal cases of severe systemic infection (also called sepsis). The adverse events cannot with certainty be causally attributed to mifepristone because of concurrent use of other drugs, other medical or surgical treatments, co-existing medical conditions, and information gaps about patient health status and clinical management of the patient. A summary report of adverse events that reflects data through December 31, 2024, is here (/media/185245/download?attachment). The FDA has reviewed this information and did not identify any new safety signals. The FDA intends to update this summary report as appropriate.

7. **What should health care providers watch for in patients who have taken mifepristone for medical termination of pregnancy through ten weeks gestation?**

   Health care providers should review the approved labeling for Mifeprex and the approved generic, Mifepristone Tablets, 200 mg. The signs and symptoms they should watch for are included in the labeling, available here (https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s025Lbl.pdf).

8. **What is an ectopic pregnancy?**

   An ectopic pregnancy is a non-viable pregnancy that develops outside of the womb. It occurs in approximately two percent of all pregnancies. An ectopic pregnancy is usually located in one of the fallopian tubes. As the fetus grows, the tube cannot hold it, causing the tube to rupture (burst) and bleed. Unless they are discovered and treated early, almost 40 percent of ectopic pregnancies rupture suddenly, causing pain and bleeding in the abdominal cavity. The other 60 percent usually cause slow bleeding in the abdomen.

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Ruptured ectopic pregnancies can be fatal. The approved labeling for Mifeprex and the approved generic, Mifepristone Tablets, 200 mg, states that the use of mifepristone, in a regimen with misoprostol, for the medical termination of pregnancy through ten weeks gestation is contraindicated in patients with a confirmed or suspected ectopic pregnancy.

9. **Does the FDA endorse this drug product?**

   The FDA does not endorse any drug product. The agency evaluates all drug applications submitted by applicants to determine whether the data and information in an application support the approval of the application. The same standards are applied to the drug applications for Mifeprex and the approved generic Mifepristone Tablets, 200 mg, as are applied to all drug applications.

The Mifepristone REMS Program

10. **Why is there a REMS for this product?**

    The FDA's determination as to whether a REMS is necessary for a particular drug is a drug-specific evaluation. The agency considers whether (based on premarketing or postmarketing risk assessments) there is a particular risk or risks associated with the use of the drug that, on balance, outweigh its benefits and whether additional risk mitigation measures beyond the FDA-approved labeling are necessary to ensure that the drug's benefits outweigh its risks.

    The Mifepristone REMS Program is intended to mitigate the risk of serious complications associated with mifepristone when used for medical termination of pregnancy through ten weeks gestation by, among other things, requiring that prescribers have the necessary qualifications to assess whether patients are appropriate candidates for the drug and to provide necessary intervention in case of complications (or have made plans to provide such care through others), ensuring that mifepristone is only dispensed by certified pharmacies or by or under the supervision of certified prescribers, and requiring that patients be informed of the risks of the treatment regimen.

11. **What are the restrictions on prescribing and dispensing mifepristone for medical termination of pregnancy through ten weeks gestation?**

    When the agency reviewed and approved the original new drug application for Mifeprex (mifepristone) in 2000, it concluded that certain restrictions were necessary to ensure the safe use of the drug. These restrictions were approved as a risk evaluation and mitigation strategy (REMS) in 2011 and have been modified since then.

    These REMS requirements also apply to the approved generic version of Mifeprex. Mifeprex and the approved generic version of Mifeprex are subject to a single, shared system REMS, known as the Mifepristone REMS Program. This program sets the requirements that must be

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followed to ensure safe use of both Mifeprex and the approved generic version of Mifeprex.

Under the Mifepristone REMS Program, these requirements include, among others:

- Mifepristone must be prescribed by a health care provider that meets certain qualifications and is certified under the Mifepristone REMS Program.
- In order to become certified to prescribe mifepristone, health care providers must complete a Prescriber Agreement Form.
- The Patient Agreement Form must be reviewed with and signed by the patient and the health care provider, and the risks of the mifepristone treatment regimen must be fully explained to the patient before prescribing mifepristone.
- The patient must be provided with a copy of the Patient Agreement Form and the mifepristone Medication Guide (FDA-approved information for patients).
- Mifepristone may only be dispensed by or under the supervision of a certified prescriber, or by a certified pharmacy on a prescription issued by a certified prescriber.
- To become certified to dispense mifepristone, pharmacies must complete a Pharmacy Agreement Form.
- Certified pharmacies must be able to ship mifepristone using a shipping service that provides tracking information.
- Certified pharmacies must ensure mifepristone is dispensed to the patient in a timely manner.

Each REMS is required to have a plan for periodic assessments by the applicants, which are reviewed by the agency to determine whether the REMS is meeting its goals or whether certain goals or elements of the REMS must be modified. The FDA may require applicants to modify a REMS if the agency determines that an element is no longer necessary to ensure that the benefits of the drug outweigh the risks or to minimize the burden on the health care delivery system.

12. **How does the Mifepristone REMS Program ensure safe use of the drug?**

    The Mifepristone REMS Program requires that in order for patients to receive mifepristone, it must be prescribed by a certified prescriber who has certain qualifications and agrees to follow certain guidelines for use. Under the Mifepristone REMS Program, mifepristone must be dispensed by or under the supervision of a certified prescriber or by a certified pharmacy on a prescription issued by a certified prescriber. The Mifepristone REMS Program is a closed system, meaning prescribers, pharmacies, and distributors are certified or authorized

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and verified under the REMS prior to distribution or dispensing of the drug. The Mifepristone REMS Program ensures that mifepristone is only distributed to health care providers and pharmacies that have agreed to the REMS requirements.

13. **How does the Mifepristone REMS Program as modified in January 2023 differ from the previous REMS requirements?**

    Prior to the modifications to the Mifepristone REMS Program approved in January 2023, the Mifepristone REMS Program required mifepristone to be dispensed in person in a clinic, medical office, or hospital. The requirement to dispense in person in one of these settings was referred to as the "in-person dispensing requirement." There were periods when the in-person dispensing requirement was not being enforced. First, from July 13, 2020, until January 12, 2021, the FDA was enjoined from enforcing the in-person dispensing requirement by an injunction issued in the ACOG v. FDA litigation, which was filed in the U.S. District Court for the District of Maryland. On April 12, 2021, the agency stated its intent to exercise enforcement discretion with respect to the in-person dispensing requirement during the COVID-19 public health emergency.

    In 2021, after conducting a comprehensive review of the Mifepristone REMS Program, the FDA determined, based on the available data and information, that the REMS must be modified to reduce burden on the health care delivery system and to ensure the benefits of the product outweigh the risks. On December 16, 2021, the FDA announced that the modifications to the Mifepristone REMS Program would consist of:

    - Removing the "in-person dispensing requirement"
    - Adding a requirement that pharmacies that dispense the drug be certified

    Consistent with the typical process for REMS modifications, the FDA sent REMS Modification Notification letters to the applicants for Mifeprex and the approved generic, Mifepristone Tablets, 200 mg. Following receipt of these letters, the applicants prepared a proposed REMS modification and submitted it to their respective applications. After reviewing the applicants' submissions, the FDA approved the REMS modification on January 3, 2023. The REMS document and materials are available at:

    - Find information on Mifeprex (mifepristone) here (https://www.earlyoptionpill.com/for-health-professionals/ordering-mifeprex/) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)
    - Find information on generic mifepristone here (https://genbiopro.com/) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)

Where can patients get mifepristone for medical termination of pregnancy through ten weeks gestation?

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Mifepristone must be prescribed by a certified prescriber who meets certain qualifications and agrees to follow certain guidelines for use. Under the Mifepristone REMS Program, mifepristone can be dispensed by or under the supervision of a certified prescriber or by a certified pharmacy on a prescription issued by a certified prescriber.

14. **What qualifications must health care providers have to become certified to prescribe mifepristone for medical termination of pregnancy through ten weeks gestation?**

    Health care providers who would like to become certified to prescribe mifepristone must review the Prescribing Information for mifepristone and must have the ability to date pregnancies accurately and the ability to diagnose ectopic pregnancies. Health care providers must also be able to provide any necessary surgical intervention or have made arrangements for others to provide for such care. Health care providers must be able to ensure that patients have access to medical facilities for emergency care, and must agree to other responsibilities, including reviewing and signing the Patient Agreement Form with the patient and providing each patient with a copy of the signed Patient Agreement Form.

    Some states allow health care providers other than physicians to prescribe medications. Health care providers should check their individual state laws.

15. **Under the Mifepristone REMS Program, are patients required to see a health care provider in person before obtaining mifepristone for medical termination of pregnancy through ten weeks gestation?**

    The Mifepristone REMS Program does not require patients to see a health care provider in person before obtaining mifepristone for medical termination of pregnancy through ten weeks gestation. Mifeprex and the approved generic, Mifepristone Tablets, 200 mg, are indicated, in a regimen with misoprostol, for the medical termination of an intrauterine pregnancy through 70 days gestation and are contraindicated for certain patients, including those with an ectopic pregnancy. The FDA has determined that it is not necessary for the REMS to mandate how providers clinically assess patients for duration of pregnancy and for ectopic pregnancy. The prescription labeling for Mifeprex and the approved generic provide guidance to prescribers regarding how they can confirm the gestational age of the pregnancy and confirm that the pregnancy is located in the uterus. Aspects of a patient's medical history that may constitute contraindications to medical termination of pregnancy may be elicited without direct physical contact with the certified prescriber and can be done in different types of health care settings, thus certified prescribers are not necessarily required to be physically present with the patient when they prescribe mifepristone. As explained above (Question 15), health care providers certified under the Mifepristone REMS Program must also be able to provide any necessary surgical intervention or have made arrangements for others to provide for such care and must be able to ensure that patients have access to medical facilities for emergency care.

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16. **What information did the FDA consider when it reviewed the Mifepristone REMS Program in 2021?**

    To determine whether a modification to the Mifepristone REMS Program was warranted, the FDA conducted a comprehensive review of the published literature, other relevant safety and adverse event data, and information provided by advocacy groups, individuals, and the applicants related to the modifications that were under consideration. Our review also included an examination of literature references provided by plaintiffs in the *Purcell v. Becerra* (previously *Chelius v. Becerra*) litigation.

17. **Prior to the FDA's action in January 2023, how was mifepristone dispensed to patients?**

    Prior to the FDA's action on the REMS modification applications submitted by the applicants for Mifeprex and the approved generic, Mifepristone Tablets, 200 mg, in 2022, the Mifepristone REMS Program required that mifepristone be dispensed in person in a clinic, medical office, or hospital. The requirement to dispense in person in one of these settings was referred to as the "in-person dispensing requirement."

    There were periods when the in-person dispensing requirement was not being enforced. First, from July 13, 2020, until January 12, 2021, the FDA was enjoined from enforcing the in-person dispensing requirement by an injunction issued in a lawsuit, *ACOG v. FDA* filed in the U.S. District Court for the District of Maryland. On April 12, 2021, the agency stated its intent to exercise enforcement discretion with respect to the in-person dispensing requirement during the COVID-19 public health emergency.

    During the periods when the in-person dispensing requirement was not being enforced, the applicants for Mifeprex and the approved generic, Mifepristone Tablets, 200 mg, used mail order pharmacies to receive and hold mifepristone on behalf of the certified prescribers who purchased the product. Pursuant to a prescription for Mifeprex or its approved generic, the mail order pharmacy would ship the product to a named patient.

18. **What is the FDA's role in overseeing the Mifepristone REMS Program?**

    As with all REMS, the FDA monitors the applicants' compliance with the Mifepristone REMS Program, including by reviewing periodic assessment information from the applicants and conducting on-site inspections, and takes action as appropriate.

19. **What is pharmacy certification and why is it a requirement of the Mifepristone REMS Program?**

    The Mifepristone REMS Program requires all pharmacies that dispense mifepristone to be specially certified. The pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS

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requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Any pharmacy that meets the requirements of the Mifepristone REMS Program is eligible to be certified.

20. **What steps are required for pharmacy certification?**

    The pharmacy certification requirement ensures that pharmacies are aware of and agree to follow applicable REMS requirements and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers.

    To become certified to dispense mifepristone, pharmacies must: (1) be able to receive Prescriber Agreement Forms by email and fax; (2) be able to ship mifepristone using a shipping service that provides tracking information; (3) designate an authorized representative to carry out the certification process on behalf of the pharmacy; and (4) ensure the authorized representative oversees implementation and compliance with the Mifepristone REMS Program, which includes, among other requirements, the completion of a Pharmacy Agreement Form.

21. **Is mifepristone available at retail pharmacies?**

    The January 2023 modification to the Mifepristone REMS Program removed the restriction that did not allow mifepristone to be dispensed by retail pharmacies. While pharmacy certification is required, any pharmacy that meets the requirements of the Mifepristone REMS Program is eligible for certification.

22. **Is mifepristone available for over-the-counter use?**

    No. Mifepristone for medical termination of a pregnancy through ten weeks gestation is only available by prescription. An applicant seeking to switch mifepristone for medical termination of pregnancy through ten weeks gestation from prescription to nonprescription (also referred to as over-the-counter) status would need to submit this information to the FDA for evaluation. In order for a drug product to be approved for nonprescription use (including switching a prescription drug product to nonprescription marketing), the applicant must provide sufficient information demonstrating that the drug can be used safely and effectively by consumers without the supervision of a health care provider.

23. **What would be required to remove the REMS?**

    The FDA may release a REMS or remove certain components of a REMS if, after review of REMS assessments or other information, the agency determines that the REMS or certain components of the REMS are no longer necessary to ensure a medication’s benefits outweigh its risks.

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Additional Information

25. **Is it possible for an individual to become pregnant again after taking mifepristone for medical termination of pregnancy through ten weeks gestation?**

    It is possible for an individual to become pregnant again soon after a pregnancy ends. A patient should consult with their health care provider regarding any specific questions they may have.

26. **Is mifepristone approved in any other countries for medical termination of pregnancy?**

    Mifepristone for medical termination of pregnancy has been approved in France since 1988, and also is approved in the United Kingdom, Sweden, and approximately 100 other countries.

27. **Does the FDA set the price of mifepristone and is the drug reimbursed by health insurance providers?**

    The FDA does not have the authority to regulate the prices of drug products in the United States. Manufacturers, distributors, and retailers establish the prices. Additionally, the FDA does not have input into or legal control over whether an insurance company does or does not cover the cost of a drug. Insurance coverage is a decision made by an insurance provider. Individuals should contact their insurance provider if they have questions about whether a particular insurance provider will cover the cost of the drug.

28. **Has FDA ever taken action regarding the sale of mifepristone online?**

    The FDA has sent warning letters to websites selling unapproved and misbranded mifepristone and misoprostol over the internet, including AidAccess (/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/aidaccessorg-575658-03082019) and Rablon (/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/rablon-1111111-03082019).

    There have also been several criminal cases related to the online sale of mifepristone for medical termination of pregnancy. We are aware of three cases about which the Agency can speak publicly. The first is *United States v. O'Neil*, in the U.S. District Court for the District of Maryland. Information about two more individual prosecutions are available here: March 28, 2017: Former Atlantic County, New Jersey, Man Charged with Smuggling and Dispensing Misbranded Drugs | FDA (/inspections-compliance-enforcement-and-criminal-investigations/press-releases/march-28-2017-former-atlantic-county-new-jersey-man-charged-smuggling-and-dispensing-misbranded) and here: New York Woman Sentenced for Selling Abortion-Inducing Pills Illegally Smuggled Into US | USAO-WDWI | Department of Justice (https://www.justice.gov/usao-wdwi/pr/new-york-woman-sentenced-selling-abortion-

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inducing-pills-illegally-smuggled-us). The FDA also issued a Final Debarment Order for Ursula Wing (https://www.federalregister.gov/documents/2021/03/26/2021-06258/ursula-wing-final-debarment-order), debarring her for a period of five years from importing or offering for import any drug into the United States. This debarment was based on her felony conviction (https://www.justice.gov/usao-wdwi/pr/new-york-woman-sentenced-selling-abortion-inducing-pills-illegally-smuggled-us) related to her importation and distribution of unapproved and misbranded mifepristone and misoprostol over the internet.

The January 2023 REMS Modification

29. **What action did the FDA take on the Mifepristone REMS Program in January 2023?**

    In response to the REMS Modification Notification letters sent on December 16, 2021, to the applicants for Mifeprex and the approved generic Mifepristone Tablets, 200 mg, the applicants submitted supplemental applications to modify the Mifepristone REMS Program to remove the in-person dispensing requirement and add pharmacy certification. The FDA reviewed the applicants' supplemental applications and approved a modification to the Mifepristone REMS Program. Under the Mifepristone REMS Program, as modified, Mifeprex and its approved generic can be dispensed by or under the supervision of a certified prescriber or by a certified pharmacy on a prescription issued by a certified prescriber.

    The Mifepristone REMS Program continues to require the Patient Agreement Form and certification of health care providers who prescribe mifepristone.

30. **What was the process for approving the current REMS modification?**

    In 2021, in order to determine whether a modification to the Mifepristone REMS Program was warranted, the FDA conducted a comprehensive review of the published literature, other relevant safety and adverse event data, and information provided by advocacy groups, individuals, and the applicants related to the modifications that were under consideration. After conducting this review, the FDA determined that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification. In accordance with the typical process for REMS modifications, the FDA sent REMS Modification Notification letters to the applicants for Mifeprex and the approved generic, Mifepristone Tablets, 200 mg. Following receipt of these letters, the applicants prepared a proposed REMS modification and submitted it to their respective applications.

31. **Why did the FDA conduct a review of the Mifepristone REMS Program in 2021?**

    The agency's comprehensive review of the Mifepristone REMS Program, which led to the agency's December 16, 2021, decision that a modification was required, was related to the litigation in *Purcell v. Becerra* (previously *Chelius v. Becerra*). On May 7, 2021, the FDA and the plaintiffs in *Purcell* filed a joint motion to stay that litigation, which involves the single,

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shared system REMS for Mifeprex and its approved generic, Mifepristone Tablets, 200 mg. The court granted the stay on May 7, 2021. The *Purcell* case was reopened on February 28, 2023, and the plaintiffs now challenge the modified Mifepristone REMS Program. The agency generally does not comment on pending litigation.

32. **Was there a change in the reported adverse events during the pandemic when the in-person dispensing requirement was not enforced?**

    No. There were periods when the in-person dispensing requirement was not being enforced. First, from July 13, 2020, until January 12, 2021, the FDA was enjoined from enforcing the in-person dispensing requirement by an injunction issued in the *ACOG v. FDA* litigation, which was filed in the U.S. District Court for the District of Maryland. On April 12, 2021, the agency stated its intent to exercise enforcement discretion with respect to the in-person dispensing requirement during the COVID-19 public health emergency. The FDA analyzed postmarketing data to determine if there was a difference in adverse events between periods when in-person dispensing was and was not enforced. Based on this review, the agency concluded that there did not appear to be a difference in adverse events between periods when in-person dispensing was and was not enforced

Litigation and Other Legal Issues

33. **Was the Mifepristone REMS Program modified in 2023 in response to the Supreme Court's 2022 decision in *Dobbs v. Jackson Women's Health Organization*?**

    No. The agency's comprehensive review of the Mifepristone REMS Program, which led to the 2021 decision that a modification was required, is related to the litigation in *Purcell v. Becerra* (previously *Chelius v. Becerra)*. In accordance with the typical process for REMS modifications, the FDA sent REMS Modification Notification letters to the applicants for Mifeprex and the approved generic, Mifepristone Tablets, 200 mg. Following receipt of these letters, the applicants prepared a proposed REMS modification and submitted it to their respective applications. The FDA reviewed the REMS modification supplements submitted by the applicants in the Mifepristone REMS Program and approved a REMS modification that removes the in-person dispensing requirement and adds pharmacy certification.

34. **Was the Mifepristone REMS Program modified in 2023 in response to state abortion laws?**

    No. See response to Question 33.

35. **What happens if a state refuses to allow mifepristone to be prescribed for medical termination of pregnancy?**

    Any questions regarding the application of state law should be directed to the Department of Justice.

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36. **What is the status of the *Alliance for Hippocratic Medicine* lawsuit about the approval of mifepristone?**

On November 18, 2022, the FDA and HHS were sued in the U.S. District Court for the Northern District of Texas by the Alliance for Hippocratic Medicine and other plaintiffs. In June 2024, the Supreme Court held that the original plaintiffs lack standing to challenge FDA's actions, and the original plaintiffs voluntarily dismissed their claims in November 2024. Several states (Missouri, Idaho, and Kansas) intervened in the case before the Supreme Court's ruling. The agency generally does not comment on pending litigation.

What is a Serious Adverse Event?

Reporting Serious Problems to FDA

What is a Serious Adverse Event?

Product Problems

Reporte problemas serios a la FDA

¿Qué es una reacción adversa grave?

Problemas con los productos

Español

Content current as of: 05/18/2023

An adverse event is any undesirable experience associated with the use of a medical product in a patient. The event is serious and should be reported to FDA when the patient outcome is:

Death

Report if you suspect that the death was an outcome of the adverse event, and include the date if known.

Life-threatening

Report if suspected that the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.

Hospitalization (initial or prolonged)

Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event.

Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

Disability or Permanent Damage

Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's

body function/structure, physical activities and/or quality of life.

Congenital Anomaly/Birth Defect

Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

Required Intervention to Prevent Permanent Impairment or Damage (Devices)

Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.

Other Serious (Important Medical Events)

Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

Resources For You

- Report a Serious Medical Product Problem Online
- Report Dietary Supplements and Tobacco Product Problems Online
- Form FDA 3500 - Voluntary Reporting

MedWatch safety alerts delivered to you
Clinically important and timely information about the drugs and devices you use, prescribe, or dispense every day, delivered to your email from the FDA.

Email Address Subscribe

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EXHIBIT B-8

APPENDIX TO PETITIONER GENBIOPRO, INC.'S CITIZEN PETITION DATED JULY 3, 2025[1]

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United States Government Accountability Office

GAO

Report to Congressional Requesters

August 2008

FOOD AND DRUG ADMINISTRATION

Approval and Oversight of the Drug Mifeprex



GAO-08-751

August 2008

GAO Accountability·Integrity·Reliability

Highlights

Highlights of GAO-08-751, a report to congressional requesters

FOOD AND DRUG ADMINISTRATION

Approval and Oversight of the Drug Mifeprex

Why GAO Did This Study

In September 2000, the Food and Drug Administration (FDA), part of the Department of Health and Human Services (HHS), approved the drug Mifeprex for use in terminating early term pregnancy. FDA approved the drug under a provision of its Subpart H regulations, allowing it to restrict the drug's distribution to assure its safe use. Critics have questioned aspects of the Mifeprex approval process, including the reliance on historically-controlled clinical trials that compare a drug's effects on a condition to the known course of the condition rather than to another drug or placebo. Critics argued that Mifeprex does not fit within the scope of Subpart H, which applies to drugs that treat serious or life-threatening illnesses. Concerns have also been raised about FDA's oversight of the drug since approval, including the agency's response to deaths in U.S. women who had taken the drug.

In this report GAO (1) describes FDA's approval of Mifeprex, including the evidence considered and the restrictions placed on its distribution; (2) compares the Mifeprex approval process to the approval processes for other Subpart H restricted drugs; and (3) compares FDA's postmarket oversight of Mifeprex to its oversight of other Subpart H restricted drugs. GAO reviewed FDA regulations, policies, and records pertaining to its approval and oversight of Mifeprex and the eight other Subpart H restricted drugs. In addition, GAO interviewed FDA officials and external stakeholders.

To view the full product, including the scope and methodology, click on GAO-08-751. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

What GAO Found

FDA approved Mifeprex after evaluating the sponsor's initial and revised new drug application through three review cycles. In the first cycle, FDA concluded that the available data supported the safety and efficacy of Mifeprex and that, because the course of pregnancy was well-documented and the effects of the drug were self-evident, the use of historical controls was consistent with FDA regulations. FDA also concluded that before the drug could be approved, the sponsor needed to provide final data from an ongoing U.S. trial, and more detail on restricting the drug's distribution. In the second cycle, FDA concluded that while the U.S. trial data confirmed the drug's safety and efficacy, the sponsor needed to revise its distribution plan and address labeling and manufacturing deficiencies. In the final review, FDA concluded that termination of unwanted pregnancy is a serious condition and imposing restrictions under Subpart H was necessary. FDA approved Mifeprex, but required that the sponsor commit to conduct two postmarketing studies, imposed several distribution restrictions intended to ensure that only qualified physicians prescribe the drug, and required that patients attest to understanding the treatment's potential complications.

The approval process for Mifeprex was consistent with the processes for the other Subpart H restricted drugs, although the details of FDA's approval depended on the unique risks and benefits of each drug. Common elements of the approval processes included that FDA needed to evaluate potential limitations in key clinical data (Mifeprex and six of the other drugs), did not approve the drugs in the first review cycle (Mifeprex and five others), and imposed similar types of distribution restrictions on Mifeprex and the other drugs, though the specific details of the restrictions varied across the drugs.

FDA's postmarket oversight of Mifeprex has been consistent with its oversight of other Subpart H restricted drugs. To oversee compliance with distribution restrictions, FDA has reviewed data from all sponsors and conducted inspections for Mifeprex and two other drugs. To oversee compliance with postmarketing study commitments, FDA has relied on required updates from sponsors and found unfulfilled commitments for most drugs, including Mifeprex. To oversee compliance with adverse event reporting requirements, FDA has evaluated data in sponsors' reports and, for Mifeprex and seven other drugs, has conducted inspections that revealed deficiencies for most of these drugs, including Mifeprex. Lastly, FDA has taken similar steps to oversee postmarket safety across the drugs, such as analyzing adverse events. For Mifeprex, FDA investigated the deaths of six U.S. women who developed a severe infection after taking the drug and concluded that the evidence did not establish a causal relationship between Mifeprex and the infections. Finally, FDA has taken similar actions to address emerging safety concerns across the drugs, such as changing labeling.

HHS reviewed a draft of this report and informed GAO that it did not have comments.

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Abbreviations

AERS	Adverse Event Reporting System
CDC	Centers for Disease Control and Prevention
ENL	erythema nodosum leprosum
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
HHS	Department of Health and Human Services
HIV/AIDS	human immunodeficiency virus / acquired immune deficiency syndrome
NDA	new drug application
REMS	risk evaluation and mitigation strategy
SGE	special government employee

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GAO
Accountability * Integrity * Reliability

United States Government Accountability Office
Washington, DC 20548

August 7, 2008

The Honorable Michael B. Enzi
Ranking Member
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Jim DeMint
United States Senate

The Honorable Roscoe G. Bartlett
House of Representatives

In September 2000, the Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) granted marketing approval to the prescription drug Mifeprex (mifepristone) for the medical termination of early term pregnancy.[1] It remains the only drug approved in the United States for this purpose. FDA approved the drug under a provision of the agency's Subpart H regulations that allows FDA to restrict the distribution or use of a drug in order to assure its safe use.[2] Under this provision FDA can require, as it did for Mifeprex, that distribution be restricted to certain health care providers with specific training or experience. Since the drug's approval, more than 900,000 women are estimated to have taken Mifeprex in the United States.

[1]Mifeprex is the trade name for the mifepristone product marketed in the United States. Mifepristone is the name of the underlying drug substance. Mifepristone is also sometimes called "RU-486," a reference to the name the drug had during laboratory testing.

[2]Subpart H of FDA's drug approval regulations—titled "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses"—applies to drugs that are intended to treat serious or life-threatening illnesses and provide a meaningful therapeutic benefit to patients over existing treatments. The regulations contain two approval provisions. One provides a process through which FDA may restrict the distribution or use of a drug to assure its safe use. The other provides FDA with flexibilities that allow the agency to accelerate the approval process for certain drugs on the basis of clinical trial endpoints that are considered reasonably likely to predict clinical benefit. See 21 C.F.R. §§ 314.500-560 (2007).

Before a drug can be marketed in the United States, the drug sponsor must submit a new drug application (NDA) to FDA containing data demonstrating the safety and efficacy of the drug.[3] FDA reviews the NDA to determine whether the drug's benefits outweigh its risks.[4] Once FDA completes its review, the agency issues an action letter in which it either approves the drug as safe and effective for its intended use (approval letter), informs the sponsor that the drug is likely to be approved once the deficiencies FDA has identified are resolved (approvable letter), or indicates that approval cannot be obtained without substantial additional information (not approvable letter).[5] If FDA issues an approvable or not approvable letter, a subsequent review cycle can begin once the sponsor has addressed the issues FDA identified. FDA may require, as a condition of approval, that a sponsor agree to restrict the drug's distribution under the agency's Subpart H regulations.[6]

Critics have raised concerns and questions regarding several aspects of FDA's approval process for Mifeprex. For example, questions have been raised about the reliance on data from historically controlled clinical trials—trials that compare a drug's effects on a condition within the study population to the known course of that same condition in patients or

[3]A drug sponsor is the person or entity who assumes responsibility for the marketing of a new drug, including responsibility for complying with applicable laws and regulations.

[4]FDA also reviews supplemental NDAs, which sponsors submit to support proposed changes to a drug's label, a new dosage or strength of the drug, a new patient population or intended use, or changes to the way the drug is manufactured after a drug has an approved NDA.

[5]FDA issued a final rule on July 10, 2008, amending its drug approval regulations. The final rule, among other things, discontinues FDA's use of approvable letters and not approvable letters. Instead, in the event that FDA determines it will not approve an application in its current form, the agency will send applicants a "complete response letter" to indicate that the review cycle for an application is complete and to describe the specific deficiencies the agency identified in the application. The amended regulations are effective on August 11, 2008. See 73 Fed. Reg. 39588-89 (July 10, 2008).

[6]21 C.F.R. § 314.520 (2007). From 1992—the year that the regulations were promulgated—through February 2007, nine drugs, including Mifeprex, had either an NDA or supplemental NDA approved under this restricted distribution provision. Under the Food and Drug Administration Amendments Act of 2007 (FDAAA), FDA may determine that a risk evaluation and mitigation strategy (REMS) is necessary to ensure that the benefits of a drug outweigh its risks. The REMS provisions of FDAAA went into effect on March 25, 2008. As part of a REMS, FDA can require "elements to assure safe use," which include restrictions similar to those that can be required under Subpart H regulations. 21 U.S.C. § 355-1(a), (e), (f); Pub. L. No. 110-85, §§ 901, 909(a), 121 Stat. 823, 922, 926-38, 950.

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populations that were not part of the trial—to support the safety and efficacy of Mifeprex.[7] FDA regulations allow for the use of such historical controls when the course of the condition in question is well-documented within a comparable population and the effect of the drug is apparent. Questions have also been raised about whether Mifeprex fit within the scope of Subpart H regulations, which apply to drugs that are intended to treat a serious or life-threatening illness. Critics have argued that unwanted pregnancy should not be considered a serious or life-threatening illness. They have also questioned whether FDA's use of Subpart H regulations was consistent with its use of the regulations to approve other drugs.

Additionally, concerns have been raised about FDA's postmarket oversight of Mifeprex, including its efforts to ensure the sponsor's compliance with conditions of approval as well as the actions the agency has taken in response to reported adverse events.[8] For approved drugs, FDA oversees sponsors' compliance with applicable reporting requirements, distribution restrictions, and other conditions of approval.[9] FDA also monitors the drugs' postmarket safety and efficacy. In the case of Mifeprex, six U.S. women have died from severe bacterial infection after taking the drug, raising questions about its safety. Some have questioned FDA's conclusion—which it discussed at a May 2006 congressional hearing—that the available evidence had not established a causal relationship between Mifeprex and the infections.

You asked us to review FDA's approval of Mifeprex and its oversight of the drug since approval. In this report we (1) examine FDA's approach to approving Mifeprex, including the types of evidence considered and the

[7]21 C.F.R. § 314.126(b)(2)(v) (2007). In contrast, clinical trials that use concurrent controls demonstrate the safety and efficacy of a drug by comparing its effects on patients in a treatment group to the effects of a different treatment—such as another drug or a placebo—on patients in a control group within the same study population.

[8]The term postmarket refers to activities occurring after a drug has been approved for marketing. FDA uses the term adverse drug event to refer to any untoward medical event associated with the use of a drug in humans.

[9]FDA regulations require sponsors of approved drugs to submit various postmarket safety reports. See 21 C.F.R. §§ 314.80, 314.81 (2007). Additionally, sponsors of approved drugs must report to FDA annually on the progress of any postmarket studies required by FDA or agreed to by the sponsor. 21 U.S.C. § 356b; 21 C.F.R. § 314.81(b)(2)(vii) (2007). FDA uses such postmarket studies to gather additional information about a drug's safety, efficacy, or use once it is marketed.

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restrictions placed on its distribution and use; (2) compare the approval process for Mifeprex to the approval processes for other drugs approved under the restricted distribution provision of Subpart H; and (3) compare FDA's oversight of the use of Mifeprex since its approval to the agency's oversight of the other drugs approved under the restricted distribution provision of Subpart H.

To examine FDA's approval of Mifeprex, we reviewed relevant laws, regulations, policies, and guidance. We reviewed FDA records including an archive of documents pertaining to the approval of Mifeprex.[10] We also reviewed documentation from an FDA advisory committee meeting,[11] testimony statements and the related transcript, FDA responses to congressional requests, an August 2002 citizen's petition and responses from outside organizations, and other documentation pertaining to FDA's approval of Mifeprex. We interviewed FDA officials and external stakeholders who had access to technical information or had conducted analyses pertaining to Mifeprex that were not available through FDA. These included a representative of the sponsor of the Mifeprex application and its licensee,[12] the American College of Obstetricians and Gynecologists and the American Association of Pro Life Obstetricians and Gynecologists.

To compare the approval process for Mifeprex to those of other drugs, we reviewed FDA documentation pertaining to FDA's approval of the other eight drugs that the agency had approved under the restricted distribution

[10]In response to a Freedom of Information Act request, FDA posted certain documents pertaining to its approval of Mifeprex on the agency's Web site (see http://www.fda.gov/cder/archives/mifepristone/default.htm). The documents, which total over 9,000 pages, include a range of sometimes redacted material such as handwritten notes or email communications, communications between the drug sponsor and FDA, meeting minutes, copies of international labeling, and study protocols.

[11]FDA may convene an advisory committee to obtain advice from scientific experts and representatives of the public regarding a drug. FDA requests advice from advisory committees on a variety of matters, including aspects of drug applications and postmarket safety concerns for drug products. The primary role of an advisory committee is to provide independent advice that will contribute to the quality of the agency's regulatory decision-making. Although the committees provide recommendations to the agency, final decisions are made by FDA.

[12]The Population Council, a non-profit organization involved in reproductive health and population issues, sponsored the Mifeprex application. During the NDA review process, the Population Council contracted with Danco Laboratories, L.L.C. to serve as its licensee with responsibility for commercial manufacturing and marketing of the drug. Following the drug's approval, the Population Council transferred ownership of the Mifeprex NDA to Danco.

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provision of Subpart H as of February 2007.[13] Specifically, we examined key documents related to FDA's internal review and approval processes as well as documentation from advisory committee meetings in order to identify commonalities and differences in FDA's process across the nine Subpart H restricted drugs, including Mifeprex. In our examination we focused on issues that had arisen during FDA's review of Mifeprex to determine whether similar issues had arisen in FDA's review of the other drugs, and how FDA had addressed those issues for the other drugs.

To compare FDA's oversight of the use of Mifeprex since approval to the agency's oversight of the other Subpart H restricted drugs, we reviewed relevant regulations and FDA guidance. We also examined FDA documentation on the agency's oversight of sponsors' compliance with distribution restrictions, postmarketing study commitments, and adverse event reporting requirements for the nine Subpart H restricted drugs. In addition, we reviewed FDA's process for evaluating and responding to postmarket data on adverse events for each drug. Lastly, we interviewed FDA officials and staff who are responsible for postmarket oversight of these drugs. We conducted our work from February 2007 through August 2008 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Results in Brief

On September 28, 2000, FDA approved Mifeprex under the restricted distribution provision of its Subpart H regulations after examining the NDA through three review cycles. In its first review, FDA concluded that the available evidence supported the safety and efficacy of Mifeprex. This conclusion was based in part on FDA's determination that because the course of pregnancy was well-documented and the effects of the treatment were self-evident, the reliance on historical controls in three key clinical trials—two conducted in France and one ongoing in the United States—was appropriate and consistent with FDA regulations. FDA issued an approvable letter in September 1996 concluding that the sponsor needed

[13]We initiated our work in February 2007. In June 2007, FDA approved one additional drug—Letairis—under the restricted distribution provision of Subpart H. This drug was not included in our review.

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to provide additional information, such as the final data from the U.S. trial and a detailed plan to restrict the drug's distribution, before an approval decision could be made. The second review cycle began when the sponsor submitted a complete response to this letter. FDA issued a second approvable letter in February 2000 after concluding that the new data confirmed the safety and efficacy of Mifeprex for the U.S. market but also that the sponsor needed to revise its distribution plan and address labeling and manufacturing deficiencies. In its final review, FDA deliberated about the distribution restrictions and conditions of use needed to assure the safe use of the drug. FDA concluded that termination of an unwanted pregnancy is a serious condition and that the drug can allow patients to avoid a surgical procedure and therefore Mifeprex fit within the scope of Subpart H. FDA further concluded that the drug could only be used safely if distribution was limited to qualified physicians. The sponsor argued that the drug did not treat a serious condition and that because they had voluntarily agreed to the restrictions FDA had requested, it was neither appropriate nor necessary to impose the restrictions under Subpart H. However, the sponsor eventually acquiesced to FDA's requirement that approval be under Subpart H. After FDA concluded that the sponsor had adequately revised its distribution plan and addressed the remaining issues identified in FDA's reviews, it approved the Mifeprex NDA under Subpart H with several restrictions. These included requiring that prescribing physicians attest to possessing specific skills, agree to fully discuss the treatment with patients, and agree to report certain adverse events to the sponsor; that the drug be distributed directly to physicians by an authorized distributor; and that patients attest to fully understanding the treatment and its potential complications. The drug was also approved subject to the sponsor's commitment to conduct two postmarket studies related to patient outcomes.

The approval process for Mifeprex was generally consistent with the approval processes for the other eight Subpart H restricted drugs, but the details of FDA's approval process for each drug depended on the drug's unique risks and benefits. One common element across the approval processes for seven of the drugs, including Mifeprex, was that FDA needed to evaluate potential limitations—such as lack of concurrent controls or small sample sizes—in key clinical trials supporting the NDA. For some of these drugs other than Mifeprex, FDA concluded that there were weaknesses in the data submitted in the NDA that needed to be addressed. Another common element for six of the drugs, including Mifeprex, was that FDA issued at least one prior action letter before ultimately approving the drug for marketing under Subpart H. Additionally, the types of distribution restrictions that FDA imposed on Mifeprex were similar to

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those the agency imposed on the other drugs, though the details of the restrictions varied depending on the drug. Lastly, eight of the drugs, including Mifeprex, were approved with two or more postmarketing study commitments, each with one or more commitments related to adverse events or patient outcomes of interest.

FDA's postmarket oversight of Mifeprex has been consistent with the agency's postmarket oversight of the other Subpart H restricted drugs. To oversee the drug sponsors' compliance with distribution restrictions, FDA has relied on data submitted by sponsors for all of the drugs. For three of the drugs, one of them Mifeprex, FDA has also completed inspections of the sponsor or its distributors. To oversee compliance with postmarketing study commitments, FDA has relied on updates in required reports from sponsors. Most of the drugs, including Mifeprex, have at least one study commitment that remains unfulfilled. To oversee compliance with adverse event reporting requirements, FDA has relied on sponsors' reports for all of the drugs and has also conducted inspections of the sponsor or its manufacturers for eight of them. FDA has cited the sponsors of seven of the drugs, including Mifeprex, for adverse event reporting deficiencies. To oversee the postmarket safety of all of the Subpart H restricted drugs, FDA has routinely conducted reviews of adverse event reports to monitor for safety concerns. In the case of Mifeprex, FDA investigated the deaths of six U.S. women who developed a fatal infection following treatment with Mifeprex for medical abortion. FDA has determined that in all six of the deaths, the women used a Mifeprex treatment regimen that has not been approved by FDA. Based on its investigations, FDA has concluded that a causal relationship between the use of Mifeprex and the fatal infections has not been established. FDA has also monitored other kinds of adverse events and has concluded that, with the exception of the cases of fatal infection, reported serious adverse events associated with Mifeprex have been within or below the ranges it expected. Additionally, for Mifeprex and the other drugs, FDA has taken similar actions—such as issuing warnings and requesting changes to the product labeling—to communicate safety information to consumers and health care providers.

HHS reviewed a draft of this report and informed us that it did not have general comments. In addition, HHS provided technical comments which we incorporated as appropriate.

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Background

The Mifeprex NDA provided for the use of Mifeprex, in combination with another drug, for the medical termination of pregnancy. The treatment regimen described in the NDA involved taking Mifeprex orally, and then taking the drug misoprostol orally 2 days later unless termination of the pregnancy had already occurred.[14] Patients return for a follow-up visit with their prescribing physician 2 weeks later to ensure that the termination of the pregnancy has been completed. The treatment regimen works by both interrupting the hormones that the body needs to maintain a pregnancy and inducing the uterine cramping necessary to cause a medical abortion.

At the time that the drug sponsor submitted the Mifeprex NDA, in March 1996, mifepristone had already been approved in multiple countries. The drug was first approved for the medical termination of pregnancy in France and China in 1988.[15] It was approved subsequently in the United Kingdom in 1991, in Sweden in 1992, and various other European countries throughout the 1990s. In general, the treatment regimens approved in these countries were similar to those studied in the Mifeprex NDA, though in some cases the specific drug used in combination with mifepristone was different.

FDA Application Review Process

FDA reviews drug applications to determine whether they provide sufficient evidence to demonstrate that a drug is safe and effective for the proposed use, including whether the benefits of the drug outweigh its risks. FDA's formal process for new drug approval begins after a drug sponsor submits an application, typically following a long period of research and development. During a preliminary review, FDA determines whether the application is sufficiently complete to be reviewed and if so, designates it for either standard or priority review, depending on the

[14]Misoprostol is one of several drugs that had been studied in combination with mifepristone for the medical termination of pregnancy because they have been shown to induce uterine contractions. However, it is approved for marketing in the United States for a different indicated use.

[15]The company that discovered mifepristone and manufactured it for marketing in France—Roussel Uclaf—did not want to produce the drug for the U.S. market. Instead, the U.S. sponsor retained a contract manufacturer. For a more detailed discussion of the history of the development of mifepristone for the U.S. market, see: Congressional Research Service, *Abortion: Termination of Early Pregnancy with RU-486 (Mifepristone)*, (Washington, D.C.: 2001).

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therapeutic potential of the drug.[16] The agency then assigns a team of reviewers—including medical officers, chemists, statisticians, microbiologists, pharmacologists, and other experts—within the relevant FDA review division. This review team, which is usually led by a medical officer, conducts a comprehensive evaluation of the clinical and non-clinical information in the application including the safety and efficacy data for the drug, the design and quality of the studies used to support the application, and the proposed labeling for the drug and also reviews the results of inspections of the facilities where the drug is manufactured.[17] The review team compiles the results of its analyses and recommends either an approval, approvable, or not approvable action.

FDA managers, usually including the review team's supervisor and senior management within the applicable review division, determine what action to take on an application, based on the recommendations of the review team. These managers examine the review team's analysis and individually decide whether to concur with the recommendation. The final decision on the action the agency should take is usually, but not always, made by the director of the applicable review division. In some cases, actions must be reviewed and agreed to by the relevant FDA office.

This review process may span several cycles. For those applications not approved during the first review cycle—both approvable and not approvable—the second FDA review cycle begins once the sponsor submits an amendment to the application providing responses to the deficiencies FDA identified in its previous review. These amendments often contain additional studies, analyses, data, or clarifying information to address FDA's concerns. The responsible review team reviews the information provided by the sponsor, conducts any additional analyses that are required, reviews the results of any additional inspections that have been conducted, and again recommends either an approval, approvable, or not approvable action. As with the first review cycle, the process ends once FDA management reviews the recommendations of the

[16]FDA may grant priority review status when it determines that a drug may provide significant benefits in the treatment, diagnosis, or prevention of a disease as compared to marketed drugs or non-drug therapies, such as surgery, or provide a treatment where no adequate therapy exists.

[17]The non-clinical data in an NDA pertains to, for example a drug's chemistry, manufacturing, and controls as well as its toxicology and pharmacology.

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review team and makes its decision on the action to take on the application.

Restricting Drug Distribution and Subpart H Regulations

To address concerns FDA identifies regarding the safe use of a drug, the agency may condition approval by requiring that the sponsor agree to restrict the drug's distribution. FDA has established restricted distribution programs for approved drugs primarily by requiring that a drug's approval be under the restricted distribution provision of Subpart H regulations. According to the scope of the regulations, Subpart H applies to new drugs that "have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments" for the condition.[18] FDA may approve a drug under the restricted distribution provision of these regulations if it meets these criteria and the agency concludes that the drug is effective but can be safely used only if distribution or use is restricted. For example, FDA may require that distribution of a drug be limited to certain facilities or physicians with special training.

As of February 2007, nine drugs—Actiq, Accutane, Lotronex, Mifeprex, Plenaxis, Revlimid, Thalomid, Tracleer, and Xyrem—had either an NDA or supplemental NDA approved under the restricted distribution provision of Subpart H.[19] For each of the drugs, either during the application review process or based on postmarket data, FDA identified concerns about the safe use of the drug that led the agency to apply Subpart H. The drugs were approved to treat a range of conditions, such as breakthrough cancer pain, specific symptoms of narcolepsy, and severe acne.

FDA has also required that drug sponsors agree to restrict the distribution of drugs without imposing Subpart H. Clozaril, Tikosyn, and Trovan are three examples of drugs that have restricted distribution programs that were imposed outside of Subpart H. (See app. I for a table describing drugs FDA has approved with restricted distribution programs and the conditions they are intended to treat). While Clozaril was first approved in

[18]21 C.F.R. § 314.500 (2007).

[19]21 C.F.R. § 314.520 (2007). The sponsor for Plenaxis—approved in 2003 for the palliative care of certain patients with advanced prostate cancer—withdrew the product from the market in 2006. Additionally, three generic versions of Accutane have been approved for marketing under this restricted distribution provision.

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1989, FDA imposed distribution restrictions on both Tikosyn and Trovan after Subpart H regulations had been promulgated.

A second approval provision of Subpart H provides FDA with flexibilities that allow the agency to accelerate the approval process for drugs that provide meaningful therapeutic benefits over alternatives for serious or life-threatening illnesses.[20] Specifically, under the provision, FDA may approve a drug on the basis of clinical trials establishing that the drug has an effect on a surrogate endpoint—such as weight gain or reduced occurrence of infections in patients with HIV—that is reasonably likely to predict a clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.[21] This allows FDA to approve a drug before measures of effectiveness that would usually be required for approval are available. However, under this approval provision, drug sponsors are ordinarily required to conduct postmarket studies to confirm and further describe the drug's clinical benefit. As of February 2007, FDA had used this provision to approve 52 drugs, most of which are intended to treat HIV/AIDS or various cancers.

FDA's Role in Postmarket Oversight

Because some risks may not become known until after a drug's approval and use in a wider segment of the population, FDA has a range of postmarket oversight responsibilities once a drug is approved for marketing in the United States. FDA's postmarket oversight responsibilities include assessing sponsors' compliance with requirements for a given drug, such as postmarketing study commitments, adverse event reporting, and restricted distribution requirements. In addition, FDA monitors reported adverse events to assess the postmarket safety of approved drugs and may take action if it develops a concern about a drug's safety.

With regard to postmarketing study commitments, FDA oversees sponsors' compliance with regulations that require sponsors of all approved drugs to report to FDA annually on their progress in meeting the

[20]See 21 C.F.R. § 314.510 (2007).

[21]According to FDA, although some surrogate endpoints are recognized as well-established and have long been a basis for approval (such as change in blood pressure or cholesterol), accelerated approval regulations allow reliance on a "surrogate endpoint that, while 'reasonably likely' to predict clinical benefit, is not so well-established as the surrogates ordinarily used as bases of approval in the past." 57 Fed. Reg. 58942, 58944 (Dec. 11, 1992).

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commitments. FDA requires that sponsors report on the status of these studies in an annual report that also includes updates on the distribution of the drug, labeling changes, clinical literature published on the drug, and the drug's marketing.[22] FDA designates unfulfilled study commitments as submitted, pending, ongoing, delayed, released, or terminated.

FDA also oversees sponsors' compliance with regulations that require sponsors of all approved drugs to report periodically to FDA on safety information and specific types of adverse events that occur in association with an approved drug.[23] Sponsors must provide in periodic reports (quarterly for the first 3 years after approval and annually thereafter) a narrative summary and analysis of adverse event information. For adverse events that are considered both serious and unexpected,[24] sponsors are required to submit a report—known as a "Postmarketing 15-day Alert Report"—to FDA within 15 calendar days from the time the sponsor was informed of the event. To assess sponsors' compliance with these adverse event reporting requirements, FDA reviews sponsors' reports and conducts inspections of the sponsors' reporting policies and procedures.

For drugs approved under the restricted distribution provision of Subpart H, FDA oversees sponsors' compliance with the restrictions placed on the drugs' distribution or use. To assess compliance with restrictions, FDA reviews information such as summaries of sponsors' distribution programs in annual reports and in some cases separate reports required by the agency to provide details and updates on distribution programs. In addition, FDA may conduct inspections of a sponsor's corporate headquarters, manufacturing sites, or contractors, such as specialty distributors, to evaluate whether distribution policies and procedures comply with the approved restrictions for a given drug. If FDA identifies deficiencies during an inspection, it may issue a formal citation—known as a Form FDA 483. In addition, FDA may communicate less serious findings as written or oral "observations" or "recommendations."[25]

[22]See 21 C.F.R. § 314.81 (2007).

[23]See 21 C.F.R. § 314.80 (2007).

[24]Unexpected events are those that are not included in the current labeling for a drug.

[25]FDA uses the same reporting scheme—noting citations, observations, or recommendations— for its inspections to assess sponsor compliance with adverse event reporting.

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To monitor postmarket safety of approved drugs, FDA reviews clinical literature, routinely evaluates the available data on reported adverse events, and conducts investigations of the nature and patterns of these events. FDA compiles data from sponsor's reports on adverse events, along with data from voluntary reports submitted to the MedWatch program, in its Adverse Event Reporting System (AERS) database.[26] FDA safety evaluators analyze data from AERS and in the clinical literature to detect signs of potential safety concerns. These evaluations may reveal the need for further studies of a drug or may result in FDA action to ensure the safety of the drug.[27]

If FDA identifies problems with a sponsor's compliance with agency requirements or identifies postmarket safety concerns, the agency can take a range of actions to address the concern and communicate safety information to healthcare providers and the public. For example, FDA may revise the restrictions on a drug's distribution, request changes to a drug's labeling, issue patient advisories or public health alerts, or request that a sponsor issue letters to health care providers or pharmacists to alert them to safety concerns. FDA may also issue a regulatory letter citing violations of laws or regulations. Typically, FDA issues a Warning letter for violations that may lead FDA to pursue further enforcement action if not corrected or issues an untitled letter for violations that do not meet this threshold. FDA also has the authority to withdraw a drug's marketing approval for safety-related and other reasons,[28] although it rarely does so. Additionally,

[26]MedWatch is a voluntary reporting program through which health professionals and consumers can report adverse reactions, product problems, and use errors related to drugs and other products approved by FDA.

[27]GAO has previously reported on and made recommendations regarding FDA's postmarket oversight of approved drugs. See GAO, *Drug Safety: Improvements Needed in FDA's Postmarket Decision-making and Oversight Process*. GAO-06-402. (Washington, D.C.: Mar. 31, 2006).

[28]21 U.S.C. § 355(e).

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Subpart H regulations establish an expedited process for withdrawing a drug's marketing approval, in certain circumstances.[29]

FDA Approved Mifeprex under the Subpart H Restricted Distribution Provision After Concluding That Clinical Evidence Supported Its Safety and Efficacy

FDA approved Mifeprex after three review cycles. In its initial review, FDA concluded that reliance on historical controls in three key clinical trials was appropriate and consistent with FDA regulations and that the available data supported the safety and efficacy of the drug. In an approvable letter, FDA notified the sponsor that it needed to provide additional data and more detail on its proposal to restrict the drug's distribution before an approval decision could be made. A second review cycle began when the sponsor submitted data responding to this letter. The agency issued a second approvable letter after finding that new data confirmed Mifeprex's safety and efficacy but also that the sponsor needed to revise its distribution plan and address labeling and manufacturing deficiencies. FDA further concluded that the drug was a candidate for approval under Subpart H. In the final review cycle, FDA concluded that the sponsor's revised distribution plan and other revisions were sufficient to address FDA's comments. FDA also concluded that Mifeprex met the scope of Subpart H and that approval under the restricted distribution provision of Subpart H was necessary to ensure that only qualified physicians prescribed the drug. On September 28, 2000, FDA approved Mifeprex under the restricted distribution provision of Subpart H with several restrictions and two postmarketing study commitments. (See table 1 for a timeline of key events in the Mifeprex approval process.)

[29]Under Subpart H regulations, FDA may withdraw a drug's marketing approval after providing for a hearing, in the following circumstances; (1) a postmarketing clinical study fails to verify clinical benefit; (2) the sponsor fails to perform the required postmarketing study with due diligence; (3) use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product; (4) the sponsor fails to adhere to the postmarketing restrictions agreed upon; (5) the promotional materials are false or misleading; or (6) other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use. 21 C.F.R. § 314.530 (2007).

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Table 1: Timeline of Key Events in FDA's Approval of Mifeprex

Date	Event
First review cycle	
March 1996	The sponsor submitted a new drug application (NDA) for the use of Mifeprex in combination with the drug misoprostol for the medical termination of intrauterine pregnancy.
July 1996	FDA Reproductive Health Drugs Advisory Committee meeting.
September 1996	FDA issued an approvable letter listing issues that the sponsor needed to address before the application could be approved.
Second review cycle	
August 1999	After delays securing a manufacturer, the sponsor completed its responses to FDA's 1996 approvable letter.
February 2000	FDA issued a second approvable letter, listing issues that the sponsor needed to address prior to approval.
Third review cycle	
March 2000	The sponsor completes its responses to FDA's second approvable letter.
September 2000	FDA approved Mifeprex under the restricted distribution provision of Subpart H.
November 2000	Distribution of Mifeprex began in the United States.

Source: GAO analysis of FDA and drug sponsor data.

FDA's Initial Review Cycle and Approvable Action (March to September 1996)

FDA's initial review began when the drug sponsor submitted the Mifeprex NDA in March 1996. After conducting a preliminary review of the NDA, FDA designated the application for priority review, establishing a goal that the agency would issue an action letter within 6 months. FDA's rationale for the designation was that as the first drug that would be approved for its particular indication, Mifeprex was a therapeutic advance because women using the drug could potentially avoid the risks of surgery and anesthesia involved in a surgical termination of a pregnancy.

FDA assigned a team of reviewers within the Division of Reproductive and Urologic Drug Products to review the evidence in the Mifeprex NDA. The key safety and efficacy data in the NDA consisted of three historically controlled clinical trials, two conducted in France and one conducted in the United States. These trials studied the Mifeprex treatment regimen—mifepristone in combination with misoprostol—in a total of more than 4,000 women. At the time the NDA was submitted, the French trials were complete and the U.S. trial was ongoing. As a result, during the first review cycle, the review team analyzed the complete safety and efficacy data from the French clinical trials, but only summary data on serious adverse events

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from the U.S. clinical trial. FDA reviewers also considered results from other trials conducted in Europe from 1983 through 1996 in which mifepristone was studied either alone or in combination with misoprostol or similar drugs. In addition, the review team considered safety information from extensive postmarketing experience in Europe, including a postmarket safety database containing information on women who had used mifepristone. Lastly, the review team considered the non-clinical data in the application, including data on the drug's chemistry and manufacturing.

In its review of the Mifeprex data, FDA reviewers determined that the reliance on historical controls in the key clinical trials was appropriate and consistent with FDA regulation. According to FDA, historical control designs can make it more difficult to evaluate which effects can be attributed to the drug being studied.[30] However, FDA regulations list historical controls as an acceptable type of control when the natural history of the condition being treated is well-documented and when the effects of the drug are self-evident.[31] In the case of the Mifeprex NDA, FDA determined that the historically controlled trials provided substantial evidence of safety and efficacy because the outcomes of women taking the Mifeprex regimen were compared with the well-documented data on the natural course of pregnancy, including rates of miscarriage, and the effect of the drug—termination of a pregnancy—was obvious.[32]

To assist the review team in its assessment of Mifeprex, FDA convened the Reproductive Health Drugs Advisory Committee in July 1996 and asked the members to examine the data and vote on their conclusions regarding the drug's safety and efficacy. Six of the eight voting members voted, with

[30]See FDA, *Guidance for Industry: E 10 Choice of Control Group and Related Issues in Clinical Tials* (Rockville, Md.: May 2001).

[31]21 C.F.R. § 314.126(b)(2)(v) (2007). The regulation also states that studies that are "adequate and well-controlled" provide the primary basis for determining whether there is "substantial evidence" in support of the claims of effectiveness for new drugs. Among other things, an adequate and well-controlled study provides sufficient details of study design, conduct, and analysis to allow critical evaluation, and the design must permit a valid comparison with a control to provide a quantitative assessment of the drug's effect.

[32]FDA has cited examples of other drugs that have relied upon historical controls. According to FDA, for contraceptives the effect of the drug can be compared to the well-documented rate of pregnancy in sexually active women between the ages of 15 and 35 in the absence of contraception. For example, FDA approved the contraceptive drug products Lybrel, Implanon, Yaz, and NuvaRing on the basis of historically controlled clinical trials.

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two abstentions, that the available evidence demonstrated that the benefits of the regimen outweighed its risks for the proposed indication in the United States. However, the members agreed unanimously that FDA should provide the final safety and efficacy data from the U.S. clinical trial for their review. The advisory committee also discussed the basic elements of a voluntary restricted distribution system proposed by the drug's sponsor, which would require that Mifeprex be distributed directly to physicians, that prescribing physicians meet certain training requirements, and that patients meet certain conditions before receiving the drug. The advisory committee voted unanimously that they agreed with the concept of restricting distribution of the drug but had reservations about how the proposed system would assure that physicians had adequate credentials. The members recommended that the sponsor conduct postmarket studies to address six unanswered questions about the treatment regimen and the distribution system. The members also provided extensive comments on the draft labeling proposed by the sponsor.

The FDA review team concluded that the NDA was approvable, based on its assessment of the clinical and non-clinical data and the input from the advisory committee. The medical officer leading the review team concluded that the available clinical data indicated "that medical abortion can be safely delivered in a wide variety of United States settings." The data from the French trials showed the treatment to be roughly 95 percent effective at terminating pregnancy through 49 days gestation. The data from the French clinical trials also showed that almost all patients experienced some side effects—such as uterine cramping and bleeding—most of which were expected based on the way the drug works. Though serious adverse events were considered rare, some women experienced bleeding that required medical intervention, and approximately 0.2 percent of patients required transfusion. The medical officer concluded that the preliminary U.S. data on adverse events did not appear to differ significantly from the French trials.[33]

[33]The medical officer noted that it was only possible to make general comparisons across these events because definitions and reporting requirements were different in the two countries. Additionally, while the sponsor had not yet completed its analysis of the safety and efficacy data from the U.S. clinical trial, information from the studies was forwarded to the sponsor weekly. The medical officer concluded, based on preliminary examination of this information, that the final results of the U.S. trials were likely to be similar to the results of the French trials.

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In September 1996, FDA issued an approvable letter for the use of Mifeprex in combination with the drug misoprostol for the termination of intrauterine pregnancy up to 49 days gestation. In memos documenting concurrence with the review team, and in the approvable letter itself, FDA management outlined the clinical and non-clinical issues the sponsor needed to address prior to approval. First, the full data from the U.S. clinical trial were needed to establish safety and efficacy of the Mifeprex regimen in the U.S. health care setting. Second, FDA agreed with the sponsor's proposal to limit the drug's distribution, but the sponsor had not yet submitted sufficient detail on how it would be implemented to allow for the plan to be fully evaluated.[34] Third, the drug labeling proposed by the sponsor needed to be revised to provide more information on the treatment and to address comments from the advisory committee. Fourth, the sponsor would need to commit to pursue the postmarket studies suggested by the advisory committee. Finally, the sponsor would need to address certain deficiencies in chemistry and manufacturing data identified in FDA's review.

FDA's Second Review Cycle and Approvable Action (August 1999 to February 2000)

FDA's second review cycle for the Mifeprex NDA officially began once the sponsor had completed its responses to the first approvable letter. However, these responses were delayed because of difficulties the sponsor encountered in securing a manufacturer for the drug product. In the interim, the sponsor submitted a range of data to FDA, including the final safety and efficacy results from the U.S. clinical trial, updated safety data from other trials of mifepristone and international postmarketing experience with the drug, formal revisions of the product labeling, and outstanding chemistry and manufacturing data. In August 1999, the sponsor completed its responses to the approvable letter by submitting an overview of the key principles of the restricted distribution system as well as responses to the postmarketing study commitments. At the time of this submission, the sponsor was still working with its planned distributor on the details of the restricted distribution system.

Based on the updated data, the review team recommended approval for the Mifeprex NDA once the sponsor had clarified the details of the drug's distribution, revised the drug labeling, and addressed deficiencies in the

[34]FDA management's concurrence memos noted that because the sponsor had voluntarily proposed a restricted distribution system, imposing restrictions through Subpart H regulations did not appear warranted.

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chemistry and manufacturing data. The medical officer concluded that the final results from the U.S. clinical trial were acceptable and confirmed the results of the French trials that the regimen was safe and effective.[35] The medical officer concluded that the comments from the July 1996 advisory committee meeting were fully considered and, to the extent possible, implemented.[36] The medical officer also concluded that additional detail was needed to determine whether the sponsor's proposed distribution plan was sufficient. The non-clinical reviews during this review cycle—which included inspections of manufacturing facilities[37]—identified deficiencies in the drug's chemistry data and manufacturing processes that needed to be addressed, as well as sections of the drug's labeling that needed to be revised.

In January 2000, the sponsor submitted a more detailed plan describing how the proposed distribution restrictions would be implemented. The plan had three key elements. First, the Mifeprex regimen would only be administered under the supervision of qualified physicians who had agreed to provide the treatment according to several guidelines. Specifically, prescribing physicians would be required to attest to being able to accurately assess the duration of a pregnancy, diagnose an ectopic pregnancy,[38] and assure that patients have access to appropriate follow up care if needed to manage complications. The physicians would also need to agree to fully explain the procedure to each patient and obtain her

[35]The U.S. clinical trial data showed the treatment to be 92 percent effective for terminating pregnancy through 49 days gestation, which was slightly lower than the 95 percent from the French trials. Adverse event rates were also slightly higher in the U.S. trials. The medical officer attributed these differences to the relative inexperience of U.S. clinicians with the treatment. In addition, the medical officer concluded that the updated information from international studies, postmarket experience, and the published literature was consistent with the results from the U.S. and French trials.

[36]In November 1999, FDA provided advisory committee members the final results from the U.S. clinical trial for their review and comment. FDA did not receive any comments from the members on these results.

[37]The drug substance (mifepristone) in the Mifeprex product was manufactured by the Shanghai Haulian Pharmaceutical Co., Ltd., with the manufacturing facilities located in China. Initial FDA inspections found the manufacturer not in compliance with FDA's good manufacturing practice standards.

[38]Ectopic pregnancy—which occurs when a fertilized egg improperly implants outside of the uterus—is a contraindication for receiving the Mifeprex regimen. Accurate screening to ensure that patients with an ectopic pregnancy do not receive the treatment was a concern because a ruptured ectopic pregnancy is a life-threatening condition and its symptoms are similar to the side effects of the Mifeprex regimen.

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signed consent, record the unique product serial number for tracking purposes, and report any serious adverse event or on-going pregnancy to the sponsor. Second, the drug would only be distributed directly to physicians after an authorized distributor had verified that the physician had registered with it and had a signed attestation on file. Third, patients would be required to meet certain conditions before receiving the drug, such as signing a patient agreement attesting to her understanding of the potential complications of the treatment.

FDA management concluded that the proposed distribution plan did not provide for adequate training and certification of prescribing physicians and needed to be revised before the NDA could be approved. In February 2000, FDA issued a second approvable letter for Mifeprex, notifying the sponsor that it needed to revise its proposed distribution plan, address deficiencies in the drug's chemistry data and manufacturing, and revise the drug's labeling. The letter also stated that FDA had considered the application under the restricted distribution provision of Subpart H and that distribution restrictions would be necessary in order to assure the safe use of the drug. The approvable letter further reminded the sponsor of its commitment to pursue postmarketing study commitments to address questions that were raised at the time of the advisory committee meeting.

FDA's Final Review Cycle and Marketing Approval for Mifeprex (March to September 2000)

In March 2000, the sponsor submitted its complete response to FDA's February 2000 approvable letter. This submission included updated safety data from ongoing trials and international postmarket experience, international product labeling, and revisions to the distribution plan. The sponsor also provided additional data and revisions—including updated chemistry and manufacturing data, a revision to the distribution plan, and revised labeling—to address comments from FDA that arose during the review cycle. The agency's review of these submissions included multiple meetings and teleconferences with the sponsor and input from a consultant who was a special government employee (SGE) and a member of the Reproductive Health Drugs Advisory Committee.[39]

[39]According to FDA, it is not uncommon for the agency to consult with members of its advisory committees who have special expertise in a particular drug under review. Generally, an SGE is defined as an officer or employee who is retained, designated, appointed, or employed by the government to perform temporary duties, with or without compensation, for not more than 130 days during any period of 365 consecutive days. 18 U.S.C. § 202(a).

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During the final review cycle, FDA's deliberations—which involved a wide range of agency staff and management, including at times the Commissioner—focused on four key issues: whether prescribing physicians should be required to participate in a formal training and certification program, whether to require that approval be under Subpart H, what conditions of use should be specified, and what postmarketing study commitments would be needed to assure the safe use of the drug.

- Physician Training: In its deliberations, FDA considered requiring that physicians participate in specific training and have their qualifications certified before being allowed to prescribe Mifeprex, as opposed to relying on the sponsor's proposed system of self-attestation. However, FDA concluded that such a requirement was not necessary. FDA officials told us that the agency determined that its concern about ensuring that prescribers were adequately qualified could be addressed by requiring that the sponsor make educational materials and training programs readily available and requiring that prescribing physicians sign an agreement attesting to their qualifications. The SGE consultant agreed with this conclusion. FDA officials also told us that the agency wanted to minimize the burden that the restricted distribution program would place on providers and patients by requiring only what was necessary to address safety concerns.[40]

  In July 2000, the sponsor submitted its revised distribution plan. This plan addressed FDA's comments by providing increased emphasis in the product labeling on the educational materials and trainings available to physicians and the importance of participating in the training. The other key elements of the plan—including the specific qualifications that physicians were required to meet and agreements regarding discussing the treatment and adverse event reporting—were essentially unchanged from those the sponsor proposed in its January 2000 plan.

- Approval under Subpart H Regulations: FDA had maintained through the first two review cycles that distribution restrictions would be required for Mifeprex. However, minutes from meetings between FDA and the sponsor indicate that the agency was still considering whether it was necessary to impose those restrictions under Subpart H during the final review cycle. During the second review cycle, FDA had concluded that the restricted

[40]Subpart H regulations state that any restrictions imposed will be commensurate with the specific safety concerns presented by the drug product. 21 C.F.R. § 314.520(b) (2007).

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distribution provision could be applied to Mifeprex.[41] FDA eventually concluded that it would be necessary to do so. In its documented rationale for this conclusion, FDA stated that the drug met the scope of the regulations because the termination of an unwanted pregnancy is a serious condition, and that the drug provided a meaningful therapeutic benefit over existing therapies by allowing patients to avoid the procedure required with surgical termination of pregnancy. FDA officials told us that the agency has broad discretion to determine which conditions or illnesses may be considered serious or life threatening, and that in the case of Mifeprex it considered the potential in any pregnancy for serious or life-threatening complications—such as hemorrhage—in its determination.[42] Additionally, FDA concluded that Mifeprex could only be used safely if distribution was limited to physicians who could assess the duration of a pregnancy, diagnose an ectopic pregnancy, and provide patients with access to surgical intervention if necessary.

Throughout the approval process, the sponsor was opposed to approval under Subpart H. Specifically, the sponsor argued that the drug did not fit within the scope of Subpart H because pregnancy itself is not a serious or life threatening illness. The sponsor also argued that the intent of the restricted distribution provision was to allow for restricted distribution of highly toxic or risky drugs, and that Mifeprex did not fit this description.[43] The sponsor also expressed concern that approving the drug under Subpart H could unfairly mark Mifeprex as risky and deter women from using the drug. Lastly, the sponsor held that imposing Subpart H was unnecessary because it had voluntarily committed to the distribution

[41]FDA had also noted that approving the drug under Subpart H would allow the agency to impose similar restrictions on any future generic mifepristone products approved for the same indication. The patent for Mifeprex expired in October 2004, but as of May 2008, no generic versions of mifepristone have been approved for marketing.

[42]The terms "serious" and "life-threatening" are not defined in Subpart H regulations, but were discussed in the preambles to the proposed and final rules. In its proposed rule, FDA stated that the seriousness of a disease is a matter of judgment, but generally is based on its impact on survival, day-to-day functioning, or other factors, and provided examples of conditions that could be within the scope of the regulation. FDA noted that many diseases or conditions can be serious for some populations in some or all of their phases and explicitly reserved the discretion to determine whether the regulations were applicable to a given product. See 57 Fed. Reg. 13234-5 (Apr. 15, 1992), 57 Fed. Reg. 58942, 58946 (Dec. 11, 1992); See also 21 C.F.R. §§ 312.34, 312.81 (2007), and FDA, *Guidance for Industry: Fast Track Drug Development Programs—Designation, Development, and Application Review* (Rockville, Md.: Jan. 2006).

[43]In support of its arguments about the intent of the regulations, the sponsor cited the pertinent language from preambles to the proposed and final rules. See footnote 42.

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restrictions requested by FDA. However, in a September 2000 letter to FDA, the sponsor agreed to FDA's requirement that approval be under Subpart H, while noting that it still believed that applying these regulations to Mifeprex was not appropriate.

- Conditions of Use: FDA reviewed data and held multiple meetings with the sponsor regarding the specific conditions of use that should be required for Mifeprex. For example, FDA deliberated about whether it was necessary to require that prescribing physicians possess the ability to perform follow-up surgical interventions in the event that it was necessary to manage complications. The sponsor maintained that such a requirement was inconsistent with the practice of medicine, because management of incomplete miscarriages was routinely handled by referring patients to outside providers with specialized surgical or emergency care training. On this issue, FDA concluded that access to follow-up care could be ensured by requiring adequate information in the labeling and requiring that physicians attest to having made arrangements for their patients to have access to any needed surgical or emergency care. The SGE consultant agreed with FDA's conclusion. FDA disagreed with the sponsor on other suggested conditions of use. For example, the sponsor provided data to support allowing patients to self-administer the misoprostol dose at home, instead of requiring them to return to their prescribing physicians. FDA concluded that the available data did not support the safety of home use of misoprostol and that such use should not be included in the final product label. As a part of its deliberations about the conditions of use, FDA also concluded that approved labeling should include a medication guide to provide patients with information about the risks and benefits of the drug and the approved conditions of use and treatment regimen.[44]

- Postmarketing Study Commitments: In both the September 1996 and February 2000 approvable letters, FDA had reminded the sponsor of its commitment to conduct a series of six postmarket studies to address comments raised in the 1996 advisory committee meeting. FDA reviewed data and met with the sponsor during the final stages of its review to revisit these commitments in light of experience gained with the treatment regimen since the advisory committee meeting, concerns about potential infringement on the privacy of patients, and the potential resources needed to fulfill all six commitments. FDA concluded that the originally proposed commitments could be sufficiently addressed in two redesigned

[44]FDA may require that a drug be distributed with a medication guide that provides patients with information about the safe and effective use of the drug. See 21 C.F.R. pt. 208 (2007).

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studies. The first was a study on the safety outcomes of a group of patients receiving the treatment under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention when necessary. The second was a surveillance study to determine the outcomes of ongoing pregnancies that were not surgically terminated after a failure of the Mifeprex regimen, including the health of any children born. FDA also concluded that the outstanding questions could be incorporated into the two postmarket studies and an audit of signed patient agreement forms.

Once the sponsor had addressed the issues that FDA raised during the third review cycle, both the review team responsible for the Mifeprex NDA and FDA management concluded that the drug should be approved. The medical officer concluded that the updated safety data did not reveal any new issues that would change the ratio of benefit-to-risk for the drug. The medical officer also reviewed revised product labeling related to the distribution of the drug. Based on these reviews, the medical officer recommended approval of the application. The non-clinical reviews during this review cycle included additional inspections of manufacturing facilities. After the sponsor had addressed several issues, including deficiencies identified in a second inspection of the drug manufacturing facilities, the non-clinical reviewers also recommended approval of the application. FDA management concurred with the recommendations of the review team that the Mifeprex NDA should be approved.

On September 28, 2000, FDA approved Mifeprex under the restricted distribution provision of Subpart H. The sponsor began distribution of Mifeprex in November 2000. FDA approved the drug with the two postmarketing study commitments discussed above and with several key restrictions on distribution. First, prescribing physicians must sign a prescriber's agreement attesting to possessing the training and skills needed to administer the treatment regimen, and also agreeing to provide patients with the approved medication guide. They must also attest that they will fully discuss the treatment with patients and report to the sponsor any serious adverse events or ongoing pregnancies that are not terminated after a failure of the Mifeprex regimen. Second, the drug must be distributed directly to prescribing physicians by an authorized distributor only after the distributor has verified that the physician has a signed agreement on file. Third, patients must sign a patient agreement attesting to having read, discussed, and understood the risks and potential complications of the treatment. For a more detailed list of the individual components of the restricted distribution program for Mifeprex, see

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appendix II. For a copy of the approved prescriber's agreement, see appendix III.

Approval Process for Mifeprex Was Generally Consistent with That of the Other Eight Subpart H Restricted Drugs

Although each drug had unique risks and benefits, the approval process for Mifeprex was generally consistent with the approval processes for the other eight Subpart H restricted drugs. Each of the drugs had unique risks and benefits that were specific to their indication and target populations. For some of the drugs, the safety issues that prompted FDA to apply Subpart H were similar, with the potential for causing birth defects, the potential for liver or other serious toxicities, and appropriate patient selection being the most common issues. However, there were also safe use concerns that were unique to particular drugs. For example, for Mifeprex, ensuring patient access to follow-up care was a key safety concern, while for Actiq a key concern was ensuring that children did not accidentally ingest the drug.[45] Each of the drugs represented potential advances in the treatment of their targeted condition and in two cases—Mifeprex and Xyrem—the drug was the first approved to treat that condition. (See app. I for a table including each of the Subpart H restricted drugs and their approved indications.)

One common element across the approval processes for the Subpart H restricted drugs was that for seven of the drugs, including Mifeprex, FDA needed to evaluate potential limitations in key clinical data supporting the NDA. Specifically, with the exception of Accutane and Lotronex, the drugs were approved on the basis of studies without concurrent controls or data that were limited by relatively small sample sizes or data collection issues.[46] FDA approved the Mifeprex NDA on the basis of historically controlled clinical trials that studied the drug in several thousand patients. FDA concluded that the use of historical controls was not a limitation

[45]Actiq contains the controlled substance fentanyl in a lozenge formulation intended to allow for more rapid delivery of the medication for pain management in patients who have developed a tolerance. Because of the formulation there are concerns that Actiq may be perceived by children as a lollipop.

[46]Both Accutane and Lotronex were approved under Subpart H after they had first been marketed in the United States. In the case of Lotronex, the sponsor withdrew the drug from the market in 2000 because of safety concerns. In 2002, FDA approved a supplemental NDA under Subpart H, allowing the drug to be marketed with a restricted distribution program and substantially more limited indication. For Accutane, which was originally approved for marketing in 1982, FDA approved a supplemental NDA under the restricted distribution provision of Subpart H in 2005 in order to require a more formal restricted distribution program that linked Accutane prescribing and dispensing to pregnancy testing results.

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because the course of pregnancy was well-documented and the effect of the treatment was self-evident. Revlimid, Thalomid, Plenaxis, and Xyrem were also each approved on the basis of data that included at least one key clinical study that lacked a concurrent control.[47] In contrast to the Mifeprex data, FDA concluded that the lack of concurrent controls in these studies was a weakness because data on the course of the disease in a comparable population was not available to be used as a reliable historical control. For example, Thalomid was approved on the basis of clinical trial data from the published literature as well as a series of retrospective case studies for several dozen patients.[48] Additionally, five of the drugs—Actiq, Revlimid, Thalomid, Tracleer, and Xyrem—were approved on the basis of key clinical studies with relatively small sample sizes of several hundred patients or less. Finally, for Actiq, Plenaxis, Thalomid, and Xyrem, FDA identified data collection issues, such as incomplete documentation, in some of the key data sources.

Another common element was that for six of the drugs, including Mifeprex, FDA issued at least one prior action letter before ultimately approving the drug for marketing. FDA issued one approvable letter before ultimately approving Thalomid and Tracleer. Both Mifeprex and Xyrem received two approvable letters. In some cases the types of issues FDA cited—such as insufficient safety or efficacy data, the need for additional information on the restricted distribution system, or chemistry and manufacturing issues—were similar. For all four of these drugs, the adequacy of proposed distribution restrictions was a significant issue. For Xyrem, FDA's initial approvable action was also linked to the sufficiency of the data provided in the application. FDA issued not approvable letters for both Actiq and Plenaxis prior to their eventual approval. In the case of Actiq, FDA cited multiple deficiencies, such as reliance on a key clinical study with flaws and an inadequate plan for risk management. For Plenaxis, FDA initially concluded that the risks of the drug exceeded its

[47]FDA approved Plenaxis on the basis of one uncontrolled clinical trial in the indicated population—men with advanced symptomatic prostate cancer—and three concurrently-controlled clinical trials in men with less advanced prostate cancer. FDA approved Xyrem on the basis of one uncontrolled key safety trial, and two concurrently-controlled clinical trials.

[48]FDA considers such case studies to be historically controlled. In this case, the reviewing division concluded that the data were not sufficient to demonstrate the safety and efficacy of Thalomid. However, that decision was overridden by both the Director of the relevant FDA office and the Director of FDA's Center for Drug Evaluation and Research, based on their individual analyses of the available data.

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benefits because of the potential for severe, systemic allergic reactions in patients.

As a result of these complexities, the approval process for the Subpart H restricted drugs was typically longer than the process for other drugs. Across the seven drugs with NDAs approved under Subpart H, an average of almost 25 months elapsed from the time that the sponsor submitted its NDA to the time FDA approved the NDA. The length of time to approval ranged from almost 9 months for Revlimid to more than 54 months for Mifeprex. In comparison, in analyses conducted for our 2006 report on new drug development, we found that it took FDA on average almost 18 months to approve NDAs submitted from 1996 through 2002.[49]

We also found that the types of distribution restrictions FDA imposed on Mifeprex were similar to those imposed on the other Subpart H restricted drugs, though the specifics of the restrictions depended on FDA's safe use concern for the drug.[50] (See table 2.) For all of the drugs except Actiq, FDA required some form of program enrollment or registration process. For example, for Mifeprex and three other drugs, FDA required that patients sign written agreements and that physicians enroll in a prescribing program and attest to their qualifications. For five of the drugs, FDA required formal registries of all prescribing physicians and patients.[51] Additionally, for seven of the drugs, FDA required that distribution be limited to authorized distributors or pharmacies.[52] And for eight of the

[49]See, GAO, *New Drug Development: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts*, GAO-07-49. (Washington, D.C.: Nov. 17, 2006). In contrast, the drugs approved under the surrogate endpoint provision of Subpart H have generally been approved more rapidly than drugs approved under the restricted distribution provision of Subpart H and than drugs approved outside of Subpart H.

[50]Additionally, except for Plenaxis, FDA convened a meeting of the relevant advisory committee prior to each drug's approval under Subpart H to obtain expert input regarding the appropriate actions to address the agency's safe use concerns, including the distribution restrictions that should be required. The advisory committee meetings that FDA has held for the drugs Accutane and Lotronex occurred after each drug was first marketed in the United States, but prior to their approvals under Subpart H.

[51]FDA has used various types of registries as a mechanism to collect data on patients, providers, and others as a tool for monitoring outcomes of interest.

[52]Two of the drugs—Actiq and Xyrem—were approved as controlled substances and therefore subject to the restrictions imposed by the Controlled Substances Act. Requirements imposed under this act are enforced by the Drug Enforcement Administration and are distinct from the distribution restrictions imposed on these drugs by FDA under Subpart H. See, e.g., 21 U.S.C. § 822; 21 C.F.R. § 1301.11 (2007).

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drugs, FDA required that the sponsor establish a process to ensure that dispensing or distribution of the drug was contingent on verification that physicians and others had enrolled or registered in the distribution program, or that patients had complied with certain safety measures. FDA also required that all of the sponsors implement some form of educational program for patients, prescribers, or pharmacists, though FDA did not require that prescribing physicians participate in formal training for any of the drugs. For six of the nine drugs, FDA required that the sponsor report periodically to the agency specifically on implementation of their restricted distribution programs. For seven of the drugs, FDA required that sponsors report to the agency on specific adverse events—such as fetal exposures or liver toxicity—more frequently than is required for other drugs. In the case of Mifeprex and Xyrem, at the time the drugs were approved, FDA did not require that the sponsors submit additional adverse event reports beyond those required for all approved drugs, but did require that physicians agree to report specific types of adverse events to the sponsor.

Table 2: Selected Features of Restricted Distribution Programs Imposed by FDA at Time of Approval under Subpart H

Features Required at Approval	Mifeprex (mifepristone)	Lotronex (alosetron hydrochloride)	Actiq (oral transmucosal fentanyl citrate)	Thalomid (thalidomide)	Tracleer (bosentan)	Xyrem (sodium oxybate)	Plenaxis (abarelix for injectable suspension)	Revlimid (lenalidomide)	Accutane (isotretinoin)
Program enrollment or registration[a]	✓	✓		✓	✓	✓	✓	✓	✓
Limited distribution channels[b]	✓			✓	✓	✓	✓	✓	✓
Dispensing or distribution contingent on verification[c]	✓	✓		✓	✓	✓	✓	✓	✓
Sponsor developed educational programs[d]	✓	✓	✓	✓	✓	✓	✓	✓	✓
Reporting specific to implementation of restricted distribution program		✓	✓	✓	✓		✓		✓
Additional adverse event reporting by the sponsor[e]		✓	✓	✓	✓		✓	✓	✓

Source: GAO analysis of FDA data.

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[a]Program enrollment or registration requirements varied across the drugs. For Accutane, Lotronex, Mifeprex, and Plenaxis, FDA required that physicians enroll in a prescribing program and attest to their qualifications. For Accutane, Revlimid, Thalomid, Tracleer, and Xyrem, FDA required formal registries of all prescribing physicians and patients. FDA also required registration of pharmacies, wholesalers, or distributors for Thalomid, Revlimid, and Accutane.

[b]The specific limitations imposed on distribution channels varied across the drugs, and in some cases more than one limitation was required. These limitations included, for example, requiring that a drug only be distributed directly to prescribing physicians, allowing only authorized distributors or wholesalers to ship a drug, and allowing only registered or centralized pharmacies to dispense a drug.

[c]The verification mechanisms varied across the drugs. For example, for Mifeprex, an authorized distributor must verify that a physician has a signed prescriber agreement on file before distributing the drug. For Lotronex, before dispensing and drug, pharmacists must verify that prescriptions include a sticker that is only available to physicians enrolled in the prescribing program. For Accutane, Revlimid, and Thalomid, a registered pharmacy is required to confirm prescription authorizations and that patients have complied with requirements to use one or more methods of contraception before dispensing the drug.

[d]In general, sponsors were required to develop educational materials (such as patient information videos) for patients, and make educational materials and training programs readily available to prescribing physicians, pharmacists, and other groups involved in the restricted distribution program. For some of the drugs, dispensing pharmacists were required to participate in formal training. At the time of Subpart H approval, FDA required medication guides for all of the drugs except Actiq, Plenaxis, and Thalomid.

[e]Sponsors for seven of the drugs were required to submit 15-day alert reports on specific adverse events. Sponsors of four of the drugs were required to provide updates more frequently than typically required for events related to FDA's safe use concern for the drug. For Mifeprex, as part of their prescriber agreement, physicians agreed to report ongoing pregnancies, hospitalizations, transfusions, and other serious events to the sponsor. For Xyrem, FDA required that physicians agree to collect and report to the sponsor information on specific adverse events and inappropriate use of the drug.

Finally, eight of the nine Subpart H restricted drugs were approved with two or more postmarketing study commitments.[53] Each of these had at least one commitment that involved developing a postmarket study to monitor adverse events or patient outcomes of interest for that drug. The number of study commitments FDA required ranged from 2 to 10, depending on the drug. Additionally, for most of the drugs, including Mifeprex, the study protocols for the various commitments had not been finalized at the time of approval.

[53]FDA's approval of Accutane under Subpart H through a supplemental NDA did not include any postmarket study commitments.

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FDA's Postmarket Oversight of Mifeprex Has Been Consistent with the Agency's Oversight of the Other Subpart H Restricted Drugs

The actions FDA has taken to oversee Mifeprex have been consistent with the actions it has taken to oversee the other Subpart H restricted drugs. FDA has relied primarily on information submitted by the sponsors of all the Subpart H restricted drugs and inspections for three of the drugs to oversee compliance with restricted distribution requirements. FDA has also relied on updates submitted by these sponsors to oversee compliance with postmarketing study commitments and has found that most have unfulfilled commitments. To oversee compliance with adverse event reporting requirements, FDA has reviewed a variety of safety information including reports submitted by the sponsors of all nine of the drugs restricted under Subpart H and has conducted inspections to evaluate compliance with reporting of adverse events for eight of the drugs. As a result, for most of the drugs, FDA has identified deficiencies in compliance with adverse event reporting requirements. To oversee reported adverse events FDA has used similar methods—such as monitoring, investigating, and addressing safety concerns—for Mifeprex and the other eight Subpart H restricted drugs. As a result of its oversight of safety data, FDA has identified postmarket safety concerns for most of the drugs and has used a variety of methods to communicate safety information to health care providers and the public. (See table 3 for an overview of FDA's postmarket oversight of these drugs.)

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Table 3: Selected Features of FDA's Oversight of Postmarket Safety for Drugs Approved under Subpart H, as of May 2008

Oversight Activities and Findings	Mifeprex (mife-pristone)	Lotronex (alosetron hydro-chloride)	Actiq (oral transmucosal fentanyl citrate)	Thalomid (thalidomide)	Tracleer (bosentan)	Xyrem (sodium oxybate)	Plenaxis (abarelix for injectable suspension)	Revlimid (lenali-domide)	Accutane (isotretinoin)
FDA has completed inspection(s) to oversee compliance with distribution restriction requirements[a]	✓				✓	✓			
FDA has classified at least one postmarketing study commitment as unfulfilled[b]	✓	✓	✓	✓	✓		✓	✓	n/a
FDA has conducted inspection(s) to oversee compliance with adverse event reporting requirements[c]	✓	✓	✓	✓	✓	✓	✓		✓
FDA has identified a postmarket safety concern leading to communication of new safety information to public or health care providers[d]	✓	✓	✓	✓	✓	✓		✓	✓

Source: GAO analysis of FDA data.

Note: FDA provided or confirmed data on these selected features of oversight through May 2008.

[a]In May 2008, FDA officials told us that they had conducted such inspections for three additional drugs. However, the reports from those inspections were not yet available. Inspections were in addition to report review.

[b]FDA classifies unfulfilled postmarketing study commitments as ongoing, pending, delayed, released, or terminated; FDA has documented that the sponsor for Xyrem has fulfilled two of its postmarketing study commitments and has submitted the final report for the third and final commitment.

[c]Inspections were in addition to report review conducted for all of the drugs. In the case of Revlimid, FDA inspected Celgene—the sponsor of both Revlimid and Thalomid—before Revlimid was approved in December 2005.

[d]Communication of new safety information includes activities such as changing product labeling, issuing Public Health Advisories and Safety Alerts, and distributing letters to health care providers.

To Oversee Compliance with Distribution Restrictions, FDA Relied on Information Submitted by All Drug Sponsors and Its Own Inspections for Some of the Drugs, Including Mifeprex

For all nine of the drugs that have been approved under the restricted distribution provision of Subpart H, FDA has relied mainly on information submitted by sponsors in required reports to oversee the sponsors' compliance with distribution restrictions. For six of the drugs—not including Mifeprex—FDA relied on reports specific to the drugs' restricted distribution programs.[54] The type of information provided by the sponsors in these documents included data on the operation of the restricted distribution program, such as requirements for distributors, pharmacies, prescribers, and patients participating in the program. In addition, to oversee compliance with the restricted distribution programs for most of the drugs—including Mifeprex—FDA has relied on annual reports, supplemental applications, or periodic reports for required updates on the postmarket use of the drugs, including summaries of updates to the restricted distribution program.[55]

Through the end of 2007, FDA had conducted inspections specifically to oversee sponsors' compliance with distribution restrictions for three of the drugs—Mifeprex, Tracleer, and Xyrem. In the case of Mifeprex, in 2002 FDA conducted routine inspections of two of the drug's distributors to oversee their compliance with distribution restrictions. FDA inspectors reviewed standard operating procedures and other information in order to oversee adherence to the requirements of the restricted distribution program such as procedures for maintaining signed provider agreements, distributing medication guides with shipments of the drug, and maintaining the physical security of the drug. For one of the inspections of Mifeprex distributors, FDA did not issue a citation. For the other inspection, FDA issued a citation in which the agency cited four

[54]FDA approved six of the nine Subpart H restricted drugs with a requirement that the sponsor report periodically to FDA specifically on implementation of the respective restricted distribution program. Under FDAAA, sponsors of all drugs with an approved REMS will be required to submit periodically to FDA an assessment of their REMS. Pub. L. No. 110-85, § 901(b), 823 Stat. 929, 932, *codified at* 21 U.S.C. § 355-1.

[55]Though FDA's Subpart H regulations provide an expedited process for withdrawing marketing approval for a drug if FDA determines that promotional materials are false or misleading, the agency has not done so for a Subpart H drug. See 21 C.F.R. § 314.530(a)(5) (2007). However, it has issued warning letters citing the sponsors for two of the drugs—Thalomid and Tracleer—for promoting unapproved use of the drug in violation of FDA regulations.

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inconsistencies between the approved distribution plan and the distributor's standard operating procedures. For example, FDA cited the distributor for the absence of certain written procedures pertaining to the distribution of the drug. The sponsor responded to this citation, noting that at the time of approval the distribution plan did not require that distributors prepare such written procedures. Other examples of the inconsistencies FDA noted were serial numbers that had not been properly recorded on a shipping label as required for tracking purposes and the requirement that a medication guide be provided with each dose of the drug was not reflected in the written procedures for processing orders. As a result of its 2006 inspection of the Tracleer restricted distribution program, FDA did not issue a formal citation, but provided recommendations to the sponsor. In its 2007 inspection of the Xyrem restricted distribution program, FDA did not identify any specific deficiencies.[56] However, many of the responsibilities for the program are contracted out to a pharmacy, which was not inspected. The inspection report notes that, for that reason, FDA could not verify whether the sponsor had fulfilled the requirements for the drug's restricted distribution program.

Although FDA's inspections for Mifeprex and Tracleer led to recommendations for improving the respective restricted distribution programs, through the end of 2007, FDA had not conducted inspections of compliance with restricted distribution requirements for six Subpart H restricted drugs. FDA officials told us that the agency has conducted

[56]FDA's inspection report notes that the sponsor refused to provide FDA access to full reports from audits that the sponsor had conducted to evaluate its contractors' compliance with agreed upon responsibilities under the restricted distribution program.

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inspections of compliance with distribution restrictions for three additional drugs since the beginning of 2008.[57, 58]

To Oversee Compliance with Postmarketing Study Commitments, FDA Relied on Sponsors' Data That Found That Most Have Unfulfilled Commitments

For the eight Subpart H restricted drugs approved with postmarketing study commitments, FDA has relied on sponsors' annual reports for updates on the status of each commitment. FDA's reviews of these reports are the basis for its determination of the status of each commitment as fulfilled, submitted, pending, ongoing, delayed, released, or terminated. FDA officials told us that the status of postmarketing study commitments for Subpart H drugs is monitored the same way as those commitments for other drugs.

Seven of the eight Subpart H restricted drugs approved with postmarketing study commitments had at least one commitment that was not fulfilled as of September 2007.[59] Of these seven drugs, most have study commitments that FDA has classified as ongoing, pending, or delayed.[60] In the case of Mifeprex, FDA had categorized both of the drug's postmarketing study commitments—to which the sponsor agreed at time of the drug's approval in 2000—as ongoing until December 2007 when the agency changed the status of one of the commitments to released. For the first commitment—a study to compare outcomes for patients whose

[57]In 2008, FDA conducted initial inspections specific to the restricted distribution programs for Accutane, Actiq, and Revlimid. In addition, FDA conducted a second such inspection for the Tracleer program. As of May 13, 2008, the results from these inspections were not available.

[58]In February 2007, agency officials told us that they were working to establish a process to conduct regular inspections to oversee sponsors' compliance with distribution restrictions for Subpart H restricted drugs. Since that time, agency officials told us that FDA had decided to combine the inspection of restricted distribution programs with inspections examining compliance with adverse event reporting requirements. However, agency officials noted in May 2008 that FDA is reevaluating its process for conducting inspections in light of recent legislative changes. Under FDAAA, FDA is required to evaluate, at least annually, for one or more drugs that have elements to assure safe use as part of their REMS, whether those elements assure the safe use of the drug, are not unduly burdensome on patient access, and to the extent practicable minimize the burden on the health care delivery system. 21 U.S.C. § 355-1(f)(5)(B).

[59]FDA has documented that the sponsor for Xyrem has fulfilled two of its postmarket study commitments and has submitted the final report for the third and final commitment.

[60]In its June 2006 report on FDA's management of postmarket studies, the Department of Health and Human Services Office of the Inspector General found that it is common across all drugs approved by FDA with postmarket study commitments for sponsors to have unfulfilled commitments.

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health care providers perform a surgical abortion with outcomes for patients who are referred to another facility for follow-up care in the event of treatment failure—the sponsor has reported difficulty in enrolling participants into the study. FDA told us that according to the sponsor, the "vast majority of prescribers" can provide surgical abortion services on site. FDA has opted not to terminate the study, and has categorized it as ongoing. FDA officials told us that this gives the agency additional flexibility in the event that provider or practice patterns change over time, making enrollment of study participants more feasible. The sponsor also has reported enrollment challenges in the case of the second study commitment for Mifeprex—to conduct surveillance of ongoing pregnancies following failure of treatment. FDA officials told us that postmarket experience with the drug has shown that most patients opt to have a surgical abortion in the event that the Mifeprex regimen is not successful in terminating the pregnancy. In December 2007, FDA released the sponsor from this commitment because it determined that the study will no longer provide helpful information because of low enrollment.

FDA has worked with some of the sponsors of the Subpart H restricted drugs to make adjustments to agreed upon commitments that have not been completed.[61] FDA officials told us that the agency has in some cases made changes to a sponsor's postmarketing study commitments or requested new commitments in addition to those specified at approval. For example, FDA recommended several additional postmarketing study commitments for Thalomid following the agency's approval of an expanded indication for the drug. In the case of Tracleer, FDA recommended changes to some of the drug's study commitments. FDA had not requested additions or changes to the postmarketing study commitments for Mifeprex until the agency released the sponsor from its commitment to conduct surveillance of ongoing pregnancies following failure of treatment.

[61]FDA may withdraw approval of a drug approved under Subpart H if a sponsor does not carry out its required postmarketing studies with due diligence. 21 C.F.R. § 314.530(a)(2) (2007). According to FDA, the regulations only require postmarketing study commitments for drugs approved under the surrogate endpoint provision (21 C.F.R. § 314.510) and not for drugs approved under the restricted distribution provision (21 C.F.R. § 314.520). FDAAA provides FDA with additional authority with regard to requiring postmarketing studies and/or trials. See 21 U.S.C. § 355(o)(3).

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To Oversee Compliance with Adverse Event Reporting Requirements, FDA Reviewed Sponsors' Data, Conducted Inspections and Identified Deficiencies for Most of the Drugs

To oversee compliance with adverse event reporting requirements, FDA has both reviewed data submitted by sponsors in required reports and conducted inspections. Sponsor reporting for the drugs has included annual reports in which the sponsor provided a summary of the adverse events reported in the previous year; periodic update reports which inform FDA of adverse events monthly, quarterly, or at some other interval established by FDA; and 15-day alert reports for events that are both serious and unexpected. In addition, in some cases sponsors have agreed or FDA has required them to provide 15-day alert reports for other types of serious adverse events. For example, the sponsor of Mifeprex agreed to provide 15-day alert reports for cases of serious infection and ruptured ectopic pregnancy in women who used the drug, and FDA required the sponsor of Thalomid to report suspected or confirmed pregnancy in women taking that drug.[62] In some cases, including for Mifeprex, FDA specifically documented its assessments of adverse event reporting contained in annual, periodic update, or 15-day alert reports or reports submitted to the AERS database. FDA officials told us that staff review all submitted reports, but do not always document their reviews.

In addition to relying on reports submitted by the sponsors, FDA has conducted inspections specifically to oversee the sponsors' compliance with adverse event reporting requirements for eight of the nine drugs, including Mifeprex.[63] Between 2001 and May 2008, FDA had conducted 19 such inspections with a range of none to four inspections conducted for each drug.[64] In the case of Mifeprex, FDA has conducted three inspections—in 2002, 2004, and 2006—related to adverse event reporting. In these inspections, FDA reviewed a variety of documents pertaining to adverse event reporting for Mifeprex, including standard operating procedures, product labeling, MedWatch reporting forms, 15-day alert

[62]Mifeprex labeling specifically cautions against the use of the drug in women with ectopic pregnancy. The sponsor has noted that the condition is not an adverse drug experience as FDA defines the term.

[63]As of May 2008 FDA had not conducted an adverse event reporting inspection for the sponsor of Revlimid since this drug was approved under Subpart H. The agency inspected Celgene—the sponsor of Revlimid and Thalomid—in 2001, 2002, 2004, and 2005, but these inspections occurred before Revlimid was approved in December 2005. FDA officials told us they did not have specific goals for how frequently sponsors are inspected to monitor compliance with adverse event reporting requirements.

[64]These inspections include two inspections of the sponsor of Accutane (isotretinoin). FDA conducted an additional four adverse event reporting inspections of sponsors or the manufacturer of generic isotretinoin products.

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reports, complaint file, periodic update reports on adverse events, and annual NDA reports. In addition, FDA documented reviews of samples of the sponsor's adverse event reports for completeness, accuracy, and timeliness.

As a result of the Mifeprex inspections, FDA issued citations for deficiencies related to the accuracy, completeness, or timeliness of some reports as well as for the sponsor's failure to follow certain procedures for handling some adverse event follow-up activities. In each of the Mifeprex inspections, FDA identified some examples of misclassified reports—events which FDA said should have been submitted as 15-day alert reports rather than in periodic reports. For example, FDA cited the sponsor for not classifying some events resulting in hospitalization as serious events and thus not reporting those events as 15-day alert reports. In another inspection, FDA found that some of the sponsor's procedures for reporting and following up on adverse events were inadequate or had not been developed. These deficiencies were similar to those FDA found for other drugs, and FDA identified fewer problematic reports for Mifeprex than for some of the other Subpart H restricted drugs. Following each of the inspections for Mifeprex, the sponsor provided a written response to FDA in which it either agreed to address FDA's findings or noted its disagreement with the deficiencies FDA cited. For example, following the first inspection, the sponsor agreed to address the examples of misclassified or incomplete reporting FDA cited and to reinforce procedures for handling adverse event-related correspondence with its staff. In some cases the sponsor disagreed with FDA's characterization of a deficiency or presented evidence to refute a claim that it had not complied with a reporting requirement or procedure.

As a result of FDA's inspections for the other seven drugs, the agency issued written citations to six of the sponsors for deficiencies. In addition, FDA noted only "oral observations" for the other sponsor. Similar to the Mifeprex inspections, FDA staff reviewed information such as sponsor documentation and standard operating procedures related to adverse event reporting for the other seven drugs for which it conducted inspections. As it did for the Mifeprex inspections, FDA reviewed samples of adverse event reports for completeness, accuracy, or timeliness for most of the other drugs. As it did with Mifeprex, FDA cited some sponsors for deficiencies such as incomplete or late reporting of adverse events or failure to adhere to certain procedures for reporting. For example, FDA cited the sponsor of Thalomid for failure to submit several reports of serious and unexpected adverse events as a 15-day alert report and for late reporting of some other adverse events that included deaths and

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hospitalizations. In addition, FDA issued an untitled letter to the sponsor citing its failure to review and submit 82 reports of serious and unexpected adverse events within the required time frame.

FDA was not always consistent in how it documented deficiencies in adverse event reporting. In some of its inspections FDA documented the same type of deficiency as a citation while in others it noted them as oral observations or discussion points. For example, FDA did not issue a citation for the sponsor of Tracleer after inspectors noted 52 late 15-day reports—instead discussing the late reports with the sponsor at the close of the inspection. However, in its first inspection of the sponsor for Mifeprex, FDA issued a citation for failure to file a single 15-day report within the required 15 days. FDA also cited the sponsor for 6 late 15-day reports in each of its two subsequent inspections, although the sponsor refuted this finding in written responses following each inspection. As in the case of Mifeprex, sponsors responded to FDA in writing to describe actions they had taken to address deficiencies or to disagree with FDA's conclusions following an inspection.

To Oversee Postmarket Safety, FDA Used Similar Methods to Review Reported Adverse Events and Took a Variety of Actions in Response to Emerging Concerns

FDA has used similar methods to oversee postmarket safety—monitoring, investigating, and taking action on emerging safety concerns—for Mifeprex and the other eight Subpart H restricted drugs. For Mifeprex, FDA has routinely reviewed the available information on reported adverse events from sources such as annual reports, periodic update reports, 15-day alerts, and data from its AERS database. Since the time Mifeprex was approved, FDA has documented regular reviews and summarized the available data on adverse event reports to monitor the drug's safety. FDA believes that, because the distribution system for Mifeprex requires that prescribing physicians agree to report hospitalizations and other serious adverse events, it is unlikely there are significant numbers of these events that are not reported to FDA. However, FDA acknowledges that because the reporting system is voluntary, the agency cannot be certain that they have reports of all serious adverse events.

FDA officials have concluded that, with the exception of the cases of fatal infection, the reported serious adverse events associated with Mifeprex have been within or below the ranges expected based upon the medical literature on adverse events following medical abortion. In its May 2006

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response to congressional inquiries regarding Mifeprex,[65] FDA stated that the most commonly reported serious adverse events had been blood loss requiring a transfusion, infection, and ectopic pregnancy. FDA estimated that 0.023 percent of U.S. women who had taken Mifeprex have required transfusion, compared to a transfusion rate of 0.15 percent observed in international studies of the drug. FDA also noted that the rate of ectopic pregnancy among U.S. women who had used Mifeprex was 0.005 percent, compared to the overall rate of 1.3 to 2 percent in all U.S. pregnancies. Based on the medical literature, FDA estimated that fewer than 1 percent of patients will develop an infection of any kind following medical abortion with Mifeprex.

According to FDA, as of May 2008, among the estimated 915,000 U.S. women who had taken Mifeprex for termination of pregnancy since its approval, the agency was aware of seven deaths that may be related to the use of the drug.[66] Six of the deaths were due to severe infection, and one death involved an undiagnosed ectopic pregnancy. Of the cases involving infection, five of the women were infected with a rare bacterium, *Clostridium sordellii*, while one woman was infected with the bacterium *Clostridium perfringens*. With assistance from the Centers for Disease Control and Prevention (CDC) and other outside experts, FDA has investigated all reported infection-related deaths in U.S. women who have taken the Mifeprex regimen for termination of pregnancy. These investigations included requesting the medical records and autopsy reports for each case; evaluating available adverse event data from the United States, the United Kingdom, and the World Health Organization; consulting with scientific experts and health care providers from inside and outside FDA; and microbiological testing to identify the bacterium involved. In addition, FDA evaluated samples from the drug lots of Mifeprex and misoprostol associated with some of the deaths to test for contamination with the bacteria.[67] FDA found that in the six cases of death

[65]FDA statement to the Subcommittee on Criminal Justice, Drug Policy, and Human Resources, Committee on Government Reform, May 17, 2006.

[66]In her testimony to Congress on May 17, 2006, Dr. Janet Woodcock stated FDA was aware of five infection-related deaths in U.S. women. In the course of GAO's research for this study, FDA reported that an additional infection-related death occurred in 2007. In her testimony, Dr. Woodcock also discussed three other cases of deaths in U.S. women who had taken Mifeprex that, following investigation, were determined unlikely to be related to the use of the drug. In addition, she discussed three women in other countries whose deaths were related to the use of mifepristone and misoprostol for medical abortion.

[67]The product tracking provision of the restricted distribution program for Mifeprex enabled FDA to locate the lot numbers for the drugs administered in each of the cases.

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due to infection, the women used a regimen of Mifeprex and misoprostol that has not been approved by FDA.[68] FDA has stated that it is aware that many health care providers use modified regimens, and while some of the regimens have been described in the medical literature, FDA has not evaluated the safety and effectiveness of any other regimen than the one described in the drug's approved labeling.

To further explore the nature of the infections, FDA initiated an interagency scientific workshop in May 2006 with CDC and the National Institutes of Health entitled "Emerging Clostridial Disease." These agencies had observed a general increase in the United States in reports of serious clostridial infections including infections in women who had used Mifeprex, that raised questions about *Clostridium's* relationship to fatal illness and pregnancy. According to the meeting minutes, participants discussed recent cases of clostridial infection—including those occurring among women who had taken Mifeprex and misoprostol for termination of pregnancy and those who had not—reviewed what was currently known about these infections, and discussed how to conduct surveillance to ensure that cases and trends of clostridial infections are monitored. At the workshop, a CDC official reported on the history of clostridial infections, including a cluster of ten fatal cases reported in the literature between 1977 and 2001 among previously healthy women. Of the ten cases, eight of the women became infected following childbirth, one became infected following a medical abortion, and the other case was unrelated to pregnancy.

As a result of its investigative efforts, FDA has concluded that the evidence does not indicate that Mifeprex caused the fatal infections. In response to congressional inquiry, FDA stated that "the nature of the relationship between taking a single dose of the drug and the reported cases of serious infection with a rare bacterium is highly uncertain."[69] Laboratory testing of samples from the drug lots of Mifeprex and misoprostol associated with some of the deaths due to infection has

[68]In the case of five of the deaths in the U.S. due to infection, the women used an oral dose of Mifeprex, followed by a dose of misoprostol taken intravaginally. In the other case of death due to infection, the woman used an oral dose of Mifeprex followed by a dose of misoprostol taken by inserting it in the pouch of the cheek. The regimen approved by FDA calls for swallowing doses of both Mifeprex and misoprostol.

[69]See FDA letter to Representative Mark E. Souder, then-Chairman of the Subcommittee on Criminal Justice, Drug Policy, and Human Resources, Committee on Government Reform, U.S. House of Representatives, July 31, 2006.

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shown no evidence of contamination with the bacteria.[70] FDA officials have said that the relationship between the infections and the use of unapproved regimens of Mifeprex and misoprostol remains unknown. Some research has suggested that the use of Mifeprex may suppress the immune system which could lead to infection. However, FDA has noted that if this were the case, the agency would expect to see a higher rate of other types of serious infections in patients who had used the drug, which has not been the case. FDA has noted that findings by the CDC and in the medical literature suggest that pregnancy itself—rather than the medication—may be the critical risk factor for women who have become infected with *Clostridium sordellii*.

FDA, working with the drug's sponsor, has taken a variety of steps—such as issuing warnings and making changes to the product labeling—to address safety concerns for Mifeprex that were identified through postmarket monitoring and investigation. For example, in response to reports of ruptured ectopic pregnancy, FDA developed a questions and answers document about the condition and worked with the drug's sponsor to alert health care providers and to highlight the importance of careful screening for the condition. In addition, FDA approved a labeling change to provide information about the importance of evaluating patients for ectopic pregnancy. In response to concerns about serious infections and associated deaths—all of which involved an off-label use of the drug—FDA issued Public Health Advisories to notify healthcare providers about patient deaths and the treatment regimens used in those cases, and to remind them of the regimen FDA has approved, and that FDA has not established the safety of alternative regimens. In addition, FDA issued a news release, reviewed letters from the sponsor to health care providers and emergency room directors to alert them to the safety concerns regarding serious infection, and approved changes to product labeling including revisions to the warning to include information about the deaths due to serious infection.[71] FDA also has established a Web site with information about Mifeprex, questions and answers about the drug, and

[70]FDA officials told us that the agency did not test for bacterial contamination of the specific lot associated with the most recent death because examination of the prior lots revealed no contamination.

[71]FDA officials told us that the sponsor distributed a letter to all health care providers who had signed the prescriber's agreement as of the time of the distribution of the letter and distributed a letter to all emergency room directors in the United States.

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links to other safety-related information.[72] FDA used labeling changes—including updating the medication guide that prescribers agree to discuss with their patients—and information posted on its Web site to remind consumers and health care providers that FDA has not assessed the safety and efficacy of any regimen other than the one approved for the drug and indicated in its labeling.

FDA has similarly monitored adverse events for the other Subpart H restricted drugs. As FDA has done with Mifeprex, the agency has documented periodic safety reviews of the available information it had on reported adverse events for all of the other drugs. FDA's reviews analyzed data on reported adverse events from sources such as annual NDA reporting, periodic update reports, 15-day alerts, and data from the AERS database. Some FDA reviews summarized the available data on a specific type of adverse event—like liver toxicity, or severe bleeding—or adverse events in general, in order to determine whether the data suggest an emerging safety concern for the drug. In addition, in some cases, as it did with Mifeprex, FDA has sought the advice and assistance of other federal agencies and outside experts to investigate serious adverse events.

As a result of its monitoring activities, FDA has identified postmarket safety concerns for most of the Subpart H restricted drugs and has taken similar actions to address them. When FDA has found safety concerns related to a Subpart H restricted drug, it has worked with the drug's sponsor to employ a variety of measures to ensure the drug's safe use. These have included adding or strengthening a warning on the label, issuing a Public Health Advisory, and sending letters to health care providers to alert them to a safety risk. FDA has approved safety-related labeling changes, such as boxed warnings, for eight of the nine drugs. In the case of four of the drugs, including Mifeprex, the agency issued a Public Health Advisory or Safety Alert. The sponsors of five of the drugs including Mifeprex sent a letter to health care providers who prescribe (or may prescribe) the drug to alert them of safety concerns or to communicate new information regarding the drug. For example, in the case of Tracleer, adverse event reports revealed an increased risk of liver damage in patients who were treated with the drug. As a result, FDA and the sponsor notified health care providers of the risk by issuing a Safety Alert, highlighting the need for continued monitoring of liver function in

[72]FDA's Web site for Mifeprex safety information is located at: http://www.fda.gov/cder/drug/infopage/mifepristone/default.htm

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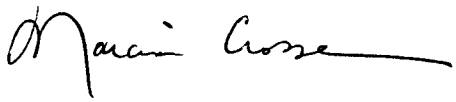
patients using the drug. The sponsor added a boxed warning about potential liver injury to the labeling and issued a letter to health care providers to alert them to the potential risk. In general, the actions FDA took in response to safety concerns were similar across all of the drugs.

Agency Comments

We provided HHS with a draft of this report for review. HHS informed us that it did not have general comments on the draft report. In addition, HHS provided technical comments, which we incorporated as appropriate.

As we agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution of it until 30 days from the date of this letter. We will then send copies to others who are interested and make copies available to others who request them. In addition, the report will be available at no charge on GAO's Web site at http://www.gao.gov.

If you or your staffs have any questions about this report, please contact me at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix IV.



Marcia Crosse
Director, Health Care

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Appendix I: Select Drugs Approved by FDA with Restricted Distribution

Drugs approved under the restricted distribution provision of Subpart H	Condition treated	Application type (year first approved under Subpart H)
Accutane (isotretinoin)	Severe recalcitrant nodular acne.	Supplemental NDA (2005)
Actiq (oral transmucosal fentanyl citrate)	Management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy.	NDA (1998)
Lotronex (alosetron hydrochloride)	Severe diarrhea predominant irritable bowel syndrome (IBS) in women who have: chronic IBS symptoms (generally lasting 6 months or longer), had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and failed to respond to conventional therapy.	Supplemental NDA (2002)
Mifeprex (mifepristone)	Medical termination of intrauterine pregnancy through 49 days' pregnancy.	NDA (2000)
Plenaxis (abarelix for injectable suspension)	Palliative treatment of men with advanced symptomatic prostate cancer, with specified risks or symptoms.	NDA (2003)
Revlimid (lenalidomide)	Treatment of a limited subset of patients with transfusion dependent anemia.	NDA (2005)
	Treatment of multiple myeloma patients who have received at least one prior therapy.	Supplemental NDA
Thalomid (thalidomide)	Acute treatment of cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) and as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrences.	NDA (1998)
	Newly diagnosed multiple myeloma.	Two Supplemental NDAs[a]
Tracleer (bosentan)	Pulmonary arterial hypertension.	NDA (2001)
Xyrem (sodium oxybate)	Cataplexy associated with narcolepsy.	NDA (2002)
Select Drugs with restricted distribution imposed outside of Subpart H		**Application type (year first approved)**
Clozaril (clozapine)	Management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia.	NDA (1989)
Tikosyn (dofetilide)	Irregular heartbeats (atrial fibrillation and atrial flutter).	NDA (1999)
Trovan (trovafloxacin/ alatrofloxacin)	Serious, life- or limb-threatening infections in an inpatient healthcare setting.	n/a[b] (1997)

Source: GAO analysis of FDA data.

Note: We list each drug by its trade name with its chemical name in parentheses.

[a]These supplemental NDAs were approved under both the restricted distribution and surrogate endpoint provisions of Subpart H.

[b]Trovan was not originally approved with distribution restrictions. Based on postmarket evidence of serious liver injury in some patients, the sponsor agreed to FDA's requests to limit the distribution of Trovan to patients with specific symptoms only in inpatient settings. However, these restrictions were not associated with a supplemental application.

Appendix II: Detailed Description of Distribution Restrictions for Mifeprex

FDA approved Mifeprex with the following specific restrictions on distribution:

- Mifeprex must be provided by or under the supervision of a physician who possesses adequate qualifications and agrees to provide the treatment according to several guidelines. To accomplish this, the system required that prescribing physicians register with an authorized distributor by providing a signed Prescriber's Agreement attesting to the following:
  - Possesses the ability to assess the duration of pregnancy accurately.
  - Possesses the ability to diagnose ectopic pregnancies.
  - Possesses the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or has made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
  - Has read and understood the prescribing information about Mifeprex.
  - Will provide each patient with a medication guide and fully explain the procedure to each patient, provide her with a copy of the medication guide and Patient Agreement, give her an opportunity to read and discuss both the medication guide and the Patient Agreement, obtain her signature on the Patient Agreement and sign it as well.
  - Will notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
  - Will report any hospitalization, transfusion or other serious events to the sponsor or its designate.
  - Will record the Mifeprex package serial number in each patient's record.
- Provisions for the physical security of the drug during distribution such as
  - Direct distribution of the drug through select authorized distributors to physicians who have signed the Prescriber's Agreement, which includes providing their medical license number. Distributors are

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required to ensure that the physician is registered before distributing the drug.

- Secure manufacturing, receiving, distribution, shipping, and return procedures, including unique serial numbers on packaging and tamper-proof seals.

Appendix III: Prescriber's Agreement for Mifeprex Distribution

The following is the prescriber's agreement at the time of the Mifeprex approval. Under the restricted distribution program for Mifeprex, the agreement is provided—by the sponsor's licensee Danco Laboratories, Inc.—to all providers to be signed and returned before the prescriber can receive any shipments of Mifeprex.

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Appendix III: Prescriber's Agreement for Mifeprex Distribution

MIFEPREX™
(Mifepristone) Tablets, 200 mg

PRESCRIBER'S AGREEMENT

We are pleased that you wish to become a provider of Mifeprex* (Mifepristone) Tablets, 200 mg, which is indicated for the medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period (see full prescribing information). Prescribing Information, Mifeprex Medication Guides and PATIENT AGREEMENT forms will be provided together with your order of Mifeprex.

Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below. If you oversee more than one office facility, you will need to list each facility on your order form prior to shipping the first order.

By signing the reverse side, you acknowledge receipt of the PRESCRIBER'S AGREEMENT and agree that you meet these qualifications and that you will follow these guidelines for use. You also understand that if you do not follow these guidelines, the distributor may discontinue distribution of the drug to you.

Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex. The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to these qualifications, you must provide Mifeprex in a manner consistent with the following guidelines.

- Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself.
- The patient's follow-up visit at approximately 14 days is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify Danco Laboratories in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the

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event of an on-going pregnancy which is not terminated subsequent to the conclusion of the treatment procedure.

- While serious adverse events associated with the use of Mifeprex are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.
- Each package of Mifeprex has a serial number. As part of maintaining complete records for each patient, you must record this serial number in each patient's record.

Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

Appendix IV: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse, (202) 512-7114 or crossem@gao.gov.

Acknowledgments

In addition to the contact named above, Martin T. Gahart, Assistant Director; Jill Center; Chad Davenport; and Cathy Hamann made key contributions to this report. Julian Klazkin also contributed.

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Report to Congressional Requesters

March 2018

FOOD AND DRUG ADMINISTRATION

Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts

GAO-18-292

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GAO Highlights

Highlights of GAO-18-292, a report to congressional requesters

Why GAO Did This Study

FDA initially approved Mifeprex in 2000 and restricted the drug's distribution to assure its safe use. In 2011, the agency approved a REMS for the drug. In March 2016, FDA approved an application for changes to the indication and dosing regimen for Mifeprex, which were reflected in revised labeling. Other changes included omitting the requirement that the prescriber be a physician. At that time, FDA also made modifications to the REMS. Some have questioned the safety implications of these changes for women using the drug.

GAO was asked to review FDA's relabeling of Mifeprex. GAO describes (1) the information FDA used to make its decisions regarding the relabeling of Mifeprex; and (2) what FDA's monitoring of Mifeprex has revealed, and stakeholders' views of FDA's monitoring and the safety of the drug.

GAO reviewed documents related to Mifeprex's relabeling, including FDA policies and regulations. GAO analyzed adverse event reports related to Mifeprex and reviewed FDA inspection reports of Mifeprex's sponsor. GAO also examined studies and data related to the safety and use of Mifeprex, and obtained information from FDA officials; Mifeprex's sponsor; and 13 stakeholder organizations, including medical associations and advocacy groups selected on the basis of their medical or scientific expertise, relevant publications, or familiarity with the drug's safety.

The Department of Health and Human Services provided technical comments on a draft of this report, which we incorporated as appropriate.

View GAO-18-292. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

What GAO Found

The Food and Drug Administration (FDA) followed its standard review process when it approved the application and revised labeling reflecting certain changes, including the indication and dosing regimen, for the drug Mifeprex, which is used for the medical termination of early pregnancy. It based its approval on reviews of peer-reviewed published studies, articles, and other information submitted by Mifeprex's sponsor. These studies focused on topics related to the proposed labeling changes, including revision of the dosing regimen, increased gestational age, method of follow-up care, and type of health care provider authorized to prescribe Mifeprex. FDA also received three letters from advocacy groups requesting that FDA revise the Mifeprex labeling in a manner that would reflect clinical practice. In addition, FDA reviewed the Risk Evaluation and Mitigation Strategy (REMS)—a set of restrictions beyond the label that FDA may impose—associated with Mifeprex, and determined it continued to be necessary. FDA also reviewed adverse events—which the agency refers to as any untoward medical event associated with the use of a drug in humans, whether or not the event is considered to be drug related—associated with Mifeprex. It determined that the rates of certain adverse events remained stable and acceptably low. In addition, FDA reviewed information regarding potential risks of specific conditions associated with the use of Mifeprex and revised the labeling accordingly. FDA determined that the information it reviewed supported the changes to the Mifeprex labeling.

FDA has conducted a variety of monitoring activities and these have not identified significant concerns with the safety and use of Mifeprex, in accordance with its approved REMS.

- FDA has conducted three inspections of Mifeprex's sponsor since 2008 regarding adverse event reporting associated with Mifeprex—in 2010, 2014, and 2016—and identified minor deficiencies, such as the use of an outdated reporting form.
- FDA conducted a REMS compliance inspection in 2014 and did not identify any deficiencies.
- FDA identified approximately 4,200 instances of adverse events associated with Mifeprex from September 28, 2000, through June 30, 2017, among the approximately 3.2 million women who have used the drug. FDA identified 20 deaths in this period—a rate much lower than for women who proceeded to live birth. FDA learned of 2 additional deaths associated with Mifeprex since June 30, 2017.

GAO found that the views of stakeholder organizations were mixed regarding FDA's monitoring of Mifeprex. Positive comments included that the agency has a comprehensive monitoring program and a robust adverse event reporting system. Criticisms included that adverse events may be underreported and that FDA may only be aware of a fraction of them. Similarly, stakeholder organizations shared mixed views on the drug's safety. Positive comments included that the mortality rate associated with Mifeprex is extremely low. Safety concerns included that the revised labeling no longer requires patients to have a second visit with a health care provider, and that certain safety issues may be exacerbated by the increased gestational age limit approved by FDA.

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Abbreviations

FDA	Food and Drug Administration
FAERS	Food and Drug Administration Adverse Event Reporting System
HHS	Department of Health and Human Services
REMS	Risk Evaluation and Mitigation Strategy

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U.S. GOVERNMENT ACCOUNTABILITY OFFICE
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March 28, 2018

Congressional Requesters

The prescription drug Mifeprex, in combination with the prescription drug misoprostol, is used for the medical termination of early pregnancy. The Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS), initially granted marketing approval of Mifeprex in September 2000. As a condition of the drug's approval, FDA imposed restrictions on the distribution of Mifeprex under its general authority to help assure the safety and effectiveness of new drugs.[1] More than 3 million women in the United States are estimated to have used this drug.

We have previously reported on FDA's approval of Mifeprex and its oversight of the drug's safety, including the restrictions the agency placed on the drug's distribution.[2] Since that time, in 2011, FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for Mifeprex, with the goal of informing patients about the benefits and risks of Mifeprex, and to minimize the risk of serious complications associated with the drug.[3] In May 2015, Mifeprex's sponsor proposed several changes to the administration of the drug.[4] It submitted a supplemental new drug application to FDA to obtain approval to revise the drug's labeling.[5]

[1]See 21 C.F.R. § 314.520 (2000).

[2]GAO, *Food and Drug Administration: Approval and Oversight of the Drug Mifeprex*, GAO-08-751, (Washington, D.C.: Aug. 7, 2008).

[3]A REMS is a set of restrictions specifically authorized by statute that FDA may impose to ensure that a drug's benefits outweigh its risks. See 21 U.S.C. § 355-1.

[4]A drug sponsor is the person or entity who assumes responsibility for the marketing of a new drug, including responsibility for complying with applicable provisions of laws, such as the Federal Food, Drug, and Cosmetic Act and related regulations. Danco Laboratories, L.L.C., the sponsor of Mifeprex, is responsible for the marketing and manufacturing of Mifeprex, and submitted the supplemental application to FDA.

[5]Supplemental new drug applications are submitted to make certain changes to already approved new drug applications, including adding or modifying an indication or claim, or revising the dose or dosing regimen. FDA review and approval of most types of supplemental new drug applications is required before the drug may be marketed with these changes. FDA characterized the supplemental application submitted for Mifeprex as an efficacy supplement that, among other things, revised its dosing regimen. See 21 C.F.R. § 314.3 (2017). Throughout this report, references to the Mifeprex application pertain to this supplemental new drug application, submitted as an efficacy supplement.

Among other things, the sponsor proposed changing the dosing regimen, increasing the gestational age limit up to which Mifeprex can be taken, and eliminating the requirement that the dose of misoprostol be administered in a medical facility. FDA approved the labeling change in March 2016 and determined that the REMS continued to be necessary, with some modifications.

You and others have questioned whether the revised Mifeprex labeling has safety implications for the women who use the drug. For example, some stakeholder organizations, such as medical associations and research organizations, have raised concerns regarding FDA's postmarketing monitoring of Mifeprex and the drug's safety.[6] You asked us to report on FDA's relabeling of Mifeprex and its monitoring activities. This report describes

1. the information FDA used to make its decisions regarding the relabeling of Mifeprex; and
2. what FDA's monitoring of Mifeprex has revealed, and stakeholders' views of FDA's monitoring and the safety of the drug.

To describe the information FDA used to make its decisions regarding the relabeling of Mifeprex, we obtained information regarding the agency's review and subsequent approval of the revised Mifeprex labeling. Specifically, we reviewed documents in FDA's approval package for the Mifeprex supplemental new drug application. The approval package included FDA's assessments of the published literature submitted by Mifeprex's sponsor to support the safety and efficacy of the proposed changes.[7] Additionally, we reviewed other documents in the approval package, including communications between FDA and Mifeprex's sponsor during the application process, and the revised Mifeprex labeling and REMS. In addition, we studied FDA's assessments of adverse events associated with Mifeprex.[8] Finally, we examined federal regulations and FDA's policies and guidance documents, and interviewed FDA officials.

[6]The term postmarketing refers to activities occurring after a drug has been approved for marketing.

[7]FDA has posted documents pertaining to its review and approval on the agency's website (see https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020TOC.cfm).

[8]FDA uses the term adverse event to refer to any untoward medical event associated with the use of a drug in humans, whether or not the event is considered to be drug related.

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To describe how FDA monitors the safety and use of Mifeprex, we analyzed FDA's postmarketing adverse event summary reports associated with the use of Mifeprex from September 28, 2000, (when the drug was approved) through June 30, 2017, and obtained information from FDA officials regarding the agency's monitoring activities.[9] We also reviewed quarterly adverse event summary reports submitted to FDA by Mifeprex's sponsor for fiscal year 2017. To further describe FDA's monitoring, we reviewed documentation from inspections the agency conducted to determine the sponsor's compliance with relevant regulations and the Federal Food, Drug, and Cosmetic Act. Specifically, we reviewed FDA's reports from inspections of Mifeprex's sponsor for compliance with adverse event reporting requirements and the Mifeprex REMS that were performed since our 2008 report was issued.[10] We obtained information from FDA on the number and results of inspections that FDA has conducted since 2008 for compliance with current good manufacturing practices.[11] We also reviewed studies and data related to the safety and use of Mifeprex from FDA, stakeholders, and other entities. We discussed FDA's data collection processes and any limitations with agency officials and determined that the data we used were sufficiently reliable for the purposes of this report. We also obtained information from Mifeprex's sponsor on its perspectives of FDA's monitoring. Finally, to describe stakeholders' views of FDA's monitoring and the safety of the drug, we obtained information from 13 organizations, including medical associations and advocacy groups with a variety of perspectives for their

[9]FDA officials said that the adverse events associated with Mifeprex in its summary reports do not necessarily reflect a conclusion by the company or FDA that the drug caused or contributed to an adverse event. See 21 C.F.R. § 314.80(l) (2017).

[10]See GAO-08-751.

[11]Current good manufacturing practices provide a framework for a manufacturer to follow to produce safe, pure, and high-quality drugs. See 21 C.F.R. pts. 210-21 (2017).

views on FDA's monitoring of Mifeprex, including any safety-related concerns they may have about the drug.[12]

We conducted this performance audit from April 2017 to March 2018 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

The treatment regimen of taking Mifeprex, in combination with misoprostol, works by both interrupting the hormones that the body needs to maintain a pregnancy and inducing the uterine cramping necessary to cause a medical abortion.[13] Mifepristone, the active ingredient in Mifeprex, was first approved in France and China in 1988, and is now approved in approximately 60 other countries, including the United States.

FDA's Review of New Drug Applications and Supplemental Applications

FDA must approve an application for a new drug before it can be marketed in the United States. FDA reviews scientific and clinical data contained in these applications as part of its process in considering them for approval to be marketed. FDA initially approved Mifeprex for use in the

[12]We obtained information from the following 13 organizations: the American Association of Pro-Life Obstetricians and Gynecologists; American College of Pediatricians; American Congress of Obstetricians and Gynecologists; Association of Reproductive Health Professionals; Bixby Center for Global Reproductive Health, University of California San Francisco; Charlotte Lozier Institute; Family Research Council; Guttmacher Institute; Gynuity Health Projects and the lead author of the Mifeprex REMS Study Group; Institute for Safe Medication Practices; National Right to Life Committee; Office of Population Research, Princeton University; and Planned Parenthood Federation of America. We selected these organizations on the basis of their medical or scientific expertise, their publication of relevant articles and web-based materials, or their familiarity with the safety and use of Mifeprex.

[13]Mifeprex is the trade name for one of the two mifepristone products approved and marketed in the United States (the trade name for the other product is Korlym, which has a different, unrelated indication). Mifepristone is the underlying drug substance and is also sometimes called RU-486, a reference to the name the drug had during laboratory testing. Medical abortion terminates a pregnancy using medications, rather than through a surgical procedure.

United States on September 28, 2000.[14] FDA approved the drug subject to restrictions that it considered necessary to ensure safe usage.

In addition to reviewing applications to market new drugs, FDA reviews supplemental new drug applications that drug sponsors submit to propose changes to an approved drug, such as adding or modifying an indication, revising the dose or dosing regimen, providing for a new route of administration, or changing the marketing status from prescription to over-the-counter use. As with original new drug applications, the agency assembles an internal team of reviewers—including medical officers, chemists, statisticians, pharmacologists, and other experts—to evaluate the information submitted in a supplemental application. During the review process, FDA may communicate with sponsors about issues that arise that may affect the approvability of the supplemental application. In response, sponsors can submit additional information to FDA in the form of amendments to the pending supplemental application. The review team compiles the results of its analyses and recommends to FDA management whether the supplemental application should be approved. Once the review is completed, the agency issues an action letter to the sponsor. FDA may approve the supplemental application (approval letter) or, if it determines it will not approve the supplemental application in its present form, it describes the specific deficiencies it identified in the supplemental application (complete response letter).

The review process for a drug application, including a supplemental application, may span several cycles before the agency approves the application.[15] For those applications that receive a complete response letter during a review cycle, the next FDA review cycle begins once the sponsor resubmits its application, providing responses to the deficiencies FDA identified in its previous review. These resubmissions often contain additional studies, analyses, data, or clarifying information to address FDA's concerns. The agency's review team examines the additional information provided by the sponsor, conducts any additional analyses

[14]In general, the mifepristone treatment regimens approved in other countries were similar to the regimen approved in the United States, although in some cases the specific drug used in combination with mifepristone was different than misoprostol.

[15]The first review cycle begins when FDA receives an application from a sponsor and ends when FDA issues an action letter. If FDA does not approve the application during the first review cycle, a new review cycle begins if the sponsor resubmits the application to provide responses to the deficiencies identified by FDA in the previous review cycle. See 21 CFR § 314.110(b)(1) (2017).

that are required, studies the results of any additional inspections that have been conducted, and again recommends either an approval or complete response action. As with the first review cycle, the process ends once FDA management reviews the recommendations of the review team and makes its decision on the action to take on the application.

Mifeprex's Supplemental Application

Prior to submitting its supplemental application, Mifeprex's sponsor met with FDA officials on January 29, 2015, to discuss the proposed labeling and Mifeprex REMS changes. At this meeting, both parties agreed that the sponsor should submit a supplemental new drug application covered by section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.[16] On May 29, 2015, Mifeprex's sponsor submitted a supplemental application to FDA to revise the dosing regimen, amend the Mifeprex labeling, and modify the Mifeprex REMS. FDA's review for this supplemental application was classified as a standard review—as opposed to a priority review—with the performance goal of completing the application review and issuing an action letter to Mifeprex's sponsor within 10 months.[17] FDA approved the supplemental application on March 29, 2016, after one review cycle, meeting the agency's performance goal for the timely review of supplemental applications.[18] Table 1 shows key components of the original Mifeprex regimen and the revised regimen.

[16]This pertains to new drug applications that rely, at least in part, on investigations that "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted . . . ." See 21 U.S.C. § 355(b)(2). For example, such an application may rely on the finding of safety or effectiveness for an approved product or on published literature in addition to studies conducted by the sponsor.

[17]FDA generally grants priority review to applications for drugs that treat serious conditions and that, if approved, would provide significant improvements in safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions compared to available therapies. FDA has a performance goal for completing priority reviews of supplemental applications in 6 months. FDA assigns a standard review designation to applications for drugs that do not meet the priority review designation criteria. FDA's goal is to generally complete review of these applications in 10 months.

[18]Food and Drug Administration, Mifeprex label, March 2016, accessed January 25, 2018, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.

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Table 1: Key Components of the Original Mifeprex Regimen and Prescriber Requirements, Approved in 2000, and the Revised Mifeprex Regimen and Prescriber Requirements, Approved in 2016

Regimen component	Original regimen	Revised regimen
Dosage	600 mg Mifeprex (mifepristone); 400 mcg misoprostol	200 mg Mifeprex (mifepristone); 800 mcg misoprostol
Dosing regimen	Day 1: 600 mg Mifeprex in a single oral dose. Day 3: 400 mcg misoprostol in a single oral dose if termination of pregnancy is not complete.	Day 1: 200 mg Mifeprex in a single oral dose. Day 2 or 3: 800 mcg misoprostol by buccal route (i.e., in the cheek pouch), 24 to 48 hours after taking Mifeprex.
Maximum gestational age (since first day of last menstrual period)	49 days	70 days
Prescriber requirements	To become certified, a licensed physician must sign and return the Prescriber Agreement Form to Mifeprex's sponsor.[a]	To become certified, a healthcare provider who prescribes must sign and return the Prescriber Agreement Form to Mifeprex's sponsor.[a]
Office visits and follow-up visits with prescriber, and location of dosing administration	Required three office visits by the patient: (1) 600 mg of Mifeprex administered to the patient by the physician or under the supervision of the physician in a clinic, medical office, or hospital. (2) Patient returns on day three for examination with physician; if termination of pregnancy is not complete, physician administers 400 mcg of misoprostol for patient to take orally. (3) Patient returns to physician for follow-up visit approximately 14 days after administration of Mifeprex to confirm complete termination of the pregnancy occurred.	Requires one office visit by the patient: (1) 200 mg of Mifeprex administered to the patient by the healthcare provider who prescribes, or under the supervision of a healthcare provider who prescribes, in a clinic, medical office, or hospital. (2) Patient takes 800 mcg of misoprostol by buccal route 24 to 48 hours after Mifeprex administration; the healthcare provider who prescribes discusses with the patient an appropriate location for her to be when she takes the misoprostol. (3) Patient should follow up with healthcare provider who prescribes approximately 7 to 14 days after Mifeprex administration to confirm complete termination of pregnancy has occurred and to evaluate the degree of bleeding.
Repeat misoprostol dose, if necessary	N/A	If the pregnancy has ended, but complete expulsion did not occur after the initial dose of misoprostol, the patient may be prescribed an additional 800 mcg of misoprostol to take buccally; women who choose to take a repeat dose of misoprostol should have a follow-up visit with their healthcare provider who prescribes in approximately 7 days to assess for complete expulsion.

Source: GAO analysis of information from the Food and Drug Administration. | GAO-18-292

[a]By signing the Prescriber Agreement Form, the prescriber certifies that he or she agrees with all specified requirements, including that the sponsor's Medication Guide will be supplied to all patients.

Mifeprex REMS

FDA initially approved a REMS for Mifeprex in June 2011.[19] When FDA approved the revised Mifeprex labeling in March 2016, the agency determined the REMS continued to be necessary, with some modifications.[20] Modifications from the original REMS to the revised REMS included

- changing the requirement that Mifeprex be provided "by or under the supervision of a physician" meeting specified qualifications to "by or under the supervision of a healthcare provider who prescribes" and meets such qualifications;
- changing the requirement for prescribers to agree to report to Mifeprex's sponsor any serious adverse event associated with Mifeprex, including hospitalizations and blood transfusions, to requiring prescribers to agree to report deaths associated with Mifeprex to the sponsor;[21]
- requiring Mifeprex's sponsor to report to FDA any death associated with Mifeprex, whether or not the death was considered drug-related, no later than 15 calendar days from the initial receipt of the information);[22] and
- removing the Medication Guide (which contained specific patient information, such as how to take Mifeprex and potential side effects) as an element of the REMS, although the Medication Guide remains part of the approved Mifeprex labeling, and the revised REMS requires the healthcare provider to provide a copy of the Medication Guide to the patient.[23]

[19]As part of a REMS, FDA can require "elements to assure safe use," 21 U.S.C. § 355-1(f)(1). This may include restrictions similar to those required to assure safe use under which Mifeprex was originally approved. 21 C.F.R. § 314.520 (2000).

[20]Food and Drug Administration, Mifeprex Risk Evaluation and Mitigation Strategy, March 2016, accessed January 25, 2018, https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_REMS_full.pdf.

[21]This requirement does not affect the sponsor's other reporting requirements under federal regulations.

[22]This requirement does not affect the sponsor's other reporting requirements under federal regulations.

[23]See 21 C.F.R. 208.24 (2017).

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As part of the REMS, Mifeprex's sponsor is required to submit REMS assessments to FDA. The first REMS assessment was due one year from the date of initial approval of the REMS. Subsequent assessments are due every three years thereafter.[24] The REMS assessments include data on the cumulative number of health care providers enrolled in the Mifeprex REMS program; the number of providers ordering Mifeprex during the assessment reporting period; and the number of women exposed to Mifeprex, both cumulative and during the reporting period. In addition, they include copies of reports for certain adverse events, including hospitalizations due to complications, blood transfusions, serious infections, and deaths, as well as the cumulative numbers of these adverse events since the approval of Mifeprex and the number during the reporting period.

FDA's Postmarketing Oversight Activities

Federal regulations require sponsors of approved drugs to report periodically to FDA on safety information and specific types of adverse events that occur in association with their use.[25] Sponsors must provide in periodic reports—quarterly for the first three years after approval and annually thereafter—a narrative summary and analysis of adverse event information to FDA. For adverse events that are considered both serious and unexpected, sponsors are required to submit a Postmarketing 15-day Alert Report to FDA within 15 calendar days of initial receipt of the information.[26]

In some instances, FDA may request sponsors to study matters that it has determined worthy of further examination. Such requests are known as postmarketing study commitments and include studies or clinical trials that FDA has requested—and sponsors have agreed to conduct—to

[24]Mifeprex's sponsor submitted its first REMS assessment to FDA in June 2012, and the second one in June 2015.

[25]See 21 C.F. R. § 314.80 (2017).

[26]Serious adverse events are those that result in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of an existing hospitalization, a significant or persistent disability or incapacity, or a congenital anomaly or birth defect. Unexpected adverse events are those that are not included in the current labeling for a drug. Adverse events associated with a drug do not necessarily imply the drug caused the event.

address such issues.[27] FDA requires sponsors to report on the status of these studies in an annual report that also includes other information such as updates on the distribution of the drug, labeling changes, clinical literature published on the drug, and the drug's marketing.[28] FDA designates unfulfilled study commitments as submitted, pending, ongoing, delayed, released, or terminated.

FDA conducts postmarketing adverse drug experience inspections of sponsors to assess compliance with adverse event reporting requirements. FDA also conducts inspections of sponsors' compliance with the REMS, as applicable.[29] In addition, FDA inspects manufacturers for compliance with current good manufacturing practices. FDA classifies the results of each type of inspection in one of three ways:

- A classification of "official action indicated" means that objectionable conditions were found that may warrant regulatory action by the agency.
- A classification of "voluntary action indicated" means that objectionable conditions that do not meet the threshold for regulatory action were identified, and any corrective actions are left to the establishment to take voluntarily.
- A classification of "no action indicated" means that no objectionable conditions or practices were found during the inspection, or that the significance of the documented objectionable conditions found does not justify further FDA action.

To monitor and analyze adverse events associated with an approved drug, FDA compiles data from sponsors' reports on adverse events, as well as data from voluntary reports submitted to the MedWatch program, all of which are entered into FDA's Adverse Event Reporting System

[27]See Pub. L. No. 105-115, § 130, 111 Stat. 2296, 2331-2 (codified at 21 U.S.C. § 356b). Sponsors may also be required to conduct additional postmarketing studies or clinical trials (i.e., in connection with accelerated approval of drugs for serious conditions or approval based on animal efficacy data, or where determined necessary to identify or assess a serious risk related to use of a drug). See 21 U.S.C. §§ 355(o) (serious risk), 356(c)(2)(A) (accelerated approval); 21 C.F.R. § 314.610(b)(1) (2017) (animal efficacy data).

[28]See 21 C.F. R. § 314.81(b)(2) (2017).

[29]In 2008, we reported that FDA conducted three postmarketing adverse drug experience inspections of Mifeprex's sponsor in 2002, 2004, and 2006. The REMS for Mifeprex was not in place at that time. See GAO-08-751.

(FAERS).[30] FDA also established the Sentinel System, which may be used to monitor drugs using electronic health care data. This system complements FDA's existing monitoring capabilities, such as FAERS, by providing administrative and claims data that can be queried to monitor the use of FDA-regulated medical products and potential outcomes of treatment. The Sentinel System currently includes reimbursement data related to diagnoses, procedures, and drugs dispensed to over 223 million patients derived from 17 different data partnerships, including national health insurers and managed care organizations. While reimbursed health care encounters, procedures, and medications are included in the Sentinel System, those that are not reimbursable—such as visits to free health care clinics, drug samples given in physicians' offices, use of low-cost generic medications that do not incur an insurance copayment, or over-the-counter medications—generally are not captured.

FDA Reviewed Published Studies that Supported the Efficacy of the Proposed Mifeprex Labeling Changes, and Evaluated Safety Information and Adverse Event Data

In considering the supplemental application to revise the Mifeprex labeling, FDA reviewed 62 studies and articles that were submitted by the drug's sponsor related to different aspects of the efficacy and safety of the proposed changes. Over the course of FDA's application review, the agency also requested and received more detailed information from the authors of select publications through communication with Mifeprex's sponsor. Additionally, FDA evaluated adverse event data associated with Mifeprex.

[30]MedWatch is a voluntary reporting system through which health professionals and consumers can report adverse reactions, product problems, and errors in use related to drugs and other products approved by FDA.

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FDA Reviewed Numerous Studies in Considering the Efficacy of the Proposed Changes to the Mifeprex Labeling

To determine the efficacy of the proposed changes to the Mifeprex labeling, FDA reviewed numerous published studies submitted by Mifeprex's sponsor, which included both U.S. and international studies.[31] Some of these studies assessed the efficacy of one component of the proposed Mifeprex labeling changes, such as the dosing regimen. Other studies assessed more than one component, such as home administration of misoprostol and the gestational age limit for Mifeprex. FDA also requested and received more detailed information from the authors of select publications through communication with Mifeprex's sponsor. In their review of the application, FDA reviewers identified what they considered major proposed changes. Some of the published studies submitted by Mifeprex's sponsor that FDA reviewed to support each of these proposed changes included the following:

- **Changes to the proposed dose and dosing regimen.** FDA reviewed 30 studies that evaluated changes to the dose and dosing regimen. For example, 22 of these studies, collectively, evaluated over 35,000 women who took the proposed dosing regimen—200 milligrams of Mifeprex orally and 800 micrograms of misoprostol buccally (i.e., in the cheek pouch) 24 to 48 hours after Mifeprex administration. The efficacy rates, defined as complete termination of the pregnancy without need for surgical intervention for any reason, ranged from 91 percent to 98 percent. One of these publications summarized the results of 20 studies, all but one of which used the proposed Mifeprex regimen in gestations through 70 days.[32] The overall efficacy rates in these 20 studies ranged from 97 percent to 98 percent for those studies that provided this information.
- **Extending the gestational age to 70 days.** FDA reviewed 19 studies that evaluated increasing the gestational age limit for taking Mifeprex. In addition to the publication discussed above that summarized the

[31]FDA accepts the use of peer-reviewed literature as primary or supportive data for an application under the framework of a 505(b)(2) application. See U.S.C. 21 § 355(b)(2). As part of its submission to FDA, Mifeprex's sponsor noted that it did not provide financial support or sponsor any of the studies submitted in its supplemental application. FDA's webpage pertaining to its review and approval of the Mifeprex supplemental application includes review documents (e.g., Cross Discipline Team Leader Review and Medical Review(s) documents) that contain lists and tables of references citing the publications FDA reviewed in the supplemental application (see https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020TOC.cfm).

[32]M.J. Chen and M.D. Creinin, "Mifepristone with Buccal Misoprostol for Medical Abortion: A Systematic Review," *Obstetrics & Gynecology,* vol. 126, no.1 (2015): 12-21.

results of 20 studies, 4 of the studies that FDA reviewed evaluated the proposed dosing regimen through 70 days gestation.[33] Three of these studies evaluated the efficacy rates for gestational ages of 64 to 70 days, which ranged from 91 percent to 96 percent. The fourth study evaluated the efficacy rates through 70 days gestation when the drug was administered by physician providers (98 percent) and by nurse providers (98 percent). An additional publication submitted by the sponsor was a systematic review of studies that covered various dosing regimens, including the proposed regimen from 64 to 70 days gestation, which had a 93 percent efficacy rate.[34] Two other studies evaluated the efficacy rates from 64 to 70 days gestation, but used different dosing regimens than the proposed regimen, with efficacy rates of 92 percent for one study and 95 percent for the other study.[35] The remaining 11 studies evaluated efficacy rates for gestation greater than the then-approved 49 days gestation, but less than 64 days, with efficacy rates ranging from 87 percent to 100 percent.

- **Home administration of misoprostol.** FDA reviewed 15 studies that evaluated home administration of misoprostol, although FDA reported that none of these studies evaluated treatment outcomes with the use of misoprostol at home compared to a clinic setting. However, one study was a large literature review of 87 studies that included over

[33]The four studies were: (1) B. Winikoff, I.G. Dzuba, E. Chong, et al., "Extending Outpatient Medical Abortion Services through 70 Days of Gestational Age," *Obstetrics & Gynecology,* vol. 120 (2012): 1070-1076; (2) A.A. Boersma, B. Meyboom-de Jong, and G. Kleiverda, "Mifepristone Followed by Home Administration of Buccal Misoprostol for Medical Abortion up to 70 days of Amenorrhoea in a General Practice in Curacao," *The European Journal of Contraception & Reproductive Health Care,* vol. 16 (2011): 61-66; (3) P. Sanhueza Smith, M. Pena, I.G. Dzuba, et al., "Safety, Efficacy and Acceptability of Outpatient Mifepristone-Misoprostol Medical Abortion through 70 days Since Last Menstrual Period in Public Sector Facilities in Mexico City," *Reproductive Health Matters,* vol. 22 (2015): 75-82; and (4) C.D. Olavarrieta, B. Ganatra, A. Sorhaindo, T.S. Karver, A. Seuc, A. Villalobos, S.G. Garcia, M. Pérez, M. Bousieguez, and P. Sanhueza, "Nurse Versus Physician-Provision of Early Medical Abortion in Mexico: A Randomized Controlled Non-Inferiority Trial," *Bulletin of the World Health Organization*, vol. 93 (2015): 249-258.

[34]D. Abbas, E. Chong, and E.G. Raymond, "Outpatient Medical Abortion is Safe and Effective through 70 Days Gestation," *Contraception,* vol. 92 (2015):197-199.

[35]The two studies were: (1) H. Bracken, R. Dabash, G. Tsertsvadze, et al., "A Two-Pill Sublingual Misoprostol Outpatient Regimen following Mifepristone for Medical Abortion through 70 Days' LMP: A Prospective Comparative Open-Label Trial," *Contraception*, vol. 89(3) (2014): 181-186; and (2) E.V. Gouk, et al., "Medical Termination of Pregnancy at 63-83 Days Gestation," *BJOG: An International Journal of Obstetrics and Gynaecology*, vol. 106 (1999): 535-539. FDA noted that these two studies were relevant because the dosage levels and routes of administration were expected to have similar or lower effectiveness than the proposed dosing regimen.

45,000 women evaluated using a variety of mifepristone treatment regimens with different misoprostol doses, routes of administration, and dosing intervals in gestations through 63 days.[36] Half of the studies in this review did not require women to take misoprostol in a clinic. The results showed that the rates of treatment failure and ongoing pregnancy were very similar regardless of whether misoprostol was taken in a clinic or at another location. A further analysis of factors leading to increased failure found no evidence that home use of misoprostol increased rates of treatment failure or serious complications.

- **Use of a repeat misoprostol dose.** FDA reviewed 10 studies to support the use of a repeat dose of misoprostol. This repeat dose would be taken in instances when complete expulsion did not occur after the initial misoprostol dose and Mifeprex dose. For example, one study evaluated 68 women who did not have complete expulsion after taking Mifeprex and were given a second vaginal dose of misoprostol, with an efficacy rate of 62 percent.[37] In another study that evaluated the proposed regimen through 70 days gestation, 5 of 330 women took a second dose of misoprostol, because of the absence of bleeding after the first dose of misoprostol. The study found that one of the five women who took the second dose did not achieve the desired result.[38] In one other study that evaluated women using the proposed regimen through 63 days gestation, 16 of 863 women received a second dose of misoprostol, with an efficacy rate of 100 percent.[39] The other 7 studies had efficacy rates for an additional dose of misoprostol ranging from 67 percent to 100 percent.[40]

[36]E.G. Raymond and D.A. Grimes, "The Comparative Safety of Legal Induced Abortion and Childbirth in the United States," *Obstetrics & Gynecology,* vol. 119 (2012): 215-219.

[37]M.F. Reeves, A. Kudva, and M. Creinin, "Medical Abortion Outcomes after a Second Dose of Misoprostol for Persistent Gestational Sac," *Contraception*, vol. 78 (2008): 332-335.

[38]Boersma, Meyboom-de Jong, and Kleiverda, "Mifepristone Followed by Home Administration of Buccal Misoprostol," 61-66.

[39]K.S. Louie, T. Tsereteli, E. Chong, F. Ailyeva, G. Rzayeva, and B. Winikoff, "Acceptability and Feasibility of Mifepristone Medical Abortion in the Early First Trimester in Azerbaijan," *The European Journal of Contraception & Reproductive Health Care,* vol. 19, no. 6 (2014): 457-464.

[40]Mifeprex's sponsor noted to FDA that approximately 1 percent to 5 percent of women will need a second dose of misoprostol following the initial Mifeprex dosing regimen.

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- **Follow-up care requirements.** FDA reviewed 11 studies that evaluated different methods for follow-up care after Mifeprex administration. One of these studies, which FDA considered a key publication on this topic, was a review of studies that assessed the impact of the timing of follow-up care.[41] This study found no differences in the failure rates between women who received follow-up care within one week of taking mifepristone compared to those who received follow-up care a week or more after taking mifepristone. The other 10 studies included a variety of study designs and dosing regimens through 63 days gestation, and FDA determined that the various methods of follow up, including home pregnancy testing and phone contact with the patient to inquire about symptoms, were acceptable alternatives to an in-clinic follow up.
- **Change in provider qualifications.** FDA reviewed four studies that addressed the efficacy of medical abortion performed by nonphysician health care providers; three of which used the proposed dosing regimen and one evaluated vaginal administration of misoprostol.[42] In these studies, almost 1,500 women had gestations through 70 days or more, and over 700 of these women had nonphysician care. In addition, almost 2,300 women had gestations up to 63 days, and over 1,000 of these women had nonphysician care. The efficacy rates were greater than or equal to 96 percent across all of the studies, regardless of gestational age or provider type.

FDA also received three letters from representatives of advocacy organizations and professional associations—some of which were signed by more than one entity—requesting that FDA revise the Mifeprex labeling in a manner that would reflect then-current clinical practice,

[41]E.G. Raymond, et al., "First-Trimester Medical Abortion with Mifepristone 200 mg and Misoprostol: A Systematic Review," *Contraception,* vol. 87 (2013): 26-37.

[42]The three studies that used the proposed regimen were (1) H. Kopp Kallner, R. Gomperts, E. Salomonsson, M. Johansson, L. Marions, and K. Gemzell-Danielsson, "The Efficacy, Safety and Acceptability of Medical Termination of Pregnancy Provided by Standard Care by Doctors or by Nurse-Midwives: A Randomized Controlled Equivalence Trial," *BJOG: An International Journal of Obstetrics and Gynaecology*, vol. 122 (2015): 510-517; (2) Olavarrieta, Ganatra, Sorhaindo, Karver, Seuc, Villalobos, Garcia, Pérez, Bousieguez, and Sanhueza, "Nurse Versus Physician-Provision of Early Medical Abortion," 249-258; and (3) M. Puri, A. Tamang, P. Shrestha, D. Joshi, "The Role of Auxiliary Nurse-Midwives and Community Health Volunteers in Expanding Access to Medical Abortion in Rural Nepal," *Reproductive Health Matters,* vol. 44 Supplement (2015): 94-103. The study that addressed vaginal misoprostol was: I.K. Warriner, D. Wang, N.T.M. Huong, K. Thapa, A. Tamang, I. Shah, et al., "Can Midlevel Health-Care Providers Administer Early Medical Abortion as Safely and Effectively as Doctors? A Randomized Controlled Equivalence Trial in Nepal," *Lancet,* vol. 377 (2011): 1155-1161.

including the new dosing regimen and extending the gestational age limit through 70 days.[43] Among others, the signers of these letters included the American Congress of Obstetricians and Gynecologists, American Public Health Association, Gynuity Health Projects, Ibis Reproductive Health, and National Abortion Federation. FDA officials told us that the peer-reviewed studies the agency received from external entities (i.e., entities other than Mifeprex's sponsor) were also submitted by Mifeprex's sponsor in the supplemental application, which FDA reviewed.[44] In addition, FDA officials told us that they received letters from organizations that were based on other than scientific perspectives, and FDA officials noted that they only considered scientific information in their review of the Mifeprex supplemental application.

FDA Evaluated Safety Information and Adverse Event Data as Part of Its Assessment of the Proposed Changes to the Mifeprex Labeling

FDA also reviewed published studies submitted by the drug's sponsor to assess the safety profile of the proposed dosing regimen, including both U.S. and international studies. Of the seven U.S. studies submitted with the Mifeprex supplemental application that examined safety issues, one specifically addressed deaths associated with Mifeprex.[45] This study noted that there were no deaths among 578 patients who received the proposed Mifeprex dosing regimen through 63 days gestation. According to FDA, because only one of these studies addressed deaths associated with Mifeprex, this may reflect the fact that it is a rare outcome and, therefore, the absence of reported deaths might not be noted by the authors of a study. In addition, FDA reviewed an observational study from Australia that was also submitted as part of the application. It identified one death from sepsis—a life-threatening complication of an infection—

[43]According to FDA, once the agency approves a drug, health care providers generally may prescribe the drug for an unapproved use when they judge that it is medically appropriate for their patient, a practice known as off-label use. FDA also indicated that the proposed changes approved in the Mifeprex supplemental application were consistent with current medical practice.

[44]According to FDA officials, the agency received one study from an external entity that was superseded by a more current publication on the same topic by one of the same authors. In this instance, FDA officials reviewed the more current publication provided by Mifeprex's sponsor.

[45]D. Grossman, K. Grindlay, T. Buchacker, K. Lane, and K. Blanchard, "Effectiveness and Acceptability of Medical Abortion Provided through Telemedicine," *Obstetrics & Gynecology,* vol. 118 (2011): 296-303.

among 13,345 pregnancy terminations using the proposed dosing regimen through 63 days gestation.[46]

In addition to reviewing published studies submitted by Mifeprex's sponsor, FDA reviewed adverse event reports from the drug's approval on September 28, 2000, through November 17, 2015. During this time, there were 17 reported deaths in the United States associated with Mifeprex, and 8 of those were associated with sepsis. Seven of the 8 sepsis cases were associated with vaginal use of misoprostol, which was, but no longer is, a common practice, according to FDA. The agency found that the adverse event data that it reviewed demonstrated that the rates of hospitalizations, severe infections, blood loss requiring transfusion, and complications related to ectopic pregnancy remained stable and acceptably low.

FDA also reviewed common adverse events, such as nausea, vomiting, diarrhea, and fever/chills, reported in U.S. and international studies submitted by Mifeprex's sponsor, and found the reporting of the frequencies of these events was higher in the U.S. studies. However, FDA determined that these differences likely reflected lower reporting of adverse events in international studies. These common adverse events are included in the Mifeprex labeling. The labeling also cites bleeding and cramping, which are expected effects of the drug regimen, according to FDA. Overall, FDA found the rate of deaths and nonfatal serious adverse events associated with Mifeprex to be acceptably low, and data for the proposed regimen did not suggest a safety profile that deviated from that of the originally approved Mifeprex regimen, which was approved as part of an application with restrictions to assure safe use. In addition, no association between adverse outcomes and increasing gestational age was identified.

In January 2016, FDA completed a review of adverse event data associated with Mifeprex in its FAERS database, as well as the published medical literature, on a potential safety concern regarding anaphylaxis and angioedema associated with mifepristone.[47] FDA's review of FAERS data found one case of anaphylaxis and six cases of angioedema with

[46]P. Goldstone, J. Michelson, and E. Williamson, "Early Medical Abortion Using Low-Dose Mifepristone Followed by Buccal Misoprostol: A Large Australian Observational Study," *Medical Journal of Australia,* vol. 197 (2012): 282-286.

[47]Anaphylaxis is a severe, potentially life-threatening allergic reaction. Angioedema is a form of severe swelling beneath the skin's surface.

mifepristone administration, with six of the seven cases seen in women using mifepristone for pregnancy termination, as opposed to using mifepristone for Cushing's syndrome.[48] The sole case of anaphylaxis could not be directly attributed to mifepristone because an oral antibiotic (doxycycline) was concomitantly administered, according to FDA. FDA did not find any additional cases of anaphylaxis or angioedema with mifepristone administration in its review of the literature. FDA noted that anaphylaxis was included in the current labeling for misoprostol. Because the approved Mifeprex regimen includes misoprostol, FDA determined that the Mifeprex labeling should also be updated to include anaphylaxis, despite the lack of anaphylaxis cases with mifepristone alone. The addition of angioedema was supported by the FAERS data documented in FDA's review. As a result, anaphylaxis and angioedema were added to the areas of the Mifeprex labeling that address allergic reactions.

The potential risk of uterine rupture was also considered in FDA's review of the Mifeprex supplemental application. FDA reviewers conducted a literature search on this topic, and identified five reports of uterine rupture in studies published from 2000 through 2014; three of which occurred with the combined mifepristone/misoprostol dosing regimen. FDA also completed a review of FAERS from January 1, 1965, through October 15, 2015, for reports of uterine rupture.[49] Of the 80 reports found in FAERS, 77 cited use of misoprostol alone, and 3 cited use of both mifepristone and misoprostol. Two reports of uterine rupture in the first trimester were identified in the FAERS review, both using misoprostol alone. One report entailed an unspecified dose and route of misoprostol at 5 weeks gestation. The other report involved vaginal administration of 800 micrograms of misoprostol at 8 weeks gestation for cervical preparation prior to a surgical abortion in a woman with a prior uterine scar. Information regarding this safety concern was added to the Mifeprex labeling when the supplemental application was approved on March 29, 2016. The agency concluded, however, that no restriction of use was needed, because this was an extremely rare adverse event.

FDA concluded that the evidence it reviewed and evaluated, including the revisions to the REMS, demonstrated acceptable safety for the proposed

[48]Cushing's syndrome is a hormonal disorder affecting both men and women caused by prolonged exposure of the body's tissues to high levels of the hormone cortisol. Mifepristone is also approved for this indication, under the brand name Korlym.

[49]According to FDA, January 1, 1965, is the date that the FAERS predecessor system was initiated.

changes to the Mifeprex regimen, and that the dosing regimen had a similar safety profile as the original regimen approved in 2000. The agency further concluded that adverse events of interest—such as deaths, serious infection, transfusions, ectopic pregnancies, and uterine rupture—remained rare, and were not necessarily attributable to Mifeprex use.[50]

FDA's Monitoring Activities Have Not Identified Significant Safety Concerns with Mifeprex; Stakeholders' Views on FDA's Monitoring and the Drug's Safety Were Mixed

FDA's monitoring of Mifeprex—primarily through inspections, and review and analysis of adverse event data—has not identified any significant concerns with the safety and use of Mifeprex. The views of the stakeholder organizations that we contacted regarding FDA's monitoring of the safety of Mifeprex and the safety of the drug itself were mixed.

FDA's Monitoring Has Not Identified Any Significant Concerns Regarding the Safety and Use of Mifeprex as Marketed with the Approved REMS

Since our prior report was issued in 2008, FDA conducted three postmarketing adverse drug experience inspections of Mifeprex's sponsor—in 2010, 2014, and 2016.[51] It identified minor deficiencies, but no significant safety concerns. These inspections each contained between two and four inspection observations—that is, the investigator observed conditions that, in his or her judgment, constituted violations of applicable federal requirements. In each of these inspections, FDA's final classification was "voluntary action indicated," meaning that objectionable conditions or practices were found, but they did not meet the threshold of regulatory significance. According to agency officials, FDA's practice for

[50]Similarly, a recently issued study by the National Academies of Sciences, Engineering, and Medicine reported that complications—such as hemorrhage, hospitalization, persistent pain, infection, or prolonged heavy bleeding—are rare after a medical abortion. This study cited some of the same studies FDA relied on and noted that complications occur in no more than a fraction of a percent of patients. National Academies of Sciences, Engineering, and Medicine, *The Safety and Quality of Abortion Care in the United States* (Washington, D.C.: prepublication copy).

[51]See GAO-08-751.

inspections resulting in this classification is to review the corrective actions taken by the establishment related to the objectionable conditions or practices during the course of the next regularly scheduled inspection. FDA officials told us that they have not yet scheduled the next postmarketing adverse drug experience inspection.

According to FDA, violations associated with postmarketing adverse drug experience inspections classified as voluntary action indicated are typically technical in nature. Examples of some of the observations from inspections of Mifeprex's sponsor include the following:

- In 2010, the sponsor was found to have used an older version of the form used for mandatory reporting of adverse events (FDA Form 3500A), rather than the more recent version.
- In 2014, two serious adverse events were not reported to FDA within the required 15-day period, and instead were included in the sponsor's subsequent quarterly adverse event report to FDA.
- In 2016, the sponsor's quarterly adverse event reports did not include the required analysis of the Postmarketing 15-day Alert Reports that occurred over the period.

In addition to postmarketing adverse drug experience inspections, Mifeprex's sponsor was subject to a REMS compliance inspection, which the agency conducted in 2014. According to FDA officials, the agency did not identify any compliance issues and determined that the final classification was no action indicated.

FDA also conducted three inspections since 2008 of the facility where Mifeprex is manufactured to ensure compliance with current good manufacturing practices. FDA did not find any deficiencies during two of these inspections; however, in the other inspection, FDA's findings resulted in a final classification of voluntary action indicated. According to the inspection report, FDA officials found an improperly performed test on a raw material used in another product produced at the same facility, not related to Mifeprex. A subsequent inspection determined that corrective action was taken by the manufacturer.

In addition to inspection data, FDA conducted ongoing monitoring of adverse event data. These data are collected through required reporting, including periodic reports on adverse events provided by the sponsor and reports by the prescriber to the sponsor, which, depending on the event, may be required under the REMS. In addition, voluntary reports may be made by the public. FDA compiled this information into periodic

postmarketing adverse event summary reports, the interval of which ranged from 2 to 18 months. These reports show that between September 28, 2000, and June 30, 2017, there were approximately 4,200 reports of adverse events associated with Mifeprex, including approximately 1,000 hospitalizations and 20 deaths.[52] These deaths represented a reporting rate of 0.0006 percent for the approximately 3.2 million women who have used Mifeprex since 2000. For context, a study of mortality among women who did not have an abortion and proceeded to a live birth estimated a mortality rate of 0.009 percent. Nonfatal adverse events, including blood loss requiring transfusion and infections, were more common among women who took Mifeprex, but still relatively low compared to the number of users. (See table 2.)

[52]Mifeprex's sponsor reported two additional deaths to FDA that had not yet been included in FDA's periodic adverse event report—one reported in September 2017 and one reported in December 2017. FDA gathers and reports data on adverse events associated with Mifeprex, which are not necessarily caused by Mifeprex. For example, an unrelated health condition observed near the time that a woman took Mifeprex may be included in FDA's adverse event summary data.

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Table 2: Adverse Events Associated with Mifeprex Reported to FDA from September 28, 2000, through June 30, 2017

	September 28, 2000 to October 31, 2012[a]	November 1, 2012 to June 30, 2017[a]
Adverse event category	**Number of cases**	**Number of cases**
Any adverse event[b]	2,740	1,439
Specific types of adverse events[c]		
Deaths[d]	14	6
Hospitalization	768	273
Blood loss with transfusion	416	182
Infections	308	103
Ectopic pregnancies	66	31
Severe infections	57	12

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-18-292

Notes: (1) Approximately 3.2 million women have taken Mifeprex since its initial approval in 2000. (2) An adverse event associated with Mifeprex does not necessarily indicate that Mifeprex caused the event.

[a]FDA implemented the FDA Adverse Event Reporting System (FAERS) in 2012, and migrated all the data from the previous reporting system to FAERS. Adverse event summary reports beginning on November 1, 2012, are based on FAERS data. Differences may exist when comparing case counts in FAERS with FDA's previous reporting system. Therefore, FDA does not recommend calculating a cumulative number for the data in table 2, with the exception of the case counts for deaths and ectopic pregnancies. These data were harmonized by FDA and may be added.

[b]Any adverse event includes all the categorized adverse events listed below it (i.e., deaths, hospitalization, blood loss with transfusion, infections and severe infections, and ectopic pregnancies), as well as other noncategorized events.

[c]Of the six types of categorized adverse events, only deaths are solely recorded as such—that is, they are not reflected in the tally for other categorized adverse events. The remaining categories are overlapping, meaning that a single case could be counted within multiple categories. Also, the hospitalization category includes both categorized and noncategorized adverse events. According to FDA, the most common adverse events among those that are not categorized (accounting for approximately 94 percent) are vaginal bleeding not requiring transfusion, retained products of conception, ongoing pregnancy, cramping, dizziness, and nausea. Among noncategorized adverse events resulting in hospitalization, the most common is dilation and curettage (accounting for approximately 81 percent).

[d]In addition to the 20 deaths included in FDA's periodic adverse event reports, the sponsor reported two additional deaths to FDA—one reported in September 2017 and one reported in December 2017—which the agency said will be included in its next periodic adverse event report.

Although postmarketing study commitments or requirements are another method for obtaining additional information about drug safety and use, in the case of Mifeprex the planned studies were deemed by FDA to be infeasible. As we previously reported, FDA originally approved Mifeprex subject to the sponsor's commitment to conduct two postmarketing studies.[53] For the first study, the sponsor agreed to assess whether

[53]See GAO-08-751.

clinical outcomes were similar for patients under the care of providers who possessed the surgical intervention skills to perform a surgical abortion compared with patients of providers who did not have such skills and referred patients for surgical abortions. FDA said the sponsor reported that the number of physicians who prescribed Mifeprex and did not possess the surgical intervention skills to perform a surgical abortion was so small that such a study was not feasible. FDA agreed and released them from that commitment in September 2008. For the second study, the sponsor was required to examine, through a surveillance and reporting system, the outcomes of pregnancies where the drug regimen failed to result in their termination. According to FDA officials, Mifeprex's sponsor reported to FDA that over nearly 2 years of monitoring (January 2006 through November 2007) there were one or two instances per year of the drug not resulting in termination. The sponsor told FDA that this was, in part, because patients had to consent to being monitored, resulting in a very small number of participants. Given these low numbers, FDA agreed that this study was also not feasible.

We also found that FDA's Sentinel System, which was developed to enhance the agency's ability to monitor postmarketing safety, is not a viable option for monitoring the use of Mifeprex. Although it contains millions of records, the Sentinel System is based on administrative and claims data, and only reimbursed health care encounters, procedures, and medications are captured in the system. Because of the REMS restrictions placed on the drug's distribution, Mifeprex is not dispensed in pharmacies. Instead, it is only available under certain conditions and from certain clinics, medical offices, and hospitals. Therefore, according to FDA officials, the Sentinel System does not include a sufficient number of Mifeprex dispensings to generate valid results. Nonetheless, we asked FDA to query the Sentinel System for mifepristone (the active pharmaceutical ingredient for Mifeprex) beginning in 2000, when the drug was first approved. The results of this query showed that, until 2012, mifepristone registered a small number of drug dispensings. Specifically, between 2000 and 2011, only 12 individuals were identified as potentially exposed to mifepristone. However, from 2012 through 2016, 243 individuals were identified, including both men and women. FDA officials explained that another drug—Korlym, which treats Cushing's syndrome and contains the same active pharmaceutical ingredient as Mifeprex—

became available in 2012.[54] Even with additional dispensings beginning in 2012, FDA officials said there were still insufficient data captured to enable a robust safety assessment.

Stakeholder Organizations Had Mixed Views on FDA's Monitoring of Mifeprex and of Mifeprex's Safety

The views of the stakeholder organizations that provided us with information on FDA's monitoring of the safety and use of Mifeprex, and the safety of the drug itself, were mixed. Stakeholders provided positive comments regarding FDA's monitoring of Mifeprex and also made suggestions to improve what they considered to be weaknesses. Positive comments included that

- FDA had a very comprehensive monitoring program that mandated the reporting of serious adverse events associated with Mifeprex up through 2016. In light of the low rates of nonfatal adverse events and the good safety profile of Mifeprex, FDA no longer requires providers to report nonfatal adverse events.
- FDA is properly monitoring the safety and use of Mifeprex through a robust adverse event reporting system, and FDA is doing its due diligence, based on the agency's mission, to identify any safety issues with the drug.
- FDA's requirement that Mifeprex be subject to a REMS has made it more likely that adverse events would be reported. Specifically, additional contacts with health care providers, as is required by the Mifeprex REMS in the form of prescriber certification and patient education, generally lead to higher adverse event reporting rates than drugs without such requirements.

Stakeholders that either commented that FDA's monitoring efforts could be improved or that expressed concern about the agency's ability to know the extent of potential safety issues said, for example, that

- FDA may only be aware of a fraction of adverse events associated with Mifeprex. There are anecdotal examples of adverse events, such as severe bleeding, that may not be reported as such or that may be interpreted by emergency health care providers as a natural

[54]The analysis that was conducted in the Sentinel System only recognizes the active pharmaceutical ingredient and does not distinguish between the drugs dispensed, according to FDA officials. The data show both men and women receiving mifepristone since 2012. Korlym's dose of mifepristone is significantly higher than that of Mifeprex and, unlike Mifeprex, the drug is taken by patients on an ongoing basis.

miscarriage. Underreporting may get worse under the revised Mifeprex label, which eliminates the follow-up visit and does not require prescribers to report nonfatal adverse events.

- FDA may not have reliable data on the number of women who have used Mifeprex, which would affect the denominator for tracking adverse events. With an unclear denominator, FDA may not have an accurate measure of adverse event rates associated with Mifeprex.

Regarding the safety of Mifeprex, stakeholders we contacted provided a mix of favorable comments about the drug, as well as certain safety concerns. Positive comments included the following

- The mortality rate associated with Mifeprex is extremely low—about one fourteenth the mortality rate associated with live birth.
- Nonfatal serious adverse events following Mifeprex use, such as hospital admission, blood transfusion, or serious infection, are also rare, occurring at rates ranging from 0.01 percent to 0.7 percent, and are almost always treatable without permanent effects. Side effects, such as bleeding, cramping, fever, and chills, are typically minor and transient.
- In the years since mifepristone's approval, multiple clinical trials, dozens of studies, and extensive experience across the globe have confirmed FDA's finding that mifepristone is a safe and reliable method of abortion. Thus, any significant concern about the safety of Mifeprex would be unwarranted.

Stakeholders also expressed some concerns about Mifeprex's safety. For example, they reported that

- Mifeprex may be linked to hemorrhaging and serious infections. A study was cited that showed adverse events were more likely to be associated with a medical abortion rather than a surgical abortion.[55] Two other studies were cited that examined the effect mifepristone may have on the body's ability to control hemorrhaging and prevent

[55]M. Niinimäki, et al., "Immediate Complications after Medical Compared with Surgical Termination of Pregnancy," *Obstetrics & Gynecology,* vol. 114, no. 4 (October 2009): 795-804. This study of over 42,000 women in Finland who had abortions from 2000 to 2006 found that, overall, medical abortion had roughly four times the rate of adverse events than surgical abortion, and hemorrhaging was experienced by 16 percent of medical abortion patients compared with 2 percent of surgical abortion patients.

serious infections.[56] For example, one of the studies found that serious bacterial infection and sepsis may occur without the usual signs of infection with the use of mifepristone for medical abortion.

- Safety issues may be exacerbated by the Mifeprex labeling changes. For example, a study was cited that found that the rates of pregnancy termination with Mifeprex dropped from 92 percent up to the 7th week of gestation to 77 percent at the 9th week.[57]
- Women in the later weeks of pregnancy who live far from a health care provider may be at increased risk of serious hemorrhaging under the revised labeling, which does not require a second visit with a health care provider.

In addition, another comment we heard was that the agency was being too restrictive by continuing to require a REMS for the drug. Specifically, we were told that Mifeprex should not continue to be restricted to being dispensed at a clinic, medical office, or hospital—as it is under the Mifeprex REMS—because ample research shows Mifeprex to be safe and adverse events to be rare. Stakeholders also noted that women in rural areas may have less access to the drug, and Mifeprex's sponsor commented that the distribution restrictions likely result in the drug being less accessible than it otherwise would be.[58]

In response to the concerns regarding Mifeprex that we heard from stakeholder organizations, FDA officials said that the agency approved the supplemental application for Mifeprex under the same approval standards that it applies to all new drug applications and supplemental applications, and found that the data and information submitted in the supplemental application demonstrated that Mifeprex is safe and effective

[56]R.P. Miech, "Pathopharmacology of Excessive Hemorrhage in Mifepristone Abortions," *Annals of Pharmacotherapy,* vol. 41, no. 12 (December 2007): 2002-2007. See also, R.P. Miech, "Pathophysiology of Mifepristone-induced Septic Shock due to *Clostridium sordellii*," *Annals of Pharmacotherapy,* vol. 39, no. 9 (September 2005): 1483-1488.

[57]I. M. Spitz, C. W. Bardin, L. Benton, and A. Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," *New England Journal of Medicine,* vol. 338, no. 18 (Apr. 30, 1998): 1241-1247.

[58]In October 2017, a doctor and several professional health associations filed a lawsuit in the U.S. District Court for the District of Hawaii to challenge the distribution restrictions imposed by FDA under the Mifeprex REMS. Chelius, et al. v. Wright, No. 17-cv- 00493 (D. Hawaii, filed Oct. 3, 2017). Plaintiffs argued that REMS requirements may be imposed only when necessary to ensure that a drug's benefits outweigh its risks, and that restrictions requiring Mifeprex to be distributed through clinics or hospitals do not meet the criteria.

for its intended use. FDA officials noted that Mifeprex also has a REMS in place to ensure safety. They also stressed that, as with all FDA-approved drugs, Mifeprex is subject to adverse event reporting requirements and continued postmarketing safety monitoring by the agency.

Agency Comments

We provided a draft of this report for comment to HHS. HHS provided technical comments, which we incorporated as appropriate.

We are sending copies of this report to the Secretary of Health and Human Services, appropriate congressional committees, and other interested parties. In addition, the report will be available at no charge on the GAO Web site at http://www.gao.gov.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs are on the last page of this report. GAO staff who made major contributions to this report are listed in appendix I.



Marcia Crosse
Director, Health Care

GBP-PET01509

List of Requesters

The Honorable Robert Aderholt
Chairman
Subcommittee on Agriculture, Rural Development,
Food and Drug Administration, and Related Agencies
Committee on Appropriations
House of Representatives

The Honorable Tom Cole
House of Representatives

The Honorable Chuck Fleischmann
House of Representatives

The Honorable Jeff Fortenberry
House of Representatives

The Honorable Tom Graves
House of Representatives

The Honorable Andy Harris
House of Representatives

The Honorable Steven Palazzo
House of Representatives

The Honorable Kevin Yoder
House of Representatives

Appendix I: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse (202) 512-7114 or crossem@gao.gov

Staff Acknowledgments

In addition to the contact above, Geri Redican-Bigott (Assistant Director), Lisa A. Lusk (Analyst-in-Charge), George Bogart, Drew Long, and Perry Parsons made key contributions to this report. Kaitlin Farquharson also made contributions to this report.

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Abortion-related emergency department visits in the United States: An analysis of a national emergency department sample

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Abstract

Background: Media depictions and laws passed in state legislatures regulating abortion suggest abortion-related medical emergencies are common. An accurate understanding of abortion-related emergencies is important for informing policy and practice. We assessed the incidence of abortion-related emergency department (ED) visits in the United States (U.S.).

Methods: We used a retrospective observational study design using 2009–2013 data from the Nationwide Emergency Department Sample, a nationally representative sample of U.S. ED visits from 947 to 964 hospitals across the U.S. per year. All ED visits among women of reproductive age (15–49) were included. We categorized ED visits by abortion relatedness and treatments received, and assessed whether the visit was for a major incident (defined as requiring blood transfusion, surgery, or overnight inpatient stay). We estimated the proportion of visits that were abortion-related and described the characteristics of patients making these visits, the diagnoses and subsequent treatments received by these patients, the sociodemographic and hospital characteristics associated with the incidents and observation care only (defined as receiving no treatments), and the rate of major incidents for all abortion patients in the U.S.

Results: Among all ED visits by women aged 15–49 (189,480,685), 0.01% ($n = 27,941$) were abortion-related. Of these visits, 51% (95% confidence interval, 95% CI 49.3–51.9%) of the women received observation care only. A total of 20% (95% CI 19.3–21.3%) of abortion-related ED visits were for major incidents. One-fifth (22%, 95% CI 20.9–23.0%) of abortion-related visits resulted in admission to the same hospital for abortion-related reasons. Of the visits, 1.4% ($n = 390$, 95% CI 1.1–1.7%) were potentially due to attempts at self-induced abortion. In multivariable models, women using Medicaid (adjusted odds ratio, AOR 1.28, 95% CI 1.08–1.52) and women with a comorbid condition (AORs 2.47–4.63) had higher odds of having a major incident than women using private insurance and those without comorbid conditions. During the study period, 0.11% of all abortions in the U.S. resulted in major incidents as seen in EDs.

Conclusions: Abortion-related ED visits comprise a small proportion of women's ED visits. Many abortion-related ED visits may not be indicated or could have been managed at a less costly level of care. Given the low rate of major incidents, perceptions that abortion is unsafe are not based on evidence.

Keywords: Abortion, Emergency department, Emergencies, Hospital admission, Complications, Health policies

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Background

Emergency departments (EDs) are key sites of health-care delivery in the United States (U.S.), with 141.4 million visits in 2014 alone [1], and 55% of these visits are made by women. Although abortion-related complications are rare [2], the surge in legislation aimed at regulating abortion access [3] suggests that complications are common and that abortion is generally unsafe.

Since 2011, state legislatures across the U.S. have passed numerous laws that regulate abortion provision, many requiring abortion providers to obtain local hospital admitting privileges and have transfer agreements with nearby hospitals [3]. These laws are passed under a presumption that they are needed to protect women's health and safety [4, 5] and that hospitalization as a result of abortion is an occurrence frequent enough to necessitate legislation formalizing the relationship between hospitals, abortion providers, and clinics.

National-level estimates of abortion-related ED visits do not exist. However, data from one state suggests that abortion-related ED visits are rare. In a study using data from California's Medicaid program, Upadhyay et al. found that 0.03% of abortions were followed by an immediate ambulance transfer to an ED and 2.6% of abortions were followed by an abortion-related ED visit within 6 weeks of the abortion [2]. Another study that examined all medication abortions done by Planned Parenthood in 2009 and 2010 found an ED treatment rate of 0.10%, although medication abortions represented only about 23% of abortions at the time, and this study included only those ED visits that involved treatment [6]. In a study of outcomes of abortion procedures by family physicians in New York and Philadelphia, 0.3% of first-trimester medication and aspiration abortion patients were referred or went to an ED for assessment [7].

There is a paucity of published national data on the incidence and outcomes of ED visits after abortion. In this study, we examine the frequency of abortion-related ED visits, the frequency of major abortion-related incidents, and the characteristics of abortion-related ED visits in the U.S. using a nationally representative sample of ED visits.

Methods

Study design and data source

We conducted a retrospective observational study of abortion-related ED visits using data from the Nationwide Emergency Department Sample (NEDS), a nationally representative sample of ED visits. NEDS is a database of ED visits from 947 to 964 hospitals across the U.S. per year. Annually it includes more than 30 million unweighted visits, which represent more than 135 million weighted visits. NEDS was developed for the Healthcare Cost and Utilization Project (HCUP) and is maintained by the Agency for Healthcare Research and Quality. Data are available from 2006 onward. For this study, we utilized the five most recent years of data available (2009–2013). The study was certified exempt by the institutional review board of the University of California, San Francisco.

Unweighted visits are data collected on actual visits, which are then weighted proportionately to the total number of ED visits in the country based on the sampling strategy. The NEDS is a stratified single-stage cluster sample of state-level ED data reported to HCUP. Using the American Hospital Association Annual Survey of Hospitals as the target universe, the available data are selected to approximate a 20% stratified sample of all U.S. hospital-based EDs. More details of the sampling of hospitals can be found on the HCUP website [8, 9]. The characteristics used for sample stratification in the NEDS are U.S. region, urban or rural location, teaching status, ownership, and trauma level (see Fig. 1 for region definitions and states contributing data).

The NEDS includes patient-level and hospital-level information. Each ED visit has patient-level demographic characteristics including age, sex, primary and secondary payment source, and zip code-based urbanicity and income quartile. Each ED visit also has clinical characteristics, including up to 15 diagnoses (International Classification of Diseases, 9th Revision [ICD-9] codes), up to 15 procedures or treatments (Healthcare Common Procedure Coding System [HCPCS] and Current Procedural Terminology [CPT] codes), injury codes, admission and discharge status, diagnosis and treatment codes for inpatient care if admitted to the same hospital, and total charges. Each visit also has the corresponding hospital code, and hospital characteristics such as region, trauma level, urban-rural location, and teaching status. In this dataset, 5 of 13 states in the West, 11 of 12 states in the Midwest, 8 of 16 states in the South, and 8 of 9 states in the Northeast were represented in the data. Midwest hospitals were represented the most. The trauma level of a hospital refers to how well equipped it is to provide care to patients with traumatic injuries. Trauma level influences patient composition and was key to sample stratification in the dataset. Hospital ownership was categorized by the data distributor according to information reported in the American Hospital Association Annual Survey Database. Ownership could be governmental, private non-profit, or private for-profit. Hospitals with religious affiliations, including Catholic hospitals, are included, but are not distinguished as such and may fall into private for-profit or private non-profit categories. Federal hospitals (Veterans Affairs and Department of Defense) were not included in the sample. Patient-level and hospital-level weights were also provided to generate nationally representative estimates. HCUP provided weights for the NEDS data and these

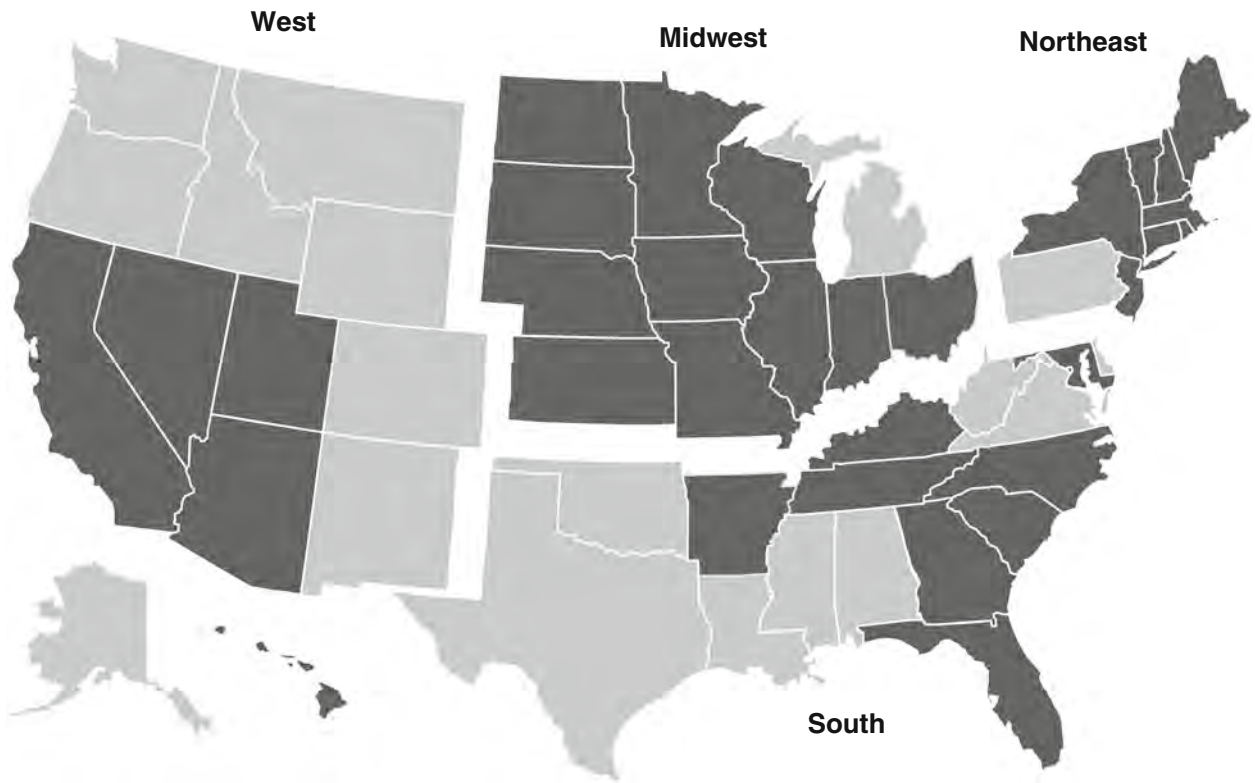

Fig. 1 U.S. regions in the National Emergency Department Sample. States in darker shades contributed data to the National Emergency Department Sample during the study period, 2009–2013

were calculated at the hospital level after sampling by hospital strata. Patient weights were calculated first by stratifying the data by hospital characteristics (region, urbanicity, trauma level, teaching status, and ownership). Within each of these strata, a weight was generated by dividing the total number of ED visits in the U.S. in that year for that stratum (from American Hospital Association data) by the number of ED visits for that stratum in the NEDS data. Weighted data thus represent all ED visits in the U.S. for a year.

Data preparation

We identified all ED visits that had an ICD-9 diagnosis code for abortion (ICD-9 diagnosis codes 635, 636, 637, and 638). We categorized ED visits by abortion relatedness and treatments received, and assessed whether the visit was for a major or minor incident. Visit categorization was based on the previously developed Procedural Abortion Incident Reporting and Surveillance (PAIRS) Framework [10]. Based on procedure codes, visits that were for observation care, repeat procedures (codes present in the dataset were CPT/HCPCS procedure codes 59812, 59820, 59821, 59840, 59841, 59851, 59855, and 59856; and ICD-9 procedure codes 6901, 6902, 6909, 6951, 6952, 6959, 734, and 750), blood transfusions (CPT/HCPCS procedure codes 36430 and P9021; and ICD-9 procedure codes 9903–9905), and abortion-related surgeries (CPT/HCPCS procedure codes 49320, 58662, 58999, 59300, and 59898; and ICD-9 procedure codes 680, 6831, 6839, 6849, 6851, 6859, 6869, and 7491) were systematically coded without individual visit review. Where procedure and diagnosis codes for a visit did not fall into one of these categories, several authors who are emergency medicine physicians or students with physician supervision provided an individual review of each visit following a modified version of the PAIRS framework (see Fig. 2). After a joint review of 100 visits with refinement of the decision rules, the physicians reviewed the remaining uncategorized visits, resulting in 1642 reviewed ED visits in total.

For each reviewed visit, the emergency medicine physicians assigned the reason for the patient's ED visit to one of five categories: abortion-related, concurrent condition, pre-existing condition, not abortion-related, or cannot determine. They classified an ED visit as abortion-related based on the constellation of diagnosis and procedure codes for that visit. Abortion-related visits included adverse events, such as hemorrhage or infection, and symptoms directly related to the procedure, such as abdominal pain and vomiting. Concurrent conditions were defined as

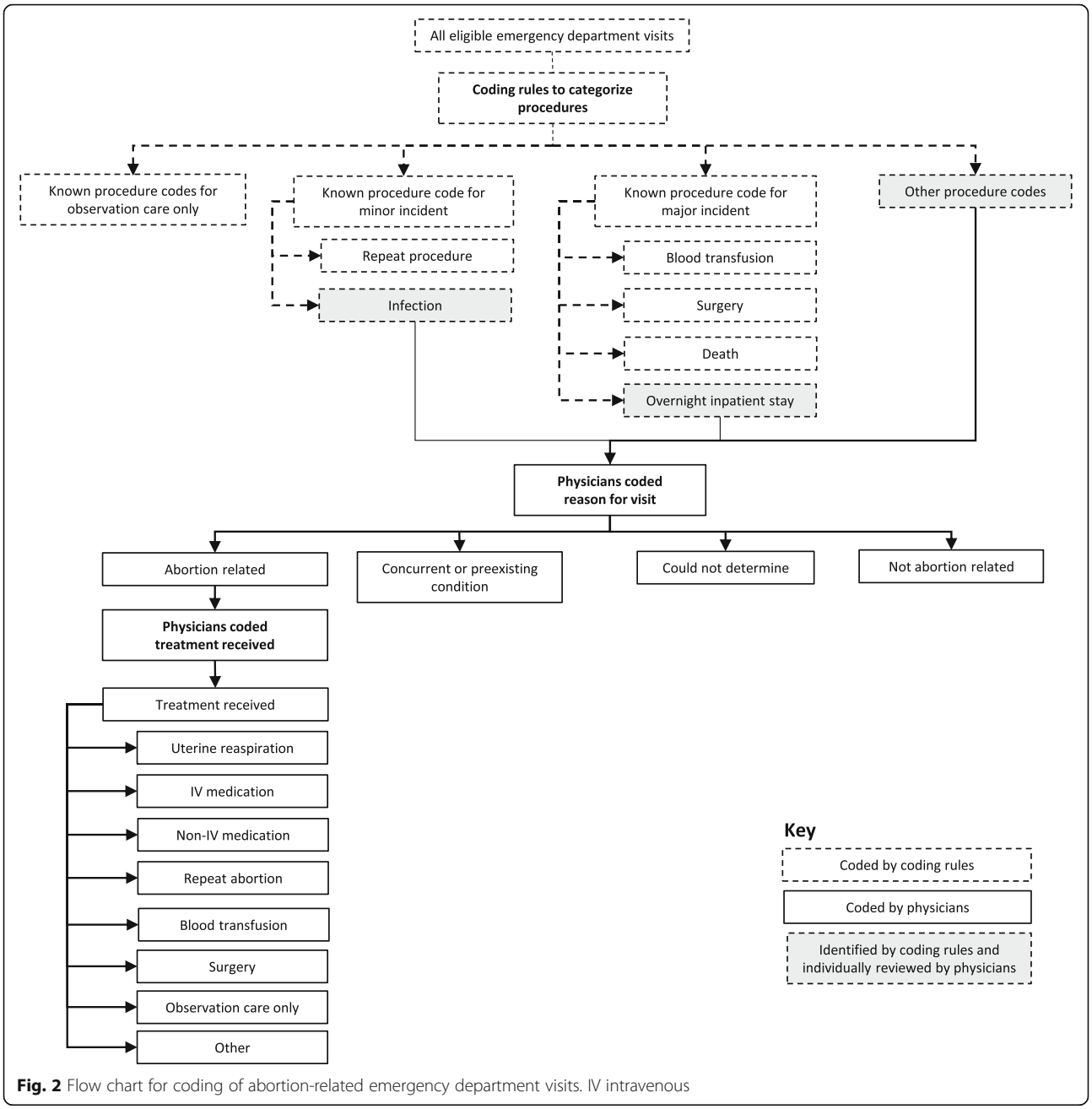

Fig. 2 Flow chart for coding of abortion-related emergency department visits. IV intravenous

conditions that may have been noticed during or exacerbated by abortion, but were not directly caused by the abortion, such as ovarian cysts, vaginitis, urinary tract infection, or anxiety/depression. Pre-existing conditions were defined as chronic conditions such as hypertension or diabetes. The data were also categorized with regards to treatments received for abortion-related complaints. Categories of treatment included uterine reaspiration (which involves suction, not an incision, and does not meet the criteria for surgery), intravenous (IV) and non-IV medication, repeat abortion, blood transfusion, surgery, observation care, or other. The medication category excluded codes for injections or infusion of a therapeutic substance if no accompanying medication was listed. The observation care category included women who had routine testing for their symptoms but did not receive any medications or other treatments. This included women who had IV fluids, blood work, testing for sexually transmitted infections, and diagnostic imaging studies, but no treatments. The NEDS dataset also included information on whether patients were admitted as an inpatient to the same hospital, discharged home, transferred to another facility, or left against medical advice. Among women who were admitted, the reason for visit

and treatment information in their chart was used to determine if the admission was likely abortion-related.

Major and minor incidents were systematically coded, with major incidents defined as those requiring an overnight inpatient stay, blood transfusion, or surgery. Minor incidents were defined as all other incidents that involved an abortion-related diagnosis or treatment. All overnight stays were further reviewed by physicians, and a group of treatments for an abortion-related diagnosis that together required the patient to stay overnight qualified as a major incident. Visits that involved concurrent conditions, pre-existing conditions, or visits that were not abortion-related were categorized as no incident. We identified the prevalence of comorbid conditions based on diagnosis codes. These included three key conditions hypothesized to be associated with abortion-related adverse events: diabetes, hypertension, and having an overweight/obese body mass index (BMI) [11–14].

ED visits were additionally categorized as being potentially indicative of a self-induced abortion. The physician team individually reviewed all abortion-related visits that had diagnosis codes of illegal abortion, failed attempted abortion, and certain injury codes (including poisonings and indications of self-harm). They looked at all of the diagnosis codes for that case and made a clinical judgement based on the group of codes together and their ED experience. Visits that were coded as illegal abortions, particularly those that included injury codes, were more often considered potentially self-induced. In addition, visits that included injury codes consistent with self-induction were categorized as such. Cases which were unlikely to have been abortion-related were removed.

Statistical analysis

We estimated the number of abortion-related ED visits annually in the U.S. and the proportion of ED visits among women of reproductive age (15–49) that were for abortion-related care. We examined the characteristics of the sample and compared these to published estimates of the characteristics of abortion patients [15]. We also described outcomes including treatments received and discharge status. Based on treatments received, ED visits were categorized as being for a major incident, a minor incident, no incident, or that the incident type could not be determined. We then built multivariable logistic regression models to examine the factors associated with major incidents and observation care, controlling for sociodemographic characteristics, comorbidities, and hospital characteristics with the ED visit as the unit of analysis. Per the recommendation of the HCUP, the organization which oversees the NEDS database, sample weights were not used in the multivariable models [16]. We also estimated the proportion of ED visits that were potentially due to attempted self-induced abortion. Because the weighted estimates are nationally representative, we were also able to use published national estimates of abortion incidence [17] to estimate the major incident rate for abortion in the U.S. during the study period. This assumes that the vast majority of major incidents go through an ED evaluation (although we acknowledge that a small percentage do not). For all analyses, we report weighted results unless otherwise specified. Where data were missing, a missing category was retained for all analyses. Statistical significance was set at $P < 0.05$ for all chi-squared tests and adjusted odds ratios (AORs). We used STATA 14 for all analyses.

Results

Among 42,493,214 unweighted visits among women of reproductive age (15–49) during the study period, 6342 visits had an abortion diagnosis. Among these, 70 visits were determined to be unrelated to abortion based on clinician review and 33 visits were duplicates (all variables were identical other than ID number); these 103 visits were excluded, leaving an analytical sample of 6239 unweighted abortion-related ED visits. We did not include an additional 101 visits with abortion diagnoses for women outside the age range of interest (younger than 15 or older than 49).

The final analytical sample corresponded to 27,941 weighted ED visits for abortion-related reasons among 189,480,685 weighted ED visits among women of reproductive age. Thus abortion-related ED visits represented 0.01% of all ED visits among women of reproductive age during the study period. All subsequent results are weighted.

The average age of the population seeking abortion-related ED care was 26, and 12.9% of visits were by women under 20 (Table 1). Women using Medicaid were most common (45.2% of visits), followed by those using private insurance (31.4%), and those who self-paid (17.1%). The population seeking abortion-related ED care was overwhelmingly of urban residence (91.0%). Low-income zip code residences were overrepresented in the sample; 27.5% of women lived in a zip code with the lowest national income quartile, while 20.5% lived in the highest income quartile. Comorbid conditions including diabetes (1.5%), hypertension (3.2%), and overweight/obese BMI (1.8%) were noted in abortion-related ED visits. Hospitals in the South (35.5%) and West (31.7%) had the largest number of abortion-related ED visits. Most visits were to non-trauma or trauma level III hospitals (62.8%) and most were to hospitals in urban locations (92.3%). Visit numbers remained approximately constant throughout the study period. Average ED costs were $4719, with 8.6% of ED visits costing $10,000 or more.

Table 1 Characteristics of abortion-related emergency department visits, 2009–2013 weighted $n = 27,941$

	Weighted *N*	Weighted %	Abortion patients in the U.S., 2014% [15]
Total	27,941	100	100
Patient characteristics			
Age			
15–19	3605	12.9	11.7
20–24	9686	34.7	33.6
25–29	6952	24.9	26.5
30–39	6809	24.4	25.0
40–49	888	0.3	3.1
Primary payer			
Private insurance	8787	31.4	31.3
Medicaid	12,624	45.2	34.6
Medicare	410	1.5	–
Self-pay	4764	17.1	27.6[A]
No charge	188	0.7	–
Other	1049	3.8	6.5[B]
Missing	118	0.4	–
Urban/rural residence			
Urban	25,435	91.0	
Rural	2401	8.6	
Missing	104	0.4	
Zip code-based national income quartile			
First quartile (low)	7686	27.5	65.3[C]
Second quartile	7014	25.1	
Third quartile	7082	25.3	21.7
Fourth quartile (high)	5721	20.5	
Missing	437	1.6	13.0
Comorbidities			
Diabetes	415	1.5	
Hypertension	879	3.1	
Overweight/obese BMI	507	1.8	
Hospital characteristics			
Region			
Northeast	4539	16.2	
Midwest	4627	16.6	
South	9912	35.5	
West	8862	31.7	
Trauma level of hospital			
Level I or II	9429	33.7	
Nontrauma or level III	17,537	62.8	
Not specified	974	3.5	
Urban/rural location of hospital			
Urban	25,796	92.3	
Rural	2145	7.7	
Visit characteristics			
ED visit day			
Weekday	20,640	73.9	
Weekend	7301	26.1	
ED visit season			
Fall	5628	20.1	
Winter	5989	21.4	
Spring	6343	22.7	
Summer	6174	22.1	
Missing	3808	13.6	
Year			
2009	5350	19.1	
2010	5899	21.1	
2011	5448	19.5	
2012	5627	20.1	
2013	5617	20.1	
Total ED charges			
<$1000	2643	9.5	
$1000–$1999	4290	15.4	
$2000–$4999	7188	25.7	
$5000–$9999	3083	11.0	
$10,000+	2407	8.6	
Missing	8330	29.8	

BMI body mass index, *ED* Emergency department
[A]Defined as no coverage
[B]Defined as had either insurance through Healthcare.gov or a different type of insurance
[C]Defined as poor (<100% federal poverty level) or low income (<200% federal poverty level). At the time of the study, the national income median was approximately equal to 200% federal poverty level

Half of abortion-related visits received observation care only (50.6%, 95% confidence interval, 95% CI 49.3–51.9%) (Table 2). Nearly a third of visits resulted in a uterine reaspiration or repeat abortion procedure (32.2%, 95% CI 31.0–33.4%). Medications were used in 16.1% of ED visits (95% CI 15.2–17.1%): IV-medications in 13.7% of visits and non-IV medications in 7.4% of visits. The most commonly administered medication was pain medication (10.4%, 95% CI 9.7–11.2%), followed by anti-nausea medication (7.4%, 95% CI 6.8–8.1%) and antibiotics (3.2%, 95% CI 2.8–3.7%). A minority of ED visits involved blood transfusion (5.0%, 95% CI 4.5–

Table 2 Diagnoses and treatments received, weighted $n = 27,941$

	Weighted *N*	Weighted percentage	Weighted percentage 95% confidence interval
Incident type			
Minor incident[A]	10,089	36.1	34.9–37.4
Major incident[B]	5673	20.3	19.3–21.3
No incident	16,087	57.6	56.3–58.8
Could not be determined	426	1.5	1.2–1.9
Treatment received			
Repeat abortion or uterine reaspiration	8994	32.2	31.0–33.4
IV medications	3838	13.7	12.9–14.6
Non-IV medications	2072	7.4	6.8–8.1
Unspecified type medication	232	0.8	0.6–1.1
Type of medication			
Pain	2912	10.4	9.7–11.2
Nausea	2080	7.4	6.8–8.1
Antibiotics	895	3.2	2.8–3.7
Other	1361	4.9	4.3–5.5
Blood transfusion	1397	5.0	4.5–5.6
Surgery	267	1.0	0.7–1.2
Observation care only	14,126	50.6	49.3–51.9
Other treatment[C]	81	0.3	0.1–0.5
Discharge status			
Routine discharge from ED	20,992	75.1	74.0–76.2
Admission to hospital	6136	22.0	20.9–23.0
Transferred to other medical facility	464	1.7	1.4–2.0
Left against medical advice	277	1.0	0.8–1.3
Other or unknown	57	0.2	0.1–0.4
Death	15	0.05	0.02–0.2

ED emergency department, *IV* intravenous
[A]Minor incident includes all other incidents that involved an abortion-related diagnosis or treatment, such as those requiring medication or repeat procedure
[B]Major incident includes those requiring overnight inpatient stay, blood transfusion, or surgery
[C]Other treatments include suture of laceration to the cervix, laminaria insertion, and abscess drainage

5.6%), abortion-related surgery (1.0%, 95% CI 0.7–1.2%), or other treatments (0.3%, 95% CI 0.2–0.5%), and 19.4% (95% CI 18.5–20.5%) of all abortion-related visits resulted in an overnight inpatient stay at the same hospital. Major incidents, treated with blood transfusion, surgery, or overnight inpatient stay, accounted for 20.3% (95% CI 19.3–21.3%) of all visits. Minor incidents accounted for 36.1% (95% CI 34.9–37.4%) of visits.

Three-quarters (75.1%) of abortion-related ED visits resulted in discharge from the ED. Another 21.2% were admitted to the same hospital for abortion-related reasons and 0.8% were admitted for non-abortion-related reasons. For the remaining 3%, the disposition was unknown or they were transferred to another medical facility or left against medical advice. Among all abortion-related ED visits over the 5 years of data ($n = 27,941$), 15 ended in the patient's death.

Several demographic and hospital factors were significantly associated with major incidents in a multivariable model (Table 3). Women over 30 were more likely than women aged 20–24 to have major incidents ($P < 0.001$), and women using Medicaid ($P = 0.004$) were more likely than women with private insurance to have a major incident. Women who paid out of pocket for the ED visit were less likely to have a major incident than women with private insurance ($P = 0.001$). The presence of any of the three examined comorbid conditions was associated with more than double the odds of a major incident compared to women without those comorbid conditions ($P < 0.01$). ED visits at trauma hospitals were more likely to be for major incidents than those at non-trauma hospitals ($P < 0.001$). ED visits in all regions were significantly more likely to be for a major incident than those in the Midwest ($P < 0.001$). There was a decreasing trend in major incidents over time. Similar significant relationships were found for factors associated with receipt of observation care only, but factors associated with increased likelihood of major incidents were associated with a lower likelihood of requiring observation care only. Two notable exceptions are a significantly higher likelihood of observation care only in the West compared to the Midwest ($P < 0.001$) and the absence of a trend over time for receipt of observation care only.

We used published rates of the total number of abortions to calculate the percentage of all abortions seen in an ED that resulted in a major incident. During the 5-year study period, there were an estimated 5,282,500 total abortions in the U.S. [17]. Using this number as the denominator, we estimate the rate of major incidents seen in EDs for abortion in the U.S. is 0.11%, or 108 per 100,000 abortions.

We identified 390 ED visits that represented potential self-induced abortion and accounted for 1.4% of abortion-related ED visits during the study period (95% CI 1.1–1.7%). There were slightly higher rates of potential self-induced abortion in the South (2.0%) than in the Midwest (1.0%), West (1.1%), and Northeast (1.3%) ($P = 0.05$) (Table 4). There were no time trends or other factors associated with self-induced abortion.

Discussion

We found that abortion-related ED visits comprised 0.01% of ED visits among women aged 15–49. In other

Table 3 Factors associated with major incidents and observation care only, weighted $n = 27,941$

	Major incident	Observation care
	Adjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Age		
15–19	0.94 (0.74–1.21)	1.18 (0.97–1.42)
20–24	Reference	Reference
25–29	1.08 (0.91–1.28)	0.81** (0.71–0.94)
30–39	1.49*** (1.24–1.79)	0.72*** (0.62–0.83)
40–49	1.75** (1.21–2.53)	0.55*** (0.39–0.77)
Primary payer		
Private insurance	Reference	Reference
Medicaid	1.28** (1.08–1.52)	0.83* (0.72–0.96)
Medicare	1.30 (0.79–2.15)	0.94 (0.55–1.62)
Self-pay	0.66** (0.52–0.85)	1.33** (1.12–1.57)
No charge	1.20 (0.39–3.69)	0.73 (0.34–1.59)
Other	1.35 (0.93–1.97)	0.95 (0.68–1.31)
Missing	0.32 (0.06–1.70)	0.85 (0.36–2.00)
Urban/rural residence		
Urban	Reference	Reference
Rural	1.02 (0.59–1.75)	0.86 (0.58–1.28)
Missing	1.67 (0.58–4.75)	0.43 (0.14–1.28)
Zip code-based income quartile		
First quartile	Reference	Reference
Second quartile	1.11 (0.90–1.36)	0.95 (0.82–1.10)
Third quartile	0.93 (0.75–1.15)	0.89 (0.76–1.04)
Fourth quartile	1.04 (0.82–1.32)	0.92 (0.77–1.11)
Missing	0.90 (0.46–1.75)	0.96 (0.54–1.70)
Diabetes indicated		
No	Reference	Reference
Yes	2.47** (1.42–4.31)	0.28*** (0.14–0.54)
Hypertension indicated		
No	Reference	Reference
Yes	3.79*** (2.46–5.83)	0.52** (0.34–0.80)
Overweight/obese BMI indicated		
No	Reference	Reference
Yes	4.63*** (2.65–8.10)	0.18*** (0.10–0.33)
Hospital characteristics		
Region		
Northeast	1.89*** (1.32–2.71)	0.65** (0.48–0.88)
Midwest	Reference	Reference
South	2.11*** (1.53–2.90)	0.69** (0.54–0.86)
West	1.80*** (1.30–2.49)	2.19*** (1.71–2.80)
Trauma level of hospital		
Level I or II	1.52*** (1.23–1.88)	0.81* (0.68–0.98)
Nontrauma or level III	Reference	Reference
Not specified	1.40 (0.88–2.23)	0.86 (0.55–1.35)
Urban or rural location of hospital		
Urban	Reference	Reference
Rural	0.65 (0.36–1.17)	1.20 (0.77–1.86)
Year		
2009	Reference	Reference
2010	0.85 (0.68–1.07)	1.04 (0.85–1.28)
2011	0.77* (0.61–0.98)	1.09 (0.88–1.36)
2012	0.73** (0.57–0.92)	0.95 (0.76–1.19)
2013	0.71** (0.56–0.90)	0.87 (0.70–1.08)

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$
BMI body mass index

words, 14 of every 100,000 ED visits among women aged 15–49 were for abortion-related reasons. The majority (51%) of these were visits involving observation care only.

These data also allowed us to estimate the national major incident rate after an abortion. The rate of 0.11% (108 per 100,000) abortion patients is slightly higher than the rate of 0.05% found in a study of first trimester abortion patients in California [18], and slightly lower than the rate of 0.23% found in a study of all abortions covered by California's Medicaid program [2]. While not all abortion-related incidents lead to an ED visit and thus, are not reflected in this estimate, we believe that the vast majority of major incidents (those involving a blood transfusion, surgery, or hospital admission) are reflected here. Those that would be missed from this analysis are cases that skip the ED and are directly admitted to a hospital or an outpatient surgicenter (usually for scheduled hospitalization) and complications arising from the small proportion (4%) of abortions done in hospitals [17] and are then directly admitted. Thus, the major incident rate may be slightly underestimated.

The major incident rate for abortion (0.1%) is lower than the published rates for pregnancy (1.4%) [19], as well as other common procedures such as colonoscopy (0.2%) [20], wisdom tooth removal (1.0%) [21], and tonsillectomy (1.4%) [22]. Abortion care is, thus, safer than many other unregulated outpatient procedures. Additionally, we found 15 deaths between 2009 and 2013, which is slightly lower than the total number of abortion-related deaths reported in 2009–2012, the most recent years available ($n = 24$) [23].

Notably, the majority of visits involved observation care only, which is consistent with a previous study [2].

Table 4 Potential self-induced abortion, by region

	Weighted *N*	Weighted percentage of all abortion-related emergency department visits	Weighted percentage 95% confidence interval	Chi-squared test *P* value
Overall	390	1.4	1.1–1.7	
Region				0.048
Northeast	58	1.3	0.7–2.2	
Midwest	44	1.0	0.5–1.9	
South	195	2.0	1.5–2.6	
West	94	1.1	0.7–1.6	

Patients experience a range of post-abortion symptoms, including ongoing uterine cramping and bleeding for up to 3 weeks after the abortion. Patients may not realize that this is normal. Some women do not start to bleed until several days after the abortion, while some stop bleeding and then start again. Increased cramping and bleeding could start several days after the abortion. Patients may not be given ample information about what to expect or they may have trouble differentiating normal post-abortion symptoms from signs of a complication. Patient visits to EDs for non-urgent care have the potential to be costly to the health system. Such visits could be due to several reasons and little research has been done on factors that contribute to patients' decisions to visit an ED after abortion. EDs offer 24-h access to care compared to abortion facilities, which have relatively limited hours and may require an appointment [24]. The long distances that many women across the U.S. must travel to reach an abortion provider may make return visits for follow-up too arduous [25, 26]. Indeed, research found that patients who travel longer distances to reach an abortion provider are more likely to visit an ED for follow-up care or to manage subsequent symptoms and less likely to return to the original abortion provider [27]. We note that patients presenting to the ED were disproportionately of urban residence (91% in the sample compared to 81% of the U.S. population) [28]. This is likely explained in that 91% of abortion patients live in urban areas [29] and 92% of EDs in the sample were in urban areas, attracting mainly local residents who may find them convenient geographically.

Post-abortion visits to the ED may also be driven by stigma, worry, or distrust of abortion providers. A perception that abortion is unsafe [30–32] may lead women to worry about mild symptoms, such as cramping and bleeding, even though they are an expected result of abortion. Such perceptions may stem from abortion portrayals in the media and popular culture. A study of abortion-related storylines in fictional American television shows found a major incident rate of 34% [33], over 34,000% greater than the real-life major incident rate of 0.1% found here. The long-term consequences of these fictional abortions were much more likely to be severe, including frequent depictions of negative mental health sequelae, infertility, and even death.

Women using Medicaid had higher odds of major incidents than those not using Medicaid and lower odds of observation care. In this context, insurance type may be a proxy for socioeconomic status, as women requiring Medicaid are low income and as a result, face a multitude of barriers to accessing health care and are known to have poorer health status, including multiple chronic conditions, than women with private insurance. Women who were self-pay were less likely to have major incidents and more likely to receive observation care only, suggesting that patients without healthcare coverage may not have been given treatments to reduce patient costs.

We found that the pre-existing chronic conditions that have previously been suspected to be associated with major abortion-related incidents were indeed associated with a significantly higher rate of those incidents in this sample. While there is limited previous research on the impact of chronic health conditions on the risk of abortion complications, it is well established that women with chronic conditions are more likely to have pregnancy-related complications [34]. Our findings are consistent with provider guidance that suggests women with multiple chronic medical conditions may be at increased risk [35], but conflicting with previous studies that find that obesity and chronic health conditions confer no increased risk among women having abortions [11–14]. This increased risk might be explained in that women who had overnight inpatient stays (one of the categories of a major incident) were more likely to have their obesity or other chronic diseases documented in their charts than those who did not have an overnight stay.

We found some cases of potential self-induced abortions using such means as poisoning or other methods of self-harm. While self-induced abortions are safe when appropriate dosages of mifepristone and misoprostol or misoprostol alone are used, other methods are hazardous, as evidenced by ED visits. Rates were highest in the South, which is known to have the most barriers to abortion access, including the fewest providers [17, 26],

and the most state-level restrictions. States that are hostile to abortion may see more ED visits due to self-induced abortion than non-hostile states, potentially due to stigma, protesters, and other barriers to in-clinic abortion.

This study included a large, nationally representative sample of ED visits, allowing us to draw national- and regional-level conclusions about abortion safety. However, using billing codes to understand the nature of the ED visit can be imprecise and incomplete. The estimates produced here may be conservative if patients did not report having had an abortion due to fear of stigmatization or if relevant diagnosis and procedure codes were not reported or were systematically misreported. The lack of full clinical data to determine abortion relatedness could cause errors. For example, the visits in this study could include cases of miscarriage. Likewise, this study may miss abortion-related incidents that were inaccurately coded as a miscarriage.

Conclusions

These new findings can inform policy debates regarding abortion regulation in the U.S. Regulations on abortion provider or facility relationships to hospitals or EDs should be considered in light of their relative impact on improving women's health. Because abortion-related ED visits comprise a very small proportion of women's ED visits, and the rate of major incidents is very low, regulations on abortion are unlikely to have any impact on women's health outcomes. Many abortion-related ED visits are for observation only and may not be indicated or could be managed at a less costly level of care. Perceptions that abortion is unsafe are not based on evidence.

Abbreviations

AOR: Adjusted odds ratio; BMI: Body mass index; CI: Confidence interval; CPT: Current Procedural Terminology; ED: Emergency department; HCPCS: Healthcare Common Procedure Coding System; HCUP: Healthcare Cost and Utilization Project; ICD-9: International Classification of Diseases, 9th Revision; IV: Intravenous; NEDS: Nationwide Emergency Department Sample; PAIRS: Procedural Abortion Incident Reporting and Surveillance; U.S.: United States

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Availability of data and materials

The HCUP databases are available for purchase online through the HCUP Central Distributor. More information is available here: https://www.hcup-us.ahrq.gov/tech_assist/centdist.jsp.

Authors' contributions

UDU, NEJ, and AFC conceived and designed the study. NEJ acquired the data and led the data analysis. RB, CT, AM, and AJM conducted the review and analysis of records. NEJ and UDU drafted the manuscript. All authors contributed to interpretation of the data, revised the draft manuscript for important intellectual content, and approved the final version.

Ethics approval and consent to participate

This study was approved by the institutional review board of the University of California, San Francisco (16-20371).

Consent for publication

No consent for publication was required.

Competing interests

The authors declare that they have no competing interests.

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Effectiveness and safety of telehealth medication abortion in the USA

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Check for updates

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Telehealth abortion has become critical to addressing surges in demand in states where abortion remains legal but evidence on its effectiveness and safety is limited. California Home Abortion by Telehealth (CHAT) is a prospective study that follows pregnant people who obtained medication abortion via telehealth from three virtual clinics operating in 20 states and Washington, DC between April 2021 and January 2022. Individuals were screened using a standardized no-test protocol, primarily relying on their medical history to assess medical eligibility. We assessed effectiveness, defined as complete abortion after 200 mg mifepristone and 1,600 µg misoprostol (or lower) without additional intervention; safety was measured by the absence of serious adverse events. We estimated rates using multivariable logistic regression and multiple imputation to account for missing data. Among 6,034 abortions, 97.7% (95% confidence interval (CI) = 97.2–98.1%) were complete without subsequent known intervention or ongoing pregnancy after the initial treatment. Overall, 99.8% (99.6–99.9%) of abortions were not followed by serious adverse events. In total, 0.25% of patients experienced a serious abortion-related adverse event, 0.16% were treated for an ectopic pregnancy and 1.3% abortions were followed by emergency department visits. There were no differences in effectiveness or safety between synchronous and asynchronous models of care. Telehealth medication abortion is effective, safe and comparable to published rates of in-person medication abortion care.

In 2021, the US Food and Drug Administration (FDA) removed the in-person dispensing requirement on mifepristone, the first drug used in a medication abortion. This ruling allowed clinicians to begin offering a 'no-test' telehealth model of medication abortion care. Clinicians could now offer entirely remote consultations, using the patient's self-reported medical history instead of ultrasonography or other tests to screen for medical eligibility.

Moving abortion out of the clinic reduced travel, cost and stigma-related barriers and increased convenience for patients[1,2]. While telehealth abortion is usually conducted through synchronous communication, with a real-time scheduled videoconference appointment with the patient, some virtual clinics rely on entirely asynchronous communication, using secure text messaging without a scheduled interaction. Follow-up for both models is usually asynchronous, through secure text messaging.

This expansion of services became critical after the June 2022 Supreme Court Dobbs v. Jackson Women's Health Organization decision allowed states to ban abortion. In states such as Illinois, Kansas and Colorado, where abortion remained legal but neighboring states banned abortion, clinics experienced large increases in patient

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volume[3]. Telehealth became vital to meeting increased demand by reducing appointment waiting times and serving patients from states with abortion bans[4]. Some individuals from US states with an abortion ban use methods such as mail forwarding and mailing medications to a friend or Post Office box close to the border in states where abortion is permitted, minimizing the travel required[5]. Additionally, some clinicians have begun to use the legal protections of their state's "shield laws" to provide medication abortion via telehealth to patients in banned states[6].

However, access to mifepristone for medication abortion has been under threat, with a federal court ruling to reverse FDA regulatory approvals of mifepristone, including the 2021 decision that allowed telehealth for abortion to continue even after the pandemic. This ruling was issued despite multiple FDA reviews and abundant evidence demonstrating the effectiveness and safety of mifepristone[7]. According to the mifepristone label, 97.4% of 16,794 patients in US clinical trials of in-person medication abortion had a complete abortion and less than 0.5% had a serious adverse event[8].

While decades of evidence support the effectiveness and safety of mifepristone provided in person, the evidence supporting no-test direct-to-patient telehealth abortion is more limited. Before 2021, US research on the effectiveness and safety of telehealth abortion was limited to clinic-to-clinic[9–11] or direct-to-patient models that required pre-abortion ultrasonography or other tests[12]. To date, only five US studies have examined the outcomes of no-test direct-to-patient telehealth abortion models; four of these had small (fewer than 350) samples of patients receiving such care; thus, they were underpowered to examine outcomes as rare as serious adverse events[13–16]. The fifth study was a retrospective examination of no-test medication abortion provided either in-person or by telehealth and mail. Among 3,779 medication abortions, 95% were complete without procedural intervention and 0.5% experienced a serious adverse event. Effectiveness and safety were similar whether medications were dispensed in-person or by mail[17,18]. However, this study did not report the effectiveness and safety outcomes of asynchronous telehealth abortion.

In this study, we used data from the California Home Abortion by Telehealth (CHAT) study to follow a large sample of patients across the US from three virtual clinics to estimate the effectiveness and safety of medication abortion care provided via telehealth. Clinicians provided telehealth abortion care via either synchronous (video) or asynchronous (secure text messaging) methods. They screened patients using a published, standardized no-test protocol, primarily relying on patient medical history to assess medical eligibility[19]. Patients who had any risk factors for or symptoms of ectopic pregnancy or were potentially beyond the gestational limit of the virtual clinic were referred for pre-abortion ultrasonography. Eligible patients received 200 mg mifepristone and 800 or 1,600 µg buccal or vaginal misoprostol via mail order pharmacy. Outcome data were collected by scheduled follow-up interactions conducted remotely 3–7 days after intake and again 2–4 weeks after medication administration (Fig. 1). Our primary aim was to assess the effectiveness and safety of telehealth medication abortion care. Our secondary aim was to compare effectiveness and safety outcomes between synchronous and asynchronous models of telehealth.

Results

We received electronic medical records for 6,974 encounters. Among those, 6,154 patients met the eligibility criteria and had abortion medications dispensed to them in 20 states and Washington, DC. We excluded cases where the patient took neither mifepristone nor misoprostol (n = 120) leaving 6,034 patients in the analytical sample (Fig. 2). Among these, 1,600 patients provided supplementary self-reported data on their outcomes via surveys (Extended Data Table 1).

All patients were pregnant and seeking abortion. Half (50.3%) were 30 years or older and 4.6% were aged under 20 years (Table 1). Race, ethnicity or ethnic grouping was unknown for one-third (34.3%)

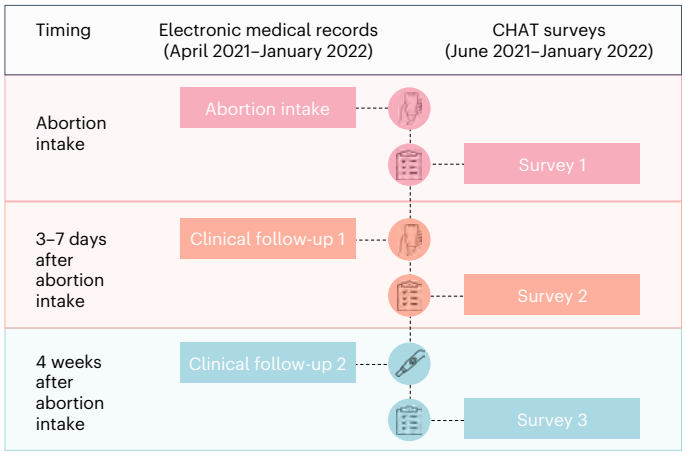

Fig. 1 | CHAT study data sources. Timing and content of the electronic medical records and survey data analyzed in the CHAT study.

of patients because one of the clinics did not record these data in their medical records for the first half of the study period. Among the subsample with known race, ethnicity or ethnic grouping, nearly two-thirds (62.7%) were white. Most (84.3%) patients had pregnancy durations under 7 weeks (≤49 days). Medical records did not document patient sex or gender.

Overall, 72.3% of patients received asynchronous care. Among patients of the clinic that offered asynchronous care but allowed patients to request a phone or video call, 0.3% requested a call with the provider. Patients who were younger (100.0% for 16–18 years, 79.3% for 18–19 years), Asian, Native Hawaiian or Pacific Islander (82.3%), Middle Eastern or North African (80.0%), living in an urban area (72.7%) and who had pregnancy durations over 56 days (74.8% for 50–56 days, 99.6% for 57–63 days and 100.0% for 64–70 days) were more likely to have received asynchronous care.

Of the sample, 76% (4,613 of 6,034) of cases had any follow-up contact with the virtual clinic or by surveys (Fig. 2). Abortion outcomes were known (ascertained using a test or the patient's history) for 74% (4,454 of 6,034) of the analytical sample. There were few sociodemographic characteristics associated with unknown outcomes. Outcomes were less likely to be known for American Indian or Alaska Native patients (57.1%), Middle Eastern or North African patients (64.0%), patients with a previous birth (70.4%), patients with a pregnancy duration of 57–63 days (66.7%) and 64–70 days (68.4%), and patients receiving asynchronous care (69.6%) (Extended Data Table 2). Among patients with unknown outcomes, two requested abortion pill reversal after they took mifepristone but before misoprostol. Both were advised that evidence-based reversal treatment does not exist and referred to urgent in-person care. No further information on their outcomes was available.

Effectiveness

Overall, results from both the complete case analysis and the imputed models found that 97.7% (95% confidence interval (CI) = 97.2–98.1%) of abortions were complete without a subsequent known intervention or ongoing pregnancy after initial treatment (Table 2 and Extended Data Table 3). The effectiveness of synchronous and asynchronous telehealth was similar; in the complete case analysis effectiveness was 98.3% (95% CI = 97.5–99.0%) in the synchronous group and 97.4% (95% CI = 96.9–98.0%) in the asynchronous group. In the final imputed analysis, effectiveness was 98.3% (95% CI = 97.7–99.0%) in the synchronous group and 97.4% (95% CI = 96.9–98.0%) in the asynchronous group. Effectiveness also did not differ according to patient age, pregnancy duration, race, ethnicity or ethnic grouping, urbanicity,

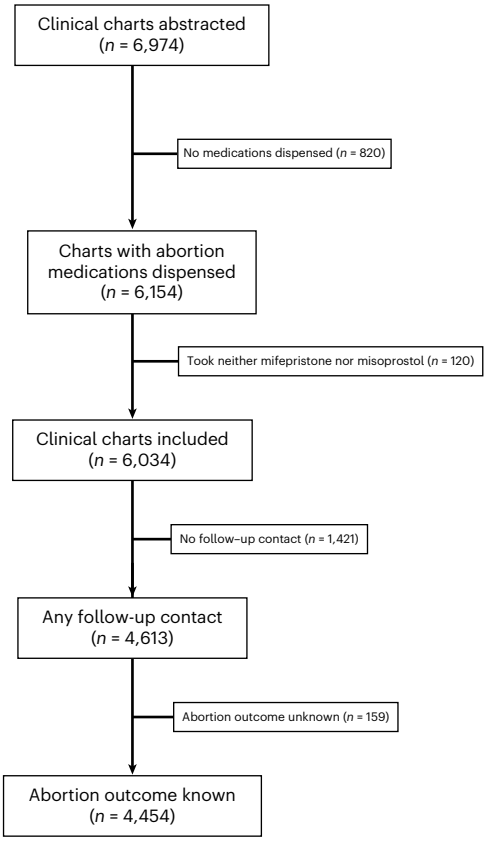

Fig. 2 | Patient flow chart. Patient flow chart depicting the exclusion criteria.

previous birth, previous abortion or whether the patient had screening ultrasonography.

Among the 2.3% (95% CI = 1.9–2.8%) of patients whose abortion was not initially complete, 0.56% were treated with more than 200 mg mifepristone, more than 1,600 µg misoprostol or other uterotonic medication to complete the abortion, 1.4% were treated with an aspiration or other abortion procedure, 0.16% were treated for an ectopic pregnancy and 0.94% had a confirmed or suspected continuing pregnancy (Table 3).

Overall, six (0.16%) patients had ectopic pregnancies; three (0.12%) were suspected ectopic pregnancies treated with methotrexate; one (0.07%) was an ectopic pregnancy treated with an unknown treatment; one (0.12%) was a cesarean scar ectopic pregnancy treated with an unknown treatment; and one (0.09%) was a ruptured ectopic pregnancy treated with a salpingectomy.

Safety

Overall, the rate of abortions that were not followed by a serious adverse event was 99.7% (95% CI = 99.5–99.8%) in the complete case analysis and 99.8% (95% CI = 99.6–99.9%) in the final imputed model (Table 2 and Extended Data Table 3). Safety was similar between patients who received synchronous and asynchronous care; in the complete case analysis, the safety rate was 99.7% (95% CI = 99.4–100.0%) in the synchronous group and 99.6% (95% CI = 99.4–99.9%) in the asynchronous group. In the final imputed model, safety was 99.8% (95% CI = 99.5–100.0%) among synchronous patients and 99.7% (95% CI = 99.6–99.9%) among asynchronous patients. In the final imputed models, safety was lower among Black or African American patients (99.3%, 95% CI = 98.7–100.0%) than among white patients (99.8%, 95% CI = 97.0–100.0%). No other factors were significantly associated with reduced safety.

Among the 0.25% of patients who experienced a serious adverse event, 0.10% received blood transfusions and 0.02% had abdominal surgery to treat a ruptured ectopic pregnancy; 0.17% of patients had hospital admissions requiring overnight stays. Among the ten (0.17%) hospital admissions, four (0.12%) received inpatient aspiration procedures, two (0.10%) were treated for infection and received an aspiration, one (0.09%) involved a blood transfusion and aspiration, one (0.09%) underwent surgery to treat a ruptured ectopic pregnancy, one (0.08%) was treated with intravenous antibiotics and one (0.09%) had a uterine infection treated with unknown treatment.

Other outcomes

Overall, 1.3% (95% CI = 1.1–1.6%) of abortions were followed by a known emergency department visit, 38.3% of which resulted in no treatment. Emergency department visits were similar between synchronous patients (1.2%, 95% CI = 0.7–1.7%) and asynchronous patients (1.4%, 95% CI = 1.0–1.7%). We identified no cases where, at the subsequent follow-up, it was determined that the abortion occurred beyond 70 days' gestation.

Sensitivity analyses

The first sensitivity analysis, where we conservatively categorized the 25 patients who were referred to in-person care and were subsequently lost to follow-up as requiring additional intervention to complete the abortion, resulted in effectiveness rates that were not significantly different from the primary analysis; overall 97.1% (95% CI = 96.5–97.6%), with 98.1% (95% CI = 97.3–98.8%) among synchronous patients and 96.7% (95% CI = 96.0–97.3%) among asynchronous patients.

In the second sensitivity analysis modeling effectiveness, we considered patients as having complete abortions regardless of the amount of misoprostol they received, which is consistent with the Medical Abortion Reporting of Efficacy (MARE) guidelines[20]. (Total misoprostol dosages according to pregnancy duration are reported in Extended Data Table 4.) This also resulted in effectiveness rates that were not significantly different from the primary analysis: 97.9% (95% CI = 97.4–98.3%) overall, 98.4% (95% CI = 97.8–99.0%) among patients who received synchronous care and 97.7% (95% CI = 97.1–98.2%) among patients who received asynchronous care.

The third sensitivity analysis, where we examined effectiveness and safety only among the subsample of patients with supplementary self-reported data on their outcomes via surveys in addition to standard clinical follow-up (n = 1,600), resulted in effectiveness rates that were not significantly different from the primary analysis: 96.7% (95% CI = 95.7–97.6%), with 97.1% (95% CI = 95.6–98.6%) among those who received synchronous care and 96.4% (95% CI = 95.2–97.6%) among those who received asynchronous care. This sensitivity analysis resulted in a similar safety rate of 99.3% (95% CI = 98.9–99.7%), and rates of 99.4% (95% CI = 98.7–100.0%) among those who received synchronous care versus 99.3% (95% CI = 98.8–99.8%) of those who received asynchronous care.

In the fourth sensitivity analysis, we conducted delta-adjusted pattern-mixture modeling to examine the potential impact of loss to follow-up on the observed results (Extended Data Table 5). Across a range of delta values, we found that the results were largely consistent with the main analysis. Under an extreme scenario in which those with unknown outcomes had ten times the odds of an incomplete abortion or serious adverse event, effectiveness for the entire sample would be 93.3% (95% CI = 92.1–94.5%) and safety would be 98.9% (95% CI = 98.3–99.4%). Under this scenario, effectiveness would be higher in the synchronous group than the asynchronous group, but there would be no differences in safety. Under the opposite and also extreme scenario in which those with unknown outcomes had ten times lower odds of an incomplete abortion, effectiveness would be 98.2% (95% CI = 97.9–98.6%) and safety would be 99.7% (95% CI = 99.6–99.9%), with no significant differences in effectiveness and safety between synchronous and asynchronous groups.

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Table 1 | Characteristics of the individuals who obtained synchronous and asynchronous telehealth medication abortion care

Characteristics	Overall	Synchronous	Asynchronous	
	n=6,034(100.0%)	*n*=1,674(27.7%)	*n*=4,360(72.3%)	
	n (column %)	*n* (row %)		*P*
Patient age at abortion intake				
16–17 years	30 (0.5%)	0 (0%)	30 (100.0%)	<0.001
18–19 years	246 (4.1%)	51 (20.7%)	195 (79.3%)	
20–24 years	1,215 (20.1%)	324 (26.7%)	891 (73.3%)	
25–29 years	1,505 (24.9%)	422 (28.0%)	1,083 (72.0%)	
30–34 years	1,587 (26.3%)	476 (30.0%)	1,111 (70.0%)	
>34 years	1,451 (24.0%)	401 (27.6%)	1,050 (72.4%)	
Race, ethnicity or ethnic grouping				
American Indian or Alaska Native	35 (0.6%)	9 (25.7%)	26 (74.3%)	<0.001
Asian, Native Hawaiian or Pacific Islander	271 (4.5%)	48 (17.7%)	223 (82.3%)	
Black or African American	413 (6.8%)	170 (41.2%)	243 (58.8%)	
Hispanic or Latinx	339 (5.6%)	135 (39.8%)	204 (60.2%)	
Middle Eastern or North African	25 (0.4%)	5 (20.0%)	20 (80.0%)	
White	2,491 (41.3%)	746 (29.9%)	1,745 (70.1%)	
Multiracial	390 (6.5%)	100 (25.6%)	290 (74.4%)	
Unknown	2,070 (34.3%)	461 (22.3%)	1,609 (77.7%)	
Urbanicity				
Suburban or rural	600 (9.9%)	189 (31.5%)	411 (68.5%)	0.030
Urban	5,434 (90.1%)	1,485 (27.3%)	3,949 (72.7%)	
Previous abortion				
No previous abortion	3,053 (50.6%)	945 (31.0%)	2,108 (69.0%)	<0.001
One or more previous abortions	1,523 (25.2%)	574 (37.7%)	949 (62.3%)	
Unknown	1,458 (24.2%)	155 (10.6%)	1,303 (89.4%)	
Previous births				
No previous birth	2,325 (38.5%)	721 (31.0%)	1,604 (69.0%)	<0.001
One or more previous births	2,144 (35.5%)	879 (41.0%)	1,265 (59.0%)	
Unknown	1,565 (25.9%)	74 (4.7%)	1,491 (95.3%)	
Pregnancy duration at abortion intake				
<35 days	1,732 (28.7%)	566 (32.7%)	1,166 (67.3%)	<0.001[a]
35–49 days	3,356 (55.6%)	960 (28.6%)	2,396 (71.4%)	
50–56 days	583 (9.7%)	147 (25.2%)	436 (74.8%)	
57–63 days	261 (4.3%)	1 (0.4%)	260 (99.6%)	
64–70 days	98 (1.6%)	0 (0%)	98 (100.0%)	
Unknown	4 (0.1%)	0 (0%)	4 (100.0%)	
Had confirmatory pre-abortion ultrasonography				
No pre-abortion ultrasonography	5,548 (91.9%)	1,527 (27.5%)	4,021 (72.5%)	0.198
Had pre-abortion ultrasonography	486 (8.1%)	147 (30.2%)	339 (69.8%)	
Known abortion outcome				
Abortion outcome unknown	1,580 (26.2%)	256 (16.2%)	1,324 (30.4%)	<0.001
Abortion outcome known	4,454 (73.8%)	1,418 (31.8%)	3,036 (69.6%)	

[a]*P* value was derived from a two-sided Fisher's exact test. *P* values were derived from two-sided chi-squared tests, unless otherwise noted.

Discussion

In this large prospective cohort study, telehealth medication abortion provided primarily without tests was effective and safe. The overall 98% effectiveness rate of our primary analysis, and the effectiveness rates from the sensitivity analyses, were similar to previous large US studies of in-person medication abortion care, which found rates of 95–98%[21–24]. The serious adverse event rate of 0.25% and ectopic pregnancy rate of 0.14% were also similar to previous studies of in-person medication abortion care, which found adverse event rates of 0.2–0.5%, and ectopic pregnancy rates of 0.2%[8,23–25]. Both effectiveness and safety rates were similar to the rates for medication abortions with in-person screening tests as published on the FDA label (Fig. 3)[8].

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Table 2 | Rate of effectiveness and safety according to the characteristics of the sample, derived from complete case and multiple imputation analyses

Characteristics	Effectiveness				Safety			
	Unadjusted complete case rate		Adjusted imputed rate		Unadjusted complete case rate		Adjusted imputed rate	
	n = 4,454	*P*	*n* = 6,034	*P*	*n* = 4,454	*P*	*n* = 6,034	*P*
	% (95% CI)		% (95% CI)		% (95% CI)		% (95% CI)	
Overall	97.7 (97.2–98.1)		97.7 (97.2–98.1)		99.7 (99.5–99.8)		99.8 (99.6–99.9)	
Asynchronous care								
Synchronous (ref)	98.3 (97.6–99.0)	Ref	98.3 (97.7–99.0)	Ref	99.7 (99.4–100.0)	Ref	99.8 (99.5–100.0)	Ref
Asynchronous	97.4 (96.8–98.0)	0.062	97.4 (96.9–98.0)	0.071	99.6 (99.4–99.9)	0.668	99.7 (99.6–99.9)	0.926
Patient age at abortion intake								
16–19 years (ref)[a]	98.5 (96.7–100.0)	Ref	98.4 (96.7–100.0)	Ref	99.5 (98.5–100.0)	Ref	99.6 (98.9–100.0)	Ref
16–17 years	100.0 (100.0–100.0)				100.0 (100.0–100.0)			
18–19 years	98.2 (96.3–100.0)				99.4 (98.3–100.0)			
20–24 years	98.2 (97.3–99.0)	0.780	98.1 (97.2–99.0)	0.789	99.6 (99.1–100.0)	0.876	99.7 (99.3–100.0)	0.932
25–29 years	97.4 (96.5–98.3)	0.382	97.5 (96.6–98.3)	0.408	99.7 (99.4–100.0)	0.575	99.8 (99.6–100.0)	0.604
30–34 years	97.4 (96.4–98.3)	0.370	97.4 (96.5–98.3)	0.398	99.7 (99.3–100.0)	0.711	99.7 (99.5–100.0)	0.745
>34 years	97.8 (96.9–98.7)	0.569	97.7 (96.7–98.6)	0.534	99.7 (99.4–100.0)	0.608	99.8 (99.6–100.0)	0.627
Race, ethnicity or ethnic grouping								
American Indian, Alaska Native, Middle Eastern, North African or Multiracial[b]	97.3 (95.6–98.9)	0.932	97.8 (96.6–99.0)	0.733	99.0 (97.5–100.0)	0.413	99.7 (99.3–100.0)	0.474
Asian, Native Hawaiian or Pacific Islander	97.4 (95.1–99.6)	0.89	97.9 (96.2–99.5)	0.716	99.9 (99.7–100.0)	0.108	99.5 (98.8–100.0)	0.185
Black or African American	96.3 (94.1–98.4)	0.37	97.1 (95.5–98.7)	0.590	98.6 (97.3–100.0)	0.017	99.3 (98.7–100.0)	0.037
Hispanic or Latinx	99.0 (97.8–100.0)	0.089	98.7 (97.5–100.0)	0.206	100.0 (100.0–100.0)	N/A	100.0 (100.0–100.0)	N/A
White (ref)	97.2 (96.5–98.0)	Ref	97.6 (97.0–98.2)	Ref	99.7 (99.5–100.0)	Ref	99.8 (99.7–100.0)	Ref
Urbanicity								
Suburban or rural (ref)	97.5 (96.0–99.0)	Ref	97.4 (95.9–98.9)	Ref	99.8 (99.3–100.0)	Ref	99.8 (99.5–100.0)	Ref
Urban	97.7 (97.2–98.2)	0.777	97.7 (97.2–98.2)	0.728	99.7 (99.5–99.8)	0.68	99.7 (99.6–99.9)	0.674
Previous abortion								
No previous abortion (ref)	97.8 (97.2–98.4)	Ref	97.9 (97.3–98.4)	Ref	99.7 (99.5–99.9)	Ref	99.8 (99.7–99.9)	Ref
One or more previous abortions	96.9 (95.9–97.9)	0.140	97.3 (96.4–98.1)	0.247	99.4 (98.9–99.8)	0.204	99.6 (99.4–99.9)	0.188
Previous births								
No previous birth (ref)	97.6 (96.9–98.3)	Ref	97.6 (96.9–98.3)	Ref	99.5 (99.2–99.9)	Ref	99.7 (99.5–99.9)	Ref
One or more previous births	97.8 (97.1–98.6)	0.671	97.8 (97.1–98.5)	0.696	99.8 (99.6–100.0)	0.215	99.8 (99.7–100.0)	0.292
Pregnancy duration at abortion intake								
<35 days (ref)	98.0 (97.2–98.8)	Ref	97.9 (97.1–98.7)	Ref	99.8 (99.6–100.0)	Ref	99.9 (99.7–100.0)	Ref
35–49 days	97.6 (97.0–98.2)	0.465	97.6 (97.0–98.2)	0.619	99.6 (99.3–99.8)	0.169	99.7 (99.5–99.9)	0.174
50–56 days	98.3 (97.1–99.6)	0.663	98.2 (97.0–99.5)	0.610	99.5 (98.9–100.0)	0.259	99.7 (99.2–100.0)	0.276
57–63 days	95.4 (92.3–98.5)	0.037	96.6 (94.3–99.0)	0.277	100.0 (100.0–100.0)	.	100.0 (100.0–100.0)	.
64–70 days	95.5 (90.6–100.0)	0.182	96.7 (93.1–100.0)	0.493	100.0 (100.0–100.0)	.	100.0 (100.0–100.0)	.
Had confirmatory pre-abortion ultrasonography								
No pre-abortion ultrasonography (ref)	97.8 (97.4–98.3)	Ref	97.8 (97.4–98.3)	Ref	99.7 (99.5–99.8)	Ref	99.7 (99.6–99.9)	Ref
Had pre-abortion ultrasonography	96.2 (94.2–98.1)	0.046	96.2 (94.1–98.2)	0.063	99.7 (99.2–100.0)	0.829	99.8 (99.4–100.0)	0.844

[a]The two youngest age categories (16–17 and 18–19 years) were collapsed in the multivariable models to facilitate model convergence.[b]American Indian, Alaska Native, Middle Eastern, North African, and Multiracial groups were collapsed in the multivariable models to facilitate model convergence. Estimates were derived from marginal estimates from logistic regressions. Estimates were not adjusted for multiple comparisons. Imputation models included patient age, urbanicity, whether the patient obtained screening ultrasonography, whether the patient obtained synchronous or asynchronous telehealth care, whether the patient participated in CHAT surveys or a virtual clinic, and whether the patient used an abortion fund to pay for any portion of their abortion.

Table 3 | Medication abortion additional interventions and serious adverse events

Effectiveness and safety outcomes	*n*=4,454	Complete case *n*=4,454	Imputed[a] *n*=6,034
	No.	Estimate (95% CI)	Estimate (95% CI)
Effectiveness			
Complete abortion without intervention	4,351	97.7 (97.2–98.1)	97.7 (97.2–98.1)
Intervention to complete abortion[b]	103	2.3 (1.9–2.8)	2.3 (1.9–2.8)
Procedure, aspiration or surgery	63	1.4 (1.1–1.8)	1.4 (1.1–1.8)
Prescribed >1,600 µg misoprostol, mifepristone or other medications	22	0.49 (0.29–0.70)	0.56 (0.32–0.81)
Treatment for an ectopic pregnancy[c]	6	0.13 (0.03–0.24)	0.16 (0.01–0.31)
Suspected or confirmed continuing pregnancy	41	0.92 (0.64–1.20)	0.94 (0.65–1.23)
Safety			
No major abortion-related adverse events[c]	4,439	99.7 (99.5–99.8)	99.8 (99.6–99.9)
Major abortion-related adverse events[b,c]	15	0.34 (0.17–0.51)	0.25 (0.12–0.37)
Blood transfusion[c]	6	0.13 (0.03–0.24)	0.10 (0.02–0.18)
Other major surgery, including treatment of an ectopic pregnancy[c]	1	0.02 (0–0.07)	0.02 (0–0.05)
Hospital admission[c]	10	0.22 (0.09–0.36)	0.17 (0.06–0.27)
Other outcomes			
Emergency department visits	81	1.8 (1.4–2.2)	1.3 (1.1–1.6)

[a]Imputation models included patient age, urbanicity, whether the patient obtained screening ultrasonography, whether the patient obtained synchronous or asynchronous telehealth care, whether the patient participated in the CHAT study surveys or a virtual clinic, and whether the patient used an abortion fund to pay for any portion of their abortion. [b]Subcategories are not mutually exclusive. [c]Outcomes are unadjusted because of small cells. Models for estimates with $n>15$ were adjusted for synchronous versus asynchronous care, patient age, race, ethnicity or ethnic grouping, urbanicity, previous abortion, pregnancy duration at intake and pre-abortion screening ultrasonography. Estimates were calculated from logistic regression models with missing outcomes and covariates imputed using multiple imputation with chained equations.

The effectiveness and safety rates found in this study are consistent with, although slightly lower than, those found in studies of no-test telehealth abortion in other countries. A national study in the UK, which included 18,435 telehealth medication abortions, found that 99% were complete without intervention and serious adverse events occurred in 0.02% (refs. 26–28). This higher documented effectiveness rate may be explained by the lack of routine follow-up after medication abortion care in the UK; additional interventions that patients may receive may not be systematically reported to the original abortion provider.

The rates in our study are also similar to the effectiveness and safety rates documented from self-managed medication abortion models (defined as using abortion pills to end a pregnancy outside of the formal healthcare system), in the USA[29] and internationally, including in contexts where abortion is legally restricted[30,31].

The effectiveness rates for both synchronous and asynchronous services were very high and similar to in-person care. These findings have important implications for service delivery and health equity. Synchronous models with videoconferencing require strong Internet connectivity. Asynchronous models can be accessed using more types of devices; they may be more private, require shorter waiting times and can be more easily integrated into work or home schedules because no appointment is needed[32–34]. Offering patients a choice between synchronous and asynchronous care is consistent with patient-centered care and may increase access for people historically excluded from healthcare, particularly those living in rural areas or those who live far from an abortion-providing facility[1,35,36].

We used a more conservative definition of effectiveness than recommended by the MARE guidelines[20] but used in previous studies[17,37]. Our definition included an additional 22 patients who received a second medication abortion (mifepristone plus misoprostol) or more than one additional dose of misoprostol. In the context of telehealth and in the wake of the *Dobbs* decision, patients living in states that have banned abortions may experience more barriers to procedural treatment for incomplete abortion and thus be more likely to obtain additional medications to complete the abortion. Therefore, our definition of effectiveness may better account for patient experience.

While safety was over 99% among all ethnic groups, Black patients had significantly higher rates of serious adverse events than white patients. This finding is consistent with research showing higher rates of adverse obstetric outcomes among Black patients. Growing consensus finds that these disparities in obstetric health are rooted in implicit biases and structural racism[38,39].

This analysis provides an initial picture of the real-world effectiveness and safety of a rapidly expanding model of abortion care among a large US cohort. However, this analysis has several limitations. One is the lack of clinic-level variation in synchronous and asynchronous models, which may limit generalizability. However, each virtual clinic had multiple providers offering care, thereby increasing variation within each clinic and thus the generalizability of our findings. For example, different providers may use different thresholds or criteria for when to refer patients to in-person care for an ultrasound or exam, which may impact effectiveness rates. This natural variation strengthens the premise that these results could be applied to other providers offering synchronous or asynchronous care. While there was no direct comparison group, we were able to compare our results to widely accepted rates in the published literature using standardized guidelines for measuring medication abortion outcomes.

Additionally, we identified no cases of unexpected pregnancy durations beyond 70 days. This is surprising given that a previous study of no-test medication abortion found a rate of 0.38%[17]. This lack of evidence may be due to underreporting. Although most patients can accurately assess their pregnancy duration[40,41], patients who later learned that they provided a date of last menstrual period that underestimated their pregnancies may have felt that they could be held responsible and thus not reported it to the virtual clinic, particularly if it resulted in an abortion beyond 70 days.

Finally, another limitation is the follow-up rate; at 74% it was similar or higher than other studies on abortion[17,31,42,43]; attrition may have introduced selection bias given that some groups had lower follow-ups than others. In particular, we observed lower follow-up rates in the asynchronous group than the synchronous group. Telehealth is a less medicalized healthcare model, and asynchronous care even less so; those who opt for it may prefer a more autonomous experience. This differential follow-up may overestimate effectiveness and safety rates for asynchronous patients if those with concerning symptoms seek additional care without informing the virtual clinic. On the other hand, it might underestimate effectiveness rates if patients who have a negative pregnancy test or clear signs of complete abortion do not feel that they must report their outcome back to the virtual clinic. We attempted to limit this potential bias with multiple imputation. We also explored this limitation through a sensitivity analysis simulating higher and lower odds of incomplete abortions and serious adverse events among those lost to follow-up relative to those with known outcomes. This analysis demonstrated that differences in effectiveness between

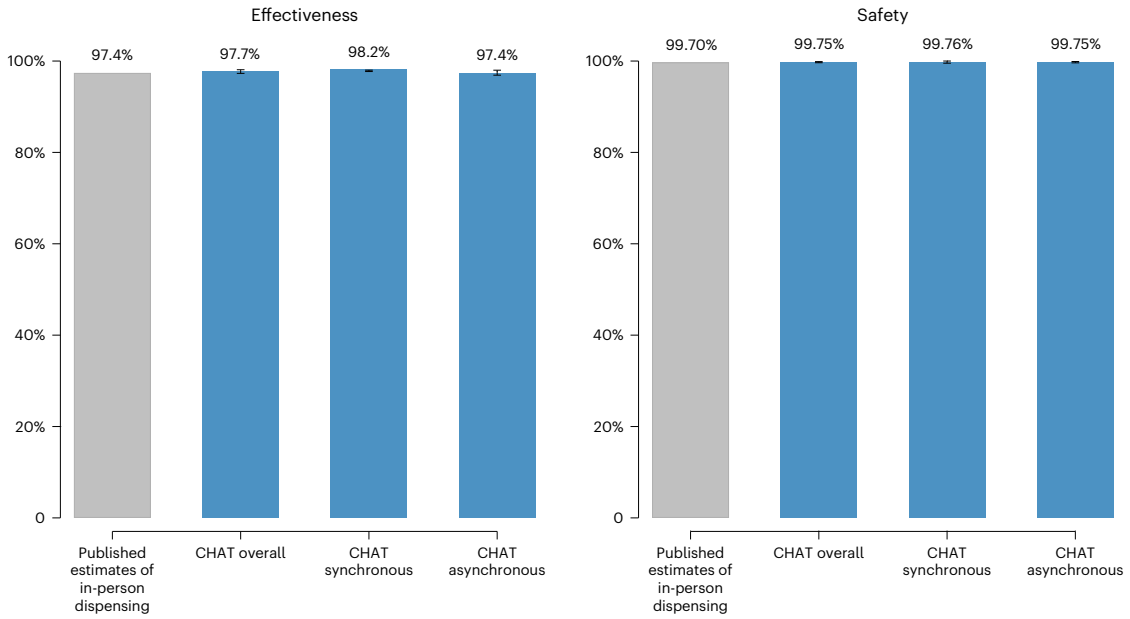

Fig. 3 | Abortion effectiveness and safety estimates: CHAT study and published estimates of in-person care. The gray bars represent published estimates from the FDA label for in-person dispensing of mifepristone; the blue bars represent the rates found in the CHAT study. Estimates for the CHAT study were calculated using marginal estimates from logistic regression analyses conducted on $n = 6{,}034$ patients. The published estimates of in-person dispensing represent the published rates drawn from the FDA label for mifepristone in 2016. The 95% CIs are represented by the black error bars.

synchronous and asynchronous groups could reach significance under extreme scenarios, but differences in safety remained nonsignificant in all scenarios tested.

These findings provide evidence that telehealth for abortion is effective and safe, with rates similar to in-person care. Additionally, synchronous and asynchronous care are comparably effective and safe. Although telehealth models cannot serve the needs and preferences of everyone, such as those who do not have electronic devices or those who are beyond the first trimester of pregnancy, offering people telehealth options has the potential to expand access to abortion care. These results are reassuring as more clinicians begin to provide telehealth abortion care to patients in US states with a ban, under the legal protections of their state's shield laws. At the same time, 11 states continue to permit abortion but have prohibitions on no-test telehealth abortion (https://www.rhites.org/state-based-resources). This study demonstrates that policies that restrict telehealth abortion owing to concerns or claims about effectiveness or safety need to be revisited and revised to ensure equitable access to this essential healthcare service.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-024-02834-w.

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Methods

Ethics

The CHAT study was approved by the University of California, San Francisco institutional review board (no. 20-32951) and registered with ClinicalTrials.gov (registration: NCT04432792). We used Strengthening the Reporting of Observational studies in Epidemiology guidelines to design and report the results of this study. All survey respondents provided consent to participate in the research.

Data source and study cohort

The CHAT study followed the patients of three US virtual abortion clinics: Choix (which opened in October 2020); Hey Jane (which opened in January 2021); and Abortion on Demand (which opened in April 2021). These virtual clinics were selected because they were among the first to open in the USA after the FDA temporarily suspended the in-person dispensing requirement during the COVID-19 emergency, and because they operated in states with large populations.

Medication protocols included 200 mg mifepristone orally and 800 µg misoprostol buccally or vaginally for pregnancy durations less than 63 days or 1,600 µg for pregnancy durations of 63 or more days. Care was provided based on a published protocol[19] by nurse practitioners, nurse midwives, physician assistants and physicians who specialize in abortion care. Clinics offered synchronous (video) or asynchronous (secure text messaging) telehealth abortion with mail order pharmacy delivery. One clinic offered only synchronous medication abortion care, one offered only asynchronous care and one offered asynchronous care with an option to have a phone or video call with the provider if preferred. Patients learned about the services through Web searches, social media or referrals.

During the study period, one clinic offered abortion care up to 56 days (8 weeks) of pregnancy, whereas the two other clinics offered it up to 70 days (10 weeks). As per the published protocol, patients were evaluated for medical eligibility based on the reported medical history. Pregnancy duration at intake was primarily based on self-reported date of last menstrual period or by ultrasonography, if available. Some patients had already had ultrasonography before contacting the virtual clinic. Additionally, patients were referred for pre-abortion ultrasonography if they had any risk factors for, or symptoms of, ectopic pregnancy[19] or were potentially beyond the gestational limit of the virtual clinic. Some of these patients returned to the virtual clinic after their eligibility was confirmed by ultrasonography and obtained a telehealth abortion; thus, they were included in the study. Others opted for in-person care and thus were excluded.

Each clinic had two scheduled follow-up interactions. The first confirmed medication administration and assessed symptoms of complete abortion 3–7 days after intake. The second was a low-sensitivity pregnancy test at 2 weeks or a high-sensitivity test at 4 weeks after medication administration. Follow-up interactions were conducted by text messaging, secure messaging or telephone. At each scheduled follow-up, clinicians made up to four attempts to contact patients. Clinicians referred patients to in-person care if any adverse event or incomplete abortion was suspected and outcomes of care were documented whenever possible.

For this analysis, we evaluated data collected from two sources, both imported into REDCap[44]. We obtained anonymized medical record data of consecutive patients receiving care from the participating virtual clinics between April 2021 and January 2022.

Additionally, each virtual clinic invited all patients seen between June 2021 and January 2022 to enroll in three surveys about their abortion experience, including any additional treatments received. After providing electronic informed consent, participants completed a baseline survey on the date of the intake, which included sociodemographic characteristics and medical history. Participants completed a second survey 3–7 days after the intake, to assess medication administration, additional medical care and any adverse events, and a final survey 4 weeks after the intake to assess additional medical care and adverse events (Fig. 1). The survey sample was powered to assess the acceptability of telehealth (published separately[2]); thus, we aimed to collect complete sets of surveys from 1,600 participants. Survey participants received a US$50 electronic debit card on completion of all three surveys.

Outcomes

The primary outcomes were effectiveness and safety based on standard definitions in previous studies[17,24,37,45]. We generally followed the MARE guidelines for reporting outcomes[20]. We defined effectiveness as the proportion of medication abortions that were complete after initial treatment with 200 mg mifepristone and 1,600 µg or less of misoprostol without known subsequent intervention. Abortions were not considered complete if (1) the patient had an aspiration, dilation and evacuation, other procedure or surgical intervention to complete the abortion; (2) the patient received more than 200 mg mifepristone, more than 1,600 µg misoprostol, or a uterotonic medication to complete the abortion; (3) the patient received treatment for suspected or confirmed ectopic pregnancy; or (4) the patient had a continuing pregnancy confirmed by ultrasonography or suspected at last contact. While MARE guidelines define effectiveness as successful expulsion of pregnancy without the need for procedural intervention, we chose a more conservative definition, recognizing that patients may view the need to have what constitutes a second medication abortion treatment as a failure of the medication abortion protocol.

We defined safety using standardized definitions from the Procedural Abortion Incident Reporting and Surveillance Framework[45] and Standardizing Abortion Research Outcomes protocol[46] as the proportion of abortions that were not followed by a known abortion-related serious adverse event. Serious adverse events included: blood transfusion; abdominal surgery (including salpingectomy, laparotomy and laparoscopy to treat an ectopic pregnancy); hospital admission requiring overnight stay; or death.

Effectiveness and safety outcomes were determined from all information collected in the medical records and surveys. Abortion completion was determined based on the virtual clinic's designation, either using a test (urine pregnancy test, ultrasonography or serum human chorionic gonadotrophin) or using the patient's medical history (using a checklist reflecting symptoms of complete abortion) without further contact related to the abortion for at least 6 weeks after the intake visit. Patients without outcomes noted in the medical records were determined to have complete abortions if they completed a survey at least 28 days after screening and did not report an intervention or ongoing pregnancy.

Secondary outcomes included the number of cases where, at the subsequent follow-up, it was determined that at intake the patient had been beyond 70 days' gestation. We also evaluated rates of suspected or confirmed ectopic pregnancy and emergency department visits.

Covariates

We examined the categorical covariates reflecting participant age at abortion intake in years (16–17 years, 18–19 years, 20–24 years, 25–29 years, 30–34 years and 35 years or older), and pregnancy duration in days at abortion intake (less than 35 days, 35–49 days, 50–56 days, 57–63 days, 64–70 days or unknown). We also included a measure of race, ethnicity or ethnic grouping indicated by participants on an intake form or in the surveys (American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, Black or African American, Middle Eastern or North African, White, Multiracial or Unknown). We included binary covariates for urbanicity (suburban or rural versus urban), whether the patient had a previous abortion, whether the patient had a previous birth and whether the patient had confirmatory pre-abortion ultrasonography.

Exposure
The key exposure was a binary measure reflecting whether the patient received care synchronously (video) or asynchronously (secure text messaging).

Statistical analysis
The study was powered to detect differences in the rarest primary outcome, that is, serious adverse events. We aimed to have outcome data from 4,202 patients. The study was designed to detect a difference of 0.4% or more in the rate of serious adverse events compared to 0.5%, the rate for in-person medication abortions as published in the FDA label[8], with 90% power and a two-sided alpha of 0.05. With a final sample size of 4,454, the study had more than 90% power to detect a difference of 2% or more in the effectiveness rate compared to the 3% rate for in-person medication abortions as published on the FDA label[8].

We described the characteristics of the overall sample and the subsample of patients who completed the surveys. We examined the extent of loss to follow-up and whether loss to follow-up differed between those who obtained synchronous and asynchronous care. We then conducted multiple imputation by chained equations to account for missing covariate and outcome data with 100 replications for primary regression analyses, assuming that missing data were related to observed patient and abortion characteristics. Multiple imputation by chained equations iteratively impute missing data using predictive models based on other variables in the dataset, and accounts for statistical uncertainty in the imputations[47]. Imputation models included patient age, urbanicity, whether the patient obtained screening ultrasonography, whether the patient obtained synchronous or asynchronous telehealth care, whether the patient participated in CHAT surveys, virtual clinics, and whether the patient used an abortion fund to pay for any portion of their abortion.

We developed logistic regression models for all effectiveness and safety outcomes. We used multivariable models for outcomes $n > 15$, adjusting for a binary measure of whether the patient received screening via synchronous or asynchronous methods. These models were also adjusted for baseline patient and abortion characteristics, including patient age, race, ethnicity or ethnic grouping, and pregnancy duration. We included binary measures reflecting whether the patient had a previous abortion or birth, and whether the patient had pre-abortion ultrasonography[21]. For rare outcomes ($n < 15$), we used unadjusted logistic regression models.

We calculated marginal estimates, the corresponding 95% CIs and *P* values from the logistic regression results to estimate the predicted probability of each effectiveness and safety outcome. Primary estimates came from logistic regression analyses performed on imputed data. *P* values correspond to a Wald test in the logistic regressions, comparing each group to the reference group. We then compared results with published estimates of effectiveness and safety. All statistical tests were two-tailed with significance set at 0.05. All analyses were conducted using Stata v.17.0 (StataCorp LLC).

We conducted several sensitivity analyses to assess the robustness of our findings. First, we replicated the effectiveness analysis, assuming that patients who were referred to in-person care after taking the medications and were then lost to follow-up required further intervention to complete the abortion. Second, we replicated the effectiveness analysis by categorizing all patients who received any additional misoprostol as completed abortions. This is consistent with the MARE guidelines and previous studies[26,48], which classified patients who received more than 1,600 µg of misoprostol (more than two doses) as successful abortions. Third, we examined both effectiveness and safety outcomes only among the subsample of patients who completed the surveys to evaluate whether the main findings held true among this sample with supplementary self-reported data on their outcomes. Finally, to test how robust our results were to the follow-up rates, we used delta-adjusted pattern-mixture model imputation[49] to simulate the outcomes under different assumptions regarding patients with missing outcome data, hypothesizing results if they had lower or higher odds of incomplete abortion or serious adverse events than those with outcome data.

Reporting summary
Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability
The datasets analyzed during this study are not publicly available because the patients who underwent an abortion did not consent to sharing their data beyond the primary researchers and because the legal status of abortion care is continually changing. The de-identified, individual-level data used to reach the study conclusions are available to qualified investigators from the corresponding author. Requesters must include a description of their research project, the qualifications of the research team, whether the analysis has institutional review board approval and how the results will be disseminated. Requesters must also sign a data use agreement to (1) use the data only for research purposes, (2) not attempt to re-identify the data or contact the study participants, (3) secure the data using appropriate computer technology and (4) destroy the data after the analyses are completed. Responses can be expected within 1 month of a request.

Code availability
Data analyses were carried out using Stata v.17.0 (StataCorp LLC) as specified in the Methods. The code is available on GitHub (https://github.com/Upadhyay-Lab).

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Author contributions

U.D.U. obtained the funding for the study. U.D.U., L.R.K., E.S.V. and K.M. conceptualized and designed the study. L.R.K. conducted the data analysis. U.D.U. supervised the data analysis. J.K. provided management and administration for the study. U.D.U., L.R.K. and M.A.B. drafted the manuscript. All authors interpreted the data, reviewed the manuscript drafts, provided substantive input on its content and approved the final version of the manuscript. U.D.U. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests

K.M. reports receiving personal fees from Danco Laboratories, a distributor of mifepristone, for staffing a US Food and Drug Administration-mandated expert hotline. The other authors declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-024-02834-w.

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Extended Data Table 1 | Characteristics of the medical records sample and survey subsample

	Total sample n=6034	Survey subsample n=1600
	% (n)	
Patient age at abortion intake		
16 - 17 years	30 (0.5%)	8 (0.5%)
18 - 19 years	246 (4.1%)	67 (4.2%)
20 - 24 years	1215 (20.1%)	381 (23.8%)
25 - 29 years	1505 (24.9%)	418 (26.1%)
30 - 34 years	1587 (26.3%)	405 (25.3%)
>34 years	1451 (24.0%)	321 (20.1%)
Race or ethnicity		
American Indian or Alaska Native	35 (0.6%)	8 (0.5%)
Asian, Native Hawaiian, or Pacific Islander	271 (4.5%)	105 (6.6%)
Black or African American	413 (6.8%)	148 (9.2%)
Hispanic or Latinx	339 (5.6%)	203 (12.7%)
Middle Eastern or North African	25 (0.4%)	9 (0.6%)
White	2491 (41.3%)	841 (52.6%)
Multiracial	390 (6.5%)	220 (13.8%)
Unknown	2070 (34.3%)	66 (4.1%)
Urbanicity		
Suburban or Rural	600 (9.9%)	146 (9.1%)
Urban	5434 (90.1%)	1454 (90.9%)
Prior abortion		
No prior abortion	3053 (50.6%)	964 (60.2%)
1 or more prior abortions	1523 (25.2%)	635 (39.7%)
Unknown	1458 (24.2%)	1 (0.1%)
Prior births		
No	2325 (38.5%)	805 (50.3%)
Yes	2144 (35.5%)	564 (35.2%)
Unknown	1565 (25.9%)	231 (14.4%)
Pregnancy duration at abortion intake		
<35 days	1732 (28.7%)	463 (28.9%)
35 - 49 days	3356 (55.6%)	883 (55.2%)
50 - 56 days	583 (9.7%)	158 (9.9%)
57 - 63 days	261 (4.3%)	71 (4.4%)
64 - 70 days	98 (1.6%)	25 (1.6%)
Unknown	4 (0.1%)	0 (0%)
Had confirmatory pre-abortion ultrasonography		
No pre-abortion ultrasonography	5548 (91.9%)	1424 (89.0%)
Had pre-abortion ultrasonography	486 (8.1%)	176 (11.0%)
Asynchronous care		
Synchronous	1674 (27.7%)	503 (31.4%)
Asynchronous	4360 (72.3%)	1097 (68.6%)
Known abortion outcome		
Abortion outcome unknown	1580 (26.2%)	141 (8.8%)
Abortion outcome known	4454 (73.8%)	1,459 (91.2%)

Article https://doi.org/10.1038/s41591-024-02834-w

Extended Data Table 2 | Characteristics of the sample with and without known abortion outcomes (*n*=6,034)

	Abortion outcome known n=4,454 73.8%	Abortion outcome unknown n=1,580 26.2%	p-value
	n (%)		
Patient age at abortion intake			
16 - 17 years	23 (76.7%)	7 (23.3%)	0.226
18 - 19 years	171 (69.5%)	75 (30.5%)	
20 - 24 years	924 (76.0%)	291 (24.0%)	
25 - 29 years	1111 (73.8%)	394 (26.2%)	
30 - 34 years	1173 (73.9%)	414 (26.1%)	
>34 years	1052 (72.5%)	399 (27.5%)	
Race or ethnicity			
American Indian or Alaska Native	20 (57.1%)	15 (42.9%)	<0.001
Asian, Native Hawaiian, or Pacific Islander	191 (70.5%)	80 (29.5%)	
Black or African American	294 (71.2%)	119 (28.8%)	
Hispanic or Latinx	292 (86.1%)	47 (13.9%)	
Middle Eastern or North African	16 (64.0%)	9 (36.0%)	
White	1828 (73.4%)	663 (26.6%)	
Multiracial	333 (85.4%)	57 (14.6%)	
Unknown	1480 (71.5%)	590 (28.5%)	
Urbanicity			
Suburban or Rural	439 (73.2%)	161 (26.8%)	0.703
Urban	4015 (73.9%)	1419 (26.1%)	
Prior abortion			
No prior abortion	2240 (73.4%)	813 (26.6%)	0.647
1 or more prior abortions	1137 (74.7%)	386 (25.3%)	
Unknown	1077 (73.9%)	381 (26.1%)	
Prior births			
No	1743 (75.0%)	582 (25.0%)	<0.001
Yes	1510 (70.4%)	634 (29.6%)	
Unknown	1201 (76.7%)	364 (23.3%)	
Pregnancy duration at abortion intake			
<35 days	1301 (75.1%)	431 (24.9%)	0.001*
35 - 49 days	2491 (74.2%)	865 (25.8%)	
50 - 56 days	421 (72.2%)	162 (27.8%)	
57 - 63 days	174 (66.7%)	87 (33.3%)	
64 - 70 days	67 (68.4%)	31 (31.6%)	
Unknown	0 (0.0%)	4 (100.0%)	
Had confirmatory pre-abortion ultrasonography			
No pre-abortion ultrasonography	4089 (73.7%)	1459 (26.3%)	0.501
Had pre-abortion ultrasonography	365 (75.1%)	121 (24.9%)	
Asynchronous care			
Synchronous	1418 (84.7%)	256 (15.3%)	<0.001
Asynchronous	3036 (69.6%)	1324 (30.4%)	

* – p-value derived from Fisher's Exact Test
P-values derived from two-sided Chi-squared tests, unless otherwise noted.

Article https://doi.org/10.1038/s41591-024-02834-w

Extended Data Table 3 | Rate of abortions not followed by a serious adverse event according to the characteristics of the sample from complete cases and multiple imputation analysis

	Effectiveness Number of abortions complete without additional intervention / row n †	Safety Number of abortions not followed by a serious adverse event / row n †
Overall	4351 / 4454	4439 / 4454
Asynchronous care		
Synchronous	1394 / 1418	1414 / 1418
Asynchronous	2957 / 3036	3025 / 3036
Patient age at abortion intake		
16 - 19 years	191 / 194	193 / 194
16 - 17 years	23 / 23	23 / 23
18 - 19 years	168 / 171	170 / 171
20 - 24 years	907 / 924	920 / 924
25 - 29 years	1082 / 1111	1108 / 1111
30 - 34 years	1142 / 1173	1169 / 1173
>34 years	1029 / 1052	1049 / 1052
Race or ethnicity		
American Indian, Alaska Native, Middle Eastern, North African, or Multiracial	359 / 369	367 / 369
Asian, Native Hawaiian, or Pacific Islander	186 / 191	189 / 191
Non-Hispanic Black or African American	283 / 294	290 / 294
Hispanic or Latinx	289 / 292	292 / 292
Non-Hispanic White	1777 / 1828	1823 / 1828
Urbanicity		
Suburban or Rural	428 / 439	438 / 439
Urban	3923 / 4015	4001 / 4015
Prior abortion		
No prior abortion	2190 / 2240	2233 / 2240
1 or more prior abortions	1102 / 1137	1130 / 1137
Prior births		
No	1701 / 1743	1735 / 1743
Yes	1477 / 1510	1507 / 1510
Pregnancy duration at abortion intake		
<35 days	1275 / 1301	1299 / 1301
35 - 49 days	2432 / 2491	2480 / 2491
50 - 56 days	414 / 421	419 / 421
57 - 63 days	166 / 174	174 / 174
64 - 70 days	64 / 67	67 / 67
Had confirmatory pre-abortion ultrasonography		
No pre-abortion ultrasonography	4000 / 4089	4075 / 4089
Had pre-abortion ultrasonography	351 / 365	364 / 365

† Numbers may not add up to 4454 due to missing covariate data.

https://doi.org/10.1038/s41591-024-02834-w

Extended Data Table 4 | Total misoprostol dosage administered after 200 mg mifepristone according to pregnancy duration (*n*=4,454)

	<9 weeks		≥9 weeks	
	N	Effectiveness	N	Effectiveness
0 µg misoprostol	1	0.0%	0	
400 µg misoprostol	1	100.0%	0	
800 µg misoprostol	4,187	98.3%	12	100.0%
1,400 µg misoprostol	1	0.0%	0	
1,600 µg misoprostol	171	90.6%	69	95.7%
2,000 µg misoprostol [a]	2		0	
2,400 µg misoprostol [a]	7		0	
3,200 µg misoprostol [a]	2		0	
4,000 µg misoprostol [a]	1		0	

Misoprostol dose taken estimated based on clinic protocol and/or medical record notes. 800 mcg is routinely provided to patients <9 weeks and 1,600 mcg is routinely provided for patients >9 weeks. Additional misoprostol is provided to all patients as needed.

Rates are estimated from simple proportions.

[a] – Misoprostol administered beyond 1,600 mcg constitutes an additional intervention.

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Extended Data Table 5 | Pattern-mixture model imputation with delta correction to explore the potential impact of informative missingness in abortion outcomes

Delta, exp	Effectiveness Rate % (95% CI)				Safety Rate % (95% CI)			
	Overall	Synchronous	Asynchronous	p-value	Overall	Synchronous	Asynchronous	p-value
0.1	93.3 (92.1, 94.5)	96.6 (95.3, 97.9)	92.0 (90.3, 93.7)	<0.001	98.9 (98.3, 99.4)	99.3 (98.7, 100.0)	98.7 (97.9, 99.4)	0.227
0.2	95.5 (94.6, 96.3)	97.5 (96.5, 98.5)	94.7 (93.5, 95.9)	0.003	99.3 (98.9, 99.7)	99.5 (99.1, 100.0)	99.2 (98.7, 99.7)	0.331
0.5	97.1 (96.5, 97.6)	98.1 (97.3, 98.9)	96.7 (95.9, 97.5)	0.035	99.6 (99.3, 99.8)	99.7 (99.4, 100.0)	99.5 (99.3, 99.8)	0.523
1.0	97.7 (97.2, 98.1)	98.3 (97.5, 99.0)	97.4 (96.9, 98.0)	0.126	99.7 (99.5, 99.8)	99.7 (99.4, 100.0)	99.6 (99.4, 99.9)	0.668
2.0	98.0 (97.6, 98.4)	98.4 (97.7, 99.0)	97.8 (97.3, 98.3)	0.267	99.7 (99.6, 99.9)	99.7 (99.5, 100.0)	99.7 (99.5, 99.9)	0.777
5.0	98.2 (97.8, 98.5)	98.4 (97.8, 99.1)	98.1 (97.6, 98.5)	0.431	99.7 (99.6, 99.9)	99.8 (99.5, 100.0)	99.7 (99.6, 99.9)	0.860
10.0	98.2 (97.9, 98.6)	98.4 (97.8, 99.1)	98.2 (97.7, 98.6)	0.506	99.7 (99.6, 99.9)	99.8 (99.5, 100.0)	99.7 (99.6, 99.9)	0.892

Delta values represent the hypothetical odds ratio for the association between missing outcomes and each abortion outcome (effectiveness or safety). For example, a Delta value of 0.1 in the effectiveness analysis represents a hypothetical and extreme scenario in which the odds of incomplete abortion are 10 times higher among those with unknown abortion outcomes, compared to those with known abortion outcomes. Meanwhile, a Delta value of 10.0 in the effectiveness analysis represents a hypothetical scenario in which the odds of incomplete abortion are 10 times lower among those with missing abortion outcomes, compared to those with known abortion outcomes. P-values correspond to two-sided Wald's test in logistic regressions comparing abortion outcomes for synchronous and asynchronous care.

nature portfolio

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For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Authors used Research Electronic Data capture (REDCap) to standardize and store electronic medical record and survey data.
Data analysis	All analyses were conducted using Stata version 17.0 (College Station, TX). Code is available on GitHub (https://github.com/Upadhyay-Lab)

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

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The data sets analyzed during this study are not publicly available because the abortion patients did not consent to sharing their data beyond the primary researchers and because the legal status of abortion care is continually changing. De-identified individual-level data used to reach the study conclusions are available to qualified investigators from the corresponding author. Requesters must include a description of their research project, the qualifications of the research team, whether the analysis has institutional review board approval, and how the results will be disseminated. Requesters must also sign a data use agreement to: i)

use the data only for research purposes, iii) not attempt to re-identify the data or contact study participants, iii) secure the data using appropriate computer technology, and iv) destroy the data after analyses are completed. Responses can be expected within one month of a request.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	This study focuses on populations who are sexually active and pregnant or able to get pregnant. This study did not exclude anyone based on their gender, but because we examined conditions related to pregnancy, participants in this study were likely assigned female at birth. We did not report information about gender identity in this study because data on gender identity were not in the electronic medical records data.
Population characteristics	This study includes a sample of consecutive patients of 3 of the major virtual clinic abortion providers in the U.S. who were provided telehealth medication abortion care in 20 states and Washington, D.C. between April 2021 and January 2022. Eligible participants were provided medication abortion care at a participating clinic and administered the provided medications. Half (50.3%) were 30 years or older and 4.6% were under 20 years old (Table 1). Race or ethnicity was unknown for one-third (34.3%) of patients, however, among the subsample with known race or ethnicities, nearly two-thirds (62.7%) were White. Most (84.3%) patients had pregnancy durations under 7 weeks (≤ 49 days).
Recruitment	Electronic medical records data included all patients provided telehealth medication abortion care by the participating virtual clinics during a defined time period, and therefore we expect the sample to be representative of patients obtaining telehealth abortion care at virtual clinics during the study period. Participants self-selected into participating in the survey subsample, however the characteristics of the survey subsample characteristics were similar to those of the medical records sample.
Ethics oversight	The study was approved by the University of California, San Francisco Institutional Review Board (#0-32951)

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The study was powered to detect differences in the rarest primary outcome, serious adverse events. We aimed to have outcome data from 4,202 patients. The study was designed to detect a difference of 0.4% or more in the rate of serious adverse events compared to 0.5%, the rate for in-person medication abortions as published in the FDA label, with 90% power and two-sided alpha 0.05. With a final sample size of 4,454, the study had >90% power to detect a difference of 2% or more in the effectiveness rate compared to the 3% rate for in-person medication abortions as published on the FDA label.
Data exclusions	Among the 6,974 encounters for which we originally received data, 820 patients were not provided with abortion medications. These patients were excluded because they not treated with the study intervention. Among the remaining sample, 120 patients were excluded from analyses of abortions safety and effectiveness because they took neither study drug (neither mifepristone nor misoprostol).
Replication	We conducted 4 sensitivity analyses using alternative assumptions to replicate our experimental findings, the results of which supported the robustness of our primary analysis. We plan to post all code used to reach the study conclusions on Github prior to publication.
Randomization	As this was an observational study, participants were not randomly assigned to exposure arms in this study. We reviewed the literature on abortion effectiveness and safety to identify covariates potentially related to abortion safety and effectiveness and controlled for the factors available in the data in our analyses when possible.
Blinding	Blinding was not relevant for this study due to its observational design in which exposures were not assigned.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
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☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
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☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT04432792
Study protocol	The study protocol is available online at: https://clinicaltrials.gov/study/NCT04432792
Data collection	This study included two sources of data. The first was anonymized electronic medical records data from consecutive patients who received care from the three participating virtual clinics between April 2021 and January 2022. Medical records data was anonymized and exported from the virtual clinic's electronic medical record. The second data source was collected from a subsample who participated in surveys. Each virtual clinic invited all patients seen between June 2021 and January 2022 to enroll in three surveys about their abortion experience. After providing electronic informed consent, participants completed a baseline survey on the date of intake, which included sociodemographic characteristics and medical history. Survey recruitment and administration took place online on the virtual clinic's care platform to maintain continuity for participants. Both data sources were standardized in REDCap.
Outcomes	We defined effectiveness as the proportion of medication abortions that were complete after initial treatment with mifepristone 200 mg and misoprostol <1,600 mcg without known subsequent intervention. Abortions were not considered complete if (1) the patient had an aspiration, dilation and evacuation, other procedure, or surgical intervention to complete the abortion; (2) the patient received >200 mg mifepristone, >1,600 mcg misoprostol, or a uterotonic medication to complete the abortion; (3) the patient received treatment for suspected or confirmed ectopic pregnancy; or (4) the patient had a continuing pregnancy confirmed by ultrasound or suspected at last contact. We defined safety as the proportion of abortions that were not followed by a known abortion-related serious adverse event. Serious adverse events included: blood transfusion, abdominal surgery (including salpingectomy, laparotomy and laparoscopy to treat ectopic pregnancy), hospital admission requiring overnight stay, or death. Effectiveness and safety outcomes were determined from all information collected in clinical charts and surveys. Abortion completion was determined based on the virtual clinic's designation, either by test (urine pregnancy test, ultrasonography, or serum human chorionic gonadotrophin), or by history (using a checklist reflecting symptoms of complete abortion) without further contact related to the abortion for at least 6 weeks following the intake visit. Patients without outcomes noted in clinical charts were determined to have complete abortions if they completed a survey at least 28 days after screening and did not report an intervention or ongoing pregnancy. Secondary outcomes included the number of cases where at subsequent follow-up, it was determined that at intake the patient had been beyond 70 days gestation. We also evaluated rates of suspected or confirmed ectopic pregnancy and emergency department visits.

EXHIBIT B-9

APPENDIX TO PETITIONER GENBIOPRO, INC.'S CITIZEN PETITION DATED JULY 3, 2025[1]

Source	Appendix Starting Page
Appendix Volume I	
108 Cong. Rec. 17366 (Aug. 23, 1962)	GBP-PET00001
Aiken, Abigail R.A. et al., *Safety and Effectiveness of Self-Managed Medication Abortion Provided Using Online Telemedicine in the United States: A Population Based Study*, 10 Lancet Reg'l Health – Ams. 1 (2022), https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(22)00017-5/fulltext	GBP-PET00010
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[1] This Appendix includes all documents cited in the accompanying July 3, 2025 Citizen Petition with the exception of certain documents not required by 21 C.F.R. § 10.20(c). Volumes I, II, III, IV, V, and IX contain copyright restricted materials.

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Original Research

Incidence of Emergency Department Visits and Complications After Abortion

Ushma D. Upadhyay, PhD, MPH, Sheila Desai, MPH, Vera Zlidar, MHS, Tracy A. Weitz, PhD, MPA, Daniel Grossman, MD, Patricia Anderson, MPH, and Diana Taylor, PhD, RNP

OBJECTIVE: To conduct a retrospective observational cohort study to estimate the abortion complication rate, including those diagnosed or treated at emergency departments (EDs).

METHODS: Using 2009–2010 abortion data among women covered by the fee-for-service California Medicaid program and all subsequent health care for 6 weeks after having an abortion, we analyzed reasons for ED visits and estimated the abortion-related complication rate and the adjusted relative risk. Complications were defined as receiving an abortion-related diagnosis or treatment at any source of care within 6 weeks after an abortion. Major complications were defined as requiring hospital admission, surgery, or blood transfusion.

RESULTS: A total of 54,911 abortions among 50,273 fee-for-service Medi-Cal beneficiaries were identified. Among all abortions, 1 of 16 (6.4%, n=3,531) was followed by an ED visit within 6 weeks but only 1 of 115 (0.87%, n=478) resulted in an ED visit for an abortion-related complication. Approximately 1 of 5,491 (0.03%, n=15) involved ambulance transfers to EDs on the day of the abortion. The major complication rate was 0.23% (n=126, 1/436): 0.31% (n=35) for medication abortion, 0.16% (n=57) for first-trimester aspiration abortion, and 0.41% (n=34) for second-trimester or later procedures. The total abortion-related complication rate including all sources of care including EDs and the original abortion facility was 2.1% (n=1,156): 5.2% (n=588) for medication abortion, 1.3% (n=438) for first-trimester aspiration abortion, and 1.5% (n=130) for second-trimester or later procedures.

CONCLUSION: Abortion complication rates are comparable to previously published rates even when ED visits are included and there is no loss to follow-up.

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LEVEL OF EVIDENCE: II

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With 1.1 million induced abortions in the United States each year,[1] accurate estimates of abortion complications are paramount to assess and improve quality of care and determine how public policies can most effectively safeguard women's health. Although national abortion-related mortality data exist for the United States,[2] no surveillance system captures abortion-related morbidity. Studies find varying complication rates[3–7] depending on the procedure, weeks of gestation, length of follow-up, and protocols used to detect complications. Furthermore, complication rates are underestimated by low follow-up rates.[5,7–9]

Published complication rates are considered incomplete because they usually do not include those diagnosed at sites other than the original source of care.[10]

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Limited research focuses on emergency department (ED) use when examining postabortion care. Because the abortion care delivery system is concentrated in urban centers maldistributed across states,[1] women often travel to obtain abortion care. Thus, women are likely to seek postabortion care at an ED near their home.

Using state Medicaid data, we examine reasons for postabortion visits, contributing to the literature

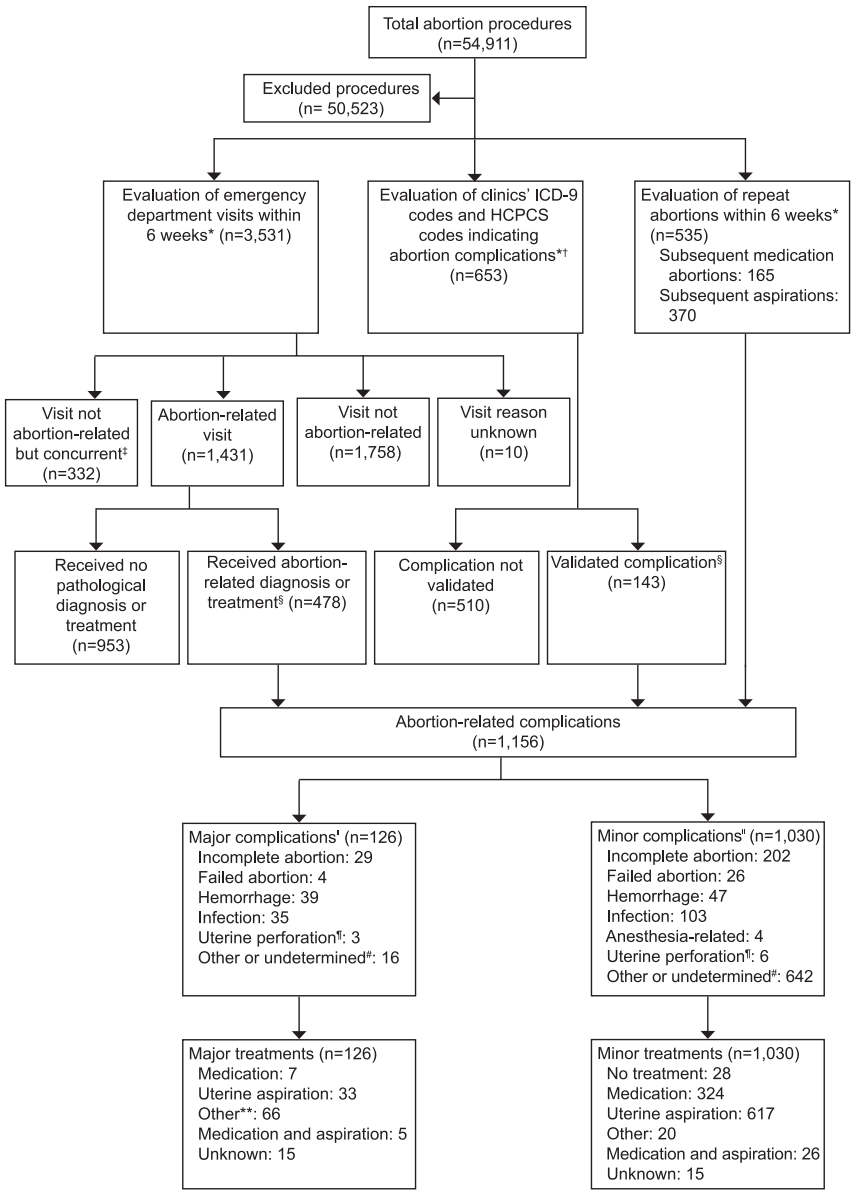

Fig. 1. Process of identification and classification of abortion complications and treatment. ICD-9, International classification of Diseases, 9th Revision; HCPCS, Healthcare Common Procedure Coding System. *Figures presented in the evaluation categories are not mutually exclusive. For example, a complication may have been identified through the evaluation of both emergency department visits and ICD-9 codes and, thus, are represented in both categories. †Includes diagnosis and treatment codes for antibiotics commonly used to treat abortion-related infections, genital tract and pelvic infection, hemorrhage, damage to pelvic organs or tissues, shock, embolism, laparoscopy, laparotomy, and hysterectomy surgeries, and blood transfusions. ‡Includes medical problems that were diagnosed and treated around the time of the abortion procedure such as ectopic pregnancy, molar pregnancy, preexisting medical condition, or concurrent problems present at the time of the procedure. §Confirmed as a complication based on the additional diagnosis or treatment codes, including laboratory tests ordered and medications. ‖Major complications were defined as serious unexpected adverse events requiring hospital admission, surgery, or blood transfusion. Minor complications were all other expected adverse events. ¶Includes one diagnosis of cervical injury requiring suture repair. #For major complications, this diagnosis includes undetermined diagnoses that required blood transfusions and surgery. For minor complications, the majority of this diagnosis consisted of cases treated with repeat abortion, but the exact diagnosis could not be determined. This category also includes diagnoses such as non-anesthesia-related allergic reactions and seizures. **Major treatments include combinations of treatments including blood transfusion (n=50) and surgery (n=13).

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on ED use among patients with public insurance.[11,12] Then, using a standardized methodology for identifying and classifying complications, we estimate the incidence of postabortion complications diagnosed, treated, or diagnosed and treated at all clinical sites to see whether the rate of complications in a closed system with complete follow-up differs from the rates found in other studies.

MATERIALS AND METHODS

We used patient-level billing data from Medi-Cal, California's State Medicaid program. Medi-Cal provides pregnant low-income women immediate, temporary Medicaid coverage. California is one of 17 states that covers abortion and subsequent care for women enrolled in Medicaid. In 2011 an estimated 512 facilities in California performed 181,730 abortions,[1] approximately 51% of which were covered by Medi-Cal.[13]

The study was approved by the institutional review boards of the University of California, San Francisco and the California Health and Human Services Agency.

Medi-Cal is administered on a fee-for-service or managed care arrangement, split approximately in half across the two. Only the fee-for-service billing records contain complete information for care provided to a particular beneficiary; therefore, we received data only for those beneficiaries with fee-for-service coverage. We obtained billing records for every fee-for-service beneficiary who had an abortion

Table 1. Characteristics of Women With Abortions Covered by Medi-Cal, 2009–2010: Abortion-Related Complications, Complication Rates, and Adjusted Relative Risk, by Beneficiary Characteristics

Characteristic	Medi-Cal–Funded Abortions* (N=54,911)	Abortion-Related Complications† (n=1,156)	Abortion-Related Complication Rate/100 Abortions (95% CI)	Adjusted RR‡ (95% CI)	*P*
Age (y)	25.1±6.5				
19 or younger	11,446 (20.8)	173 (15.0)	1.51 (1.30–1.75)	0.87 (0.71–1.07)	.20
20–24	18,051 (32.9)	371 (32.1)	2.06 (1.86–2.27)	Reference	—
25–29	12,481 (22.7)	290 (25.1)	2.32 (2.07–2.60)	1.07 (0.91–1.26)	.40
30–39	11,508 (21.0)	296 (25.6)	2.57 (2.30–2.88)	1.20 (1.02–1.40)	.03
40 or older	1,400 (2.6)	25 (2.2)	1.79 (1.21–2.63)	0.83 (0.55–1.26)	.55
Race or ethnicity					
Non-Hispanic white	12,614 (23.0)	337 (29.1)	2.67 (2.40–2.97)	Reference	—
Non-Hispanic black	7,144 (13.0)	140 (12.1)	1.96 (1.66–2.31)	0.90 (0.73–1.12)	.35
Hispanic	23,110 (42.1)	471 (40.7)	2.04 (1.86–2.22)	0.76 (0.65–0.89)	<.001
Asian	2,771 (5.1)	62 (5.4)	2.24 (1.75–2.86)	0.87 (0.65–1.16)	.34
Other§	2,602 (4.7)	60 (5.2)	2.31 (1.79–2.96)	0.91 (0.68–1.21)	.50
Abortion procedure type					
Medication	11,319 (20.6)	588 (50.9)	5.19 (4.79–5.60)	5.96 (5.11–6.94)	<.001
1st-trimester aspiration	34,755 (63.3)	438 (37.9)	1.26 (1.14–1.38)	Reference	—
2nd trimester or later	8,837 (16.1)	130 (11.2)	1.47 (1.22–1.72)	0.98 (0.79–1.23)	.88
Site of procedure					
Hospital	1,667 (3.0)	84 (7.3)	5.04 (4.09–6.20)	4.74 (3.40–6.61)	<.001
Outpatient clinic	30,778 (56.1)	583 (50.4)	1.89 (1.75–2.05)	Reference	—
Physician's office or group	22,466 (40.9)	489 (42.3)	2.18 (1.99–2.38)	1.70 (1.32–2.17)	<.001
Residence type					
Urban	43,566 (90.5)	935 (80.9)	2.15 (2.01–2.29)	Reference	—
Rural	4,587 (9.5)	132 (11.4)	2.88 (2.43–3.40)	1.23 (1.00–1.52)	.05
Year of abortion					
2009	28,823 (52.5)	559 (48.4)	1.94 (1.79–2.11)	Reference	—
2010	26,088 (47.5)	597 (51.6)	2.29 (2.11–2.48)	1.03 (0.91–1.16)	.69

CI, confidence interval; RR, relative risk.
Data are mean±standard deviation or n (%) unless otherwise specified.
* The unit of analysis is women's abortions; the same woman may be represented more than once here if she had multiple abortions during the study period. Plus–minus values are mean±standard deviation. Data on age were missing for 25 abortions, data on woman's race or ethnicity were missing for 6,670 women, and data on woman's residence type were missing for 6,758 abortions.
† Cases may not add up to 1,156 as a result of missing data.
‡ Adjusted for age, race or ethnicity, abortion procedure type, site of procedure, residence type, and year of abortion.
§ Other includes Alaskan, American Indian, Hawaiian, Samoan, unknown, or other race or ethnicity.

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Table 2. Reasons for Emergency Department Visits Within 6 Weeks of Initial Abortion

Characteristic of Visit	Total ED Visits (n=3,531)	Proportion of ED Visits (95% CI)
Reason for visit		
Not abortion-related	1,758	49.8 (48.14–51.44)
Abortion-related	1,431	40.5 (38.92–42.15)
Not abortion-related but concurrent*	332	9.4 (8.48–10.41)
Unknown	10	0.3 (0.15–0.53)
Abortion-related ED visit	1,431	40.5 (38.92–42.15)
Received treatment†	478	33.4 (31.00–35.89)
Did not receive treatment‡	953	66.6 (64.11–69.00)
Abortion procedure type		
Medication	770	21.8 (20.47–23.20)
1st-trimester aspiration	2,266	64.2 (62.57–65.74)
2nd trimester or later	495	14.0 (12.91–15.20)

ED, emergency department; CI, confidence interval.

* These are medical problems that were diagnosed, treated, or diagnosed and treated at the time of the abortion procedure (eg, ectopic or molar pregnancy, preexisting medical condition, or concurrent problems present at the time of the procedure).

† These are cases in which a patient received an abortion-related diagnosis or treatment and therefore were considered a complication.

‡ These are cases in which a patient presented with abortion-related symptoms but did not receive a pathologic diagnosis or treatment (eg, observation only).

in 2009 and 2010 and all billing records for all clinical encounters for each of those beneficiaries up to 6 weeks after the abortion. Each clinical encounter results in multiple ($\bar{x}$=12) billing records; thus, we acquired 659,361 records.

Data included an encrypted beneficiary identification number, date of birth, race or ethnicity, city, state, zip code, date(s) of service, type of facility, diagnosis (International Classification of Diseases, 9th Revision [ICD-9] codes), procedure or treatment (Healthcare Common Procedure Coding System, Current Procedural Terminology [CPT] codes), facility type, and amount paid per treatment. For each abortion, we calculated the beneficiary's age and urban or rural residence (determined by zip code).

Abortions were identified using Healthcare Common Procedure Coding System codes (59840–59841, 59850–59852 and 59855–59857, X7724, Z0336); these codes also indicated the abortion type: 1) "medication abortions," which includes use of mifepristone and misoprostol up to 9 weeks of gestation; 2) "first-trimester aspiration," which includes both manual and electric aspiration abortions as well as dilation and curettage "in the first 12–14 weeks of gestation"[14]; and 3) "second-trimester or later procedures." Included in this latter category are medical and surgical abortions performed using multiple abortion techniques such as dilation and evacuation, with or without osmotic dilators and misoprostol as well as full or partial inductions used "after 12–14 weeks of gestation."[14] The billing data that we had did not allow us to make a determination of weeks of gestation nor the specific technique used.

We searched for additional claims made to MediCal up to 6 weeks after the abortion for each abortion identified. Postabortion ED visits (not including urgent care) within 6 weeks were identified using codes associated with ED use (Healthcare Common Procedure Coding System codes: 99281–99285, and Z7502). Clinically trained reviewers evaluated all available billing data (including all ICD-9 and Healthcare Common Procedure Coding System or CPT procedure codes) for each beneficiary who had an ED visit and assigned the visit to one of three categories: 1) not abortion-related; 2) not abortion-related but for a concurrent problem (diagnosed, treated, or diagnosed and treated at the time of the abortion); and 3) abortion-related. An ED visit was classified as abortion-related based on the constellation of ICD-9

Table 3. Major and Minor Abortion-Related Complication Rates by Procedure Type

Complication Type	Medication Abortion (n=11,319) Rate/100 (95% CI)	n	1st-Trimester Aspiration (n=34,755) Rate/100 (95% CI)	n
Major	0.31 (0.21–0.41)	35	0.16 (0.12–0.21)	57
Minor	4.88 (4.49–5.28)	553	1.10 (0.99–1.21)	381
Total complications	5.19 (4.79–5.60)	588	1.26 (1.14–1.38)	438

CI, confidence interval.

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and Healthcare Common Procedure Coding System or CPT procedure codes for that visit. For example, in many cases, it was a combination of an ICD-9 code for an abortion, postabortion complication, or abdominal pain that indicated that the visit was abortion related along with a Healthcare Common Procedure Coding System or CPT procedure code for a pregnancy test, pelvic examination, transvaginal ultrasonography, abdominal ultrasonography, or dose of misoprostol.

Each abortion-related visit was then classified as 1) woman received an abortion-related diagnosis, treatment, or both; or 2) woman presented with abortion-related symptoms such as abdominal pain or cramping but received no pathologic diagnosis or treatment. When ED visits took place for multiple reasons, only the reason most closely related to the abortion was recorded (Fig. 1).

Additionally, we identified all ambulance transfers (Healthcare Common Procedure Coding System codes: X0030, X0034, X0036, X0400, X0402, X0412) and all self-referred ED visits on the day of the abortion regardless of whether the visit resulted in an abortion-related diagnosis or treatment.

The process of identifying and classifying abortion complications involved several steps. We defined a complication as any postabortion adverse event that received an abortion-related diagnosis or treatment at any source of care, including EDs and the original abortion facility within 6 weeks of an abortion procedure. To identify complications, the clinically trained reviewers evaluated all: 1) abortion-related diagnoses and treatments identified through the ED visit analysis described previously (excluding visits having no pathologic diagnosis or treatment); 2) ICD-9 codes that indicate abortion-related complications (635.00–635.82) and Healthcare Common Procedure Coding System or CPT codes for laparoscopy, laparotomy, and hysterectomy surgeries (49000, 49320, 49329, 58150, 58578, 58960), blood transfusions (86970, P9016–P9021, P9048, 390), and antibiotics commonly used to treat abortion-related infections and sepsis at least 1 day after the abortion; and 3) subsequent medication abortions and aspirations within 6 weeks.

The reviewers examined each case identified through this process and applied a systematic classification scheme developed by several of this study's authors and used in a recent study of abortion safety.[3] The classification system comprised a list of known abortion complications with standard definitions that included specific criteria (signs, symptoms, laboratory findings) to indicate the complication diagnosis. To validate the system, first, outside experts who work with the U.S. Agency for Health Research & Quality Evidence-Based Practice Centers and from abortion-related research or service delivery reviewed the classification system. Second, a Data and Clinical Safety Monitoring Committee reviewed incident data to further clarify complication definitions and criteria.

For this study, the clinician reviewers categorized each identified case into one of seven diagnoses: incomplete abortion, failed abortion, hemorrhage, infection, uterine perforation, anesthesia-related, and other or undetermined. The clinically trained reviewers examined all available billing data for the beneficiary, including laboratory tests ordered and medications, to validate each diagnosis. For example, to confirm a diagnosis of failed abortion, they checked for additional confirmatory evidence such as codes for aspiration or prenatal care. For diagnoses of hemorrhage, the reviewers looked for treatments such as aspiration, Methergine, or blood transfusion. One diagnosis category was assigned per abortion; when the billing records indicated more than one diagnosis, the highest level diagnosis was selected. Cases identified based on subsequent medication abortion, misoprostol dose, or aspiration within 6 weeks of the initial abortion without any ICD-9 code indicating a complication were categorized as "other or undetermined."

2nd Trimester or Later (n=8,837)		Total (N=54,911)		*P*	
Rate/100 (95% CI)	n	Rate/100 (95% CI)	n	Medication Abortion vs 1st-Trimester Abortion	1st-Trimester Abortion vs 2nd Trimester or Later
0.41 (0.27–0.54)	36	0.23 (0.19–0.27)	126	.003	<.001
1.09 (0.87–1.30)	96	1.88 (1.76–1.99)	1,030		
1.47 (1.22–1.72)	130	2.11 (1.99–2.23)	1,156	<.001	.12

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Table 4. Distribution of Abortion-Related Complication Diagnoses by Type of Procedure and Type of Treatment

Characteristic	Complication Diagnosis			
	Incomplete Abortion	Failed Abortion	Hemorrhage	Infection
Abortion procedure type‡				
Medication abortion (11,319)	99 (0.87)	15 (0.13)	16 (0.14)	26 (0.23)
1st-trimester aspiration (34,755)	116 (0.33)	14 (0.04)	44 (0.13)	94 (0.27)
2nd trimester or later (8,837)	16 (0.18)	1 (0.01)	26 (0.29)	18 (0.20)
Total (54,911)	231 (0.42)	30 (0.05)	86 (0.16)	138 (0.25)
Type of treatment§				
No treatment	0 (0.00)	5 (16.67)	0 (0.00)	0 (0.00)
Medication	2 (0.87)	0 (0.00)	20 (23.27)	100 (72.46)
Uterine aspiration	198 (85.71)	22 (73.33)	22 (25.58)	8 (5.80)
Both medication and aspiration	18 (7.79)	0 (0.00)	5 (5.81)	8 (5.80)
Other‖	13 (5.63)	3 (10.00)	34 (39.53)	6 (4.35)
Undetermined	0 (0.00)	0 (0.00)	5 (5.81)	16 (11.59)
Total	231 (100.0)	30 (100.0)	86 (100.0)	138 (100.0)

Data are n (%).
* Includes one diagnosis of cervical injury requiring suture repair.
† For major complications, this diagnosis includes undetermined diagnoses that required blood transfusions and surgery. For minor complications, the majority of this diagnosis consisted of cases treated with repeat abortion, but the exact diagnosis could not be determined. This category also includes diagnoses such as nonanesthesia-related allergic reactions and seizures.
‡ Row percentages reported.
§ Column percentages reported.
‖ Includes treatments such as blood transfusion (n=50 for major complications), surgical repair (n=13 for major complications), and tamponade.

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Cases with the ICD-9 code "635.8 Abortion with unspecified complication" were also categorized as other or undetermined. To produce the most conservative estimate, we included undetermined diagnoses in the overall complications estimate.

Each complication was then classified as receiving one of six treatment categories: no treatment, medication (including mifepristone and misoprostol, misoprostol alone, or other medications), uterine aspiration, both medication and aspiration, other treatment, or undetermined. Abortion-related complications were classified as major if they required hospital admission (vendor codes 50, 60), surgery, or blood transfusion with all others classified as minor.

The data analysis was done in several steps. Using Stata 13, first we described the sample characteristics: age, race, residence, abortion procedure type, facility type, and year of abortion. Second, we estimated ED visits on the day of the abortion and within 6 weeks and present reasons for visits. Third, we estimated the abortion-related complication rate by the sample characteristics and the relative risk of a complication adjusted for all other characteristics using a generalized linear mixed model that accounts for lack of independence between multiple abortions by the same woman and those performed by the same health care provider; *P* values were determined from z tests derived from the model. Women who had missing data for any characteristic were retained in the model. Fourth, we compared major and minor complications by abortion procedure type using Pearson χ^2 tests. Finally, we described complication diagnoses by abortion procedure type and treatment. The abortion was the unit of analysis because 8.3% (n=4,165) of women in the data set had more than one abortion. Statistical significance was set at $P<.05$ for all comparisons; 95% confidence intervals (CIs) are reported.

RESULTS

Among the 659,361 records received, we identified 54,911 abortions among 50,273 fee-for-service Medi-Cal beneficiaries in 2009 and 2010. The largest proportions of women were ages 20–29 years, Hispanic, urban, had a first-trimester aspiration abortion, and were seen at an outpatient clinic (Table 1).

Among all 54,911 abortions, one in 1,036 (0.10%, n=53) were followed by an ED visit on the day of the abortion, including 1 of 5,491 (0.03%, n=15) transferred by ambulance for immediate care, although not all resulted in an abortion-related diagnosis or treatment.

Among all abortions (N=54,911), 1 of 16 (6.4%, n=3,531) was followed by an ED visit within 6 weeks of the abortion. Of these, 49.8% (n=1,758) were

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Complication Diagnosis			
Uterine Perforation*	Anesthesia-Related	Other or Undetermined†	Total (N=54,911)
0 (0.00)	0 (0.00)	432 (3.82)	588 (5.19)
2 (0.01)	2 (0.01)	166 (0.48)	438 (1.26)
7 (0.08)	2 (0.02)	60 (0.68)	130 (1.47)
9 (0.02)	4 (0.01)	658 (1.20)	1,156 (2.11)
1 (11.11)	0 (0.00)	22 (3.34)	28 (2.42)
0 (0.00)	4 (100.0)	205 (31.16)	331 (28.63)
0 (0.00)	0 (0.00)	400 (60.79)	650 (56.23)
0 (0.00)	0 (0.00)	2 (0.30)	31 (7.44)
5 (55.56)	0 (0.00)	23 (3.50)	86 (2.68)
3 (33.33)	0 (0.00)	6 (0.91)	30 (2.60)
9 (100.0)	4 (100.0)	658 (100.0)	1,156 (100.0)

unrelated to the abortion, 9.4% (n=332) were conditions unrelated to but concurrent with the abortion, and 40.5% (n=1,431) were abortion-related. Among abortion-related visits, two thirds (66.6%, n=953) were cases in which a patient presented with abortion-related symptoms but did not receive a pathologic diagnosis or treatment. Thus, 1 of 115 (0.87%, n=478) abortions resulted in an ED visit receiving a diagnosis, treatment, or diagnosis and treatment. Among all abortion-related ED visits (n=1,431), 21.8% (n=770) followed a medication abortion, 64.2% (n=2,266) followed a first-trimester aspiration abortion, and 14.0% (n=495) followed a second-trimester or later procedure (Table 2).

Among all abortions (N=54,911), 1,156 (2.1%, 95% CI 1.99–2.23) resulted in an abortion-related complication diagnosed or treated at any source of care, including EDs and the original abortion facility. The unadjusted complication rate was 5.2% (n=588) for medication abortions, 1.3% (n=438) for first-trimester aspiration abortions, and 1.5% (n=130) for second-trimester or later procedures. Adjusted results indicate that women ages 30–39 years were 1.20 (95% CI 1.02–1.40) times as likely to have a complication compared with women ages 20–24 years, and Hispanic women were significantly less likely to have a complication compared with white women. Medication abortions were 5.96 (95% CI 5.11–6.94) times as likely to result in a complication as first-trimester aspiration abortions. Women receiving abortion care at hospitals or physician's offices or groups were significantly more likely to have a complication than women receiving care at outpatient clinics (Table 1).

The rate of major complications among all 54,911 abortions was 0.23% (95% CI 0.19–0.27) (n=126, 1/436), 0.31% (n=35) among women who had medication abortions, 0.16% (n=57) among women who had first-trimester aspiration abortions, and 0.41% (n=34) among women who had second-trimester or later procedures (Table 3). Among all women, 0.20% (n=108) were admitted to hospitals, 0.02% (n=13) had surgery, and 0.09% (n=50) received blood transfusions (data not shown). These three categories are not mutually exclusive; some women were admitted to a hospital and had surgery, received a blood transfusion, or had surgery and a blood transfusion.

The most common complications were other or undetermined diagnoses (1.20%, n=658), comprised mostly of undetermined diagnoses that lead to repeat abortion, and incomplete abortions (0.42%, n=231) (Table 4). The majority of incomplete abortions (85.7%, n=198) and failed abortions (73.3%, n=22) were treated with uterine aspiration. The majority of hemorrhage cases were treated by other treatments (including blood transfusion) (39.5%, n=34) or medication (23.3%, n=20). All anesthesia-related cases were treated with medication as were the majority of infections (72.5%, n=100).

DISCUSSION

We observed a 2.1% abortion-related complication rate after nearly 55,000 abortions diagnosed or treated at all sources of care. The majority were minor. Rates of transfers to an ED, hospital admissions, surgeries, and blood transfusions were low. The complication rate is much lower than that found during childbirth[15] and comparable to that found in the literature[3,7] even when ED visits are included and there is no loss to follow-up.

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We observed the highest rate of complications among women obtaining medication abortions (5.2%, n=588), the vast majority of which were minor and expected. This rate may be overestimated with aspirations performed presumptively or to alleviate bleeding or cramping symptoms.[16] Nevertheless, this rate is consistent with intervention rates found in other studies.[17,18]

The complication rate for second-trimester or later procedures is lower than other studies.[4,19] This may be because the second-trimester or later category includes a large number of abortions performed earlier in the second trimester when complication rates are closer to those in the first trimester. Only 1.4% of all abortions nationally occur after 20 weeks of gestation[20]; our data should not be used to make determinations about the complication rate among the small number of procedures performed later in pregnancy.

We found a high rate (6.4%) of ED visits after abortion, half of which were not abortion-related. This finding is consistent with previous research and could reflect Medi-Cal beneficiaries' use of the ED as the health care provider of first resort.[11] Additionally, the Medi-Cal fee-for-service population has been noted as having greater health risks and more costly use compared with the Medi-Cal managed care population.[21]

Two thirds of abortion-related ED visits did not result in a diagnosis or treatment, representing visits primarily for symptoms, not complications. Strategies to reduce ED visits include increasing the number and types of Medi-Cal primary care providers, particularly in underserved areas, who can provide abortion care, postabortion care, or both, and improving health care provider–patient communication on nonurgent postprocedure side effects.

This study examines postabortion ED visits and complications up to 6 weeks and across multiple facilities without loss to follow-up, addressing a common methodologic limitation of other studies. In other studies, follow-up periods ranged from 2 to 4 weeks with most considering follow-up a return visit to the original abortion facility. When reported, loss to follow-up varies widely: 9% at 1 week,[7] 2–34% at 2 weeks,[5,8,9] and between 8 and 65% in studies where duration is not specified.[22,23] Additionally, this study has the sample size necessary to robustly estimate rare events.

Using billing codes to identify complications has methodologic limitations. Administrative data sets often contain erroneous codes[24]; however, our clinical reviewers examined all related billing records for patients with complications for inconsistencies and errors. Also, by relying on Medi-Cal codes, we could not assess whether any of the complications lead to deaths or detect complications not documented by billing codes. It is possible that complications seen or treated at the original abortion facility did not result in any Medi-Cal reimbursements, thereby underestimating the complication rate.

We were unable to determine the exact week of gestation of each abortion, which is known to be a strong predictor of complication risk.[6] Additionally, repeat abortions performed within 6 weeks were assumed to be for the same pregnancy, but they may have been for new pregnancies. This, too, may lead to overestimating the complication rate, although the proportion of new pregnancies is likely too small to have much effect.

Regarding generalizability to the national abortion population, demographically, our sample had higher rates of Hispanics, lower rates of blacks,[25] and presumably higher rates of low-income women. Medi-Cal beneficiaries may have more health problems than the general population[21] and given that the sample had insurance coverage, they may differ from women whose follow-up care is self-pay. These differences would mean that the reported complication rate is overestimated.

These new data can inform policy debates regarding abortion regulation in the United States. State legislatures have passed regulations such as ambulatory surgical center requirements (23 states), transfer agreement laws (eight states), and hospital admitting privileges requirements (13 states)[26] with the stated intent to increase safety. Given that in practice their ultimate effect often is the closure of abortion facilities,[27] there is a need to consider the public health effect of these policies, weighing any theoretical incremental reduction in patient risk that may occur against any increases in risk that may occur with reduced access to abortion care.

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Outcomes and Safety of History-Based Screening for Medication Abortion
A Retrospective Multicenter Cohort Study

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IMPORTANCE Screening for medication abortion eligibility typically includes ultrasonography or pelvic examination. To reduce physical contact during the COVID-19 pandemic, many clinicians stopped requiring tests before medication abortion and instead screened patients for pregnancy duration and ectopic pregnancy risk by history alone. However, few US-based studies have been conducted on the outcomes and safety of this novel model of care.

OBJECTIVE To evaluate the outcomes and safety of a history-based screening, no-test approach to medication abortion care.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study included patients obtaining a medication abortion without preabortion ultrasonography or pelvic examination between February 1, 2020, and January 31, 2021, at 14 independent, Planned Parenthood, academic-affiliated, and online-only clinics throughout the US.

EXPOSURES Medications for abortion provided without preabortion ultrasonography or pelvic examination and dispensed to patients in person or by mail.

MAIN OUTCOMES AND MEASURES Effectiveness, defined as complete abortion after 200 µg of mifepristone and up to 1600 µg of misoprostol without additional intervention, and major abortion-related adverse events, defined as hospital admission, major surgery, or blood transfusion.

RESULTS The study included data on 3779 patients with eligible abortions. The study participants were racially and ethnically diverse and included 870 (23.0%) Black patients, 533 (14.1%) Latinx/Hispanic patients, 1623 (42.9%) White patients, and 327 (8.7%) who identified as multiracial or with other racial or ethnic groups. For most (2626 [69.5%]), it was their first medication abortion. Patients lived in 34 states, and 2785 (73.7%) lived in urban areas. In 2511 (66.4%) abortions, the medications were dispensed in person; in the other 1268 (33.6%), they were mailed to the patient. Follow-up data were obtained for 2825 abortions (74.8%), and multiple imputation was used to account for missing data. Across the sample, 12 abortions (0.54%; 95% CI, 0.18%-0.90%) were followed by major abortion-related adverse events, and 4 patients (0.22%; 95% CI, 0.00%-0.45%) were treated for ectopic pregnancies. Follow-up identified 9 (0.40%; 95% CI, 0.00%-0.84%) patients who had pregnancy durations of greater than 70 days on the date the mifepristone was dispensed that were not identified at screening. The adjusted effectiveness rate was 94.8% (95% CI, 93.6%-95.9%). Effectiveness was similar when medications were dispensed in person (95.4%; 95% CI, 94.1%-96.7%) or mailed (93.3%; 95% CI, 90.7%-95.9%).

CONCLUSIONS AND RELEVANCE In this cohort study, screening for medication abortion eligibility by history alone was effective and safe with either in-person dispensing or mailing of medications, resulting in outcomes similar to published rates of models involving ultrasonography or pelvic examination. This approach may facilitate more equitable access to this essential service by increasing the types of clinicians and locations offering abortion care.

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Each year nearly 1 million people in the US seek an induced abortion.[1] Medication abortion with mifepristone and misoprostol is currently approved by the US Food and Drug Administration (FDA) for use through 70 days of pregnancy,[2] although based on evidence, many clinicians offer it up to 77 days.[3,4] Typically, clinicians perform ultrasonography or a pelvic examination before treatment to determine the duration and location of the pregnancy. However, during the COVID-19 pandemic, some clinics relied on patient history alone, without ultrasonography or pelvic examination, to reduce physical contact.[5-8] In 2020, the FDA temporarily relaxed its in-person dispensing requirement on mifepristone for the duration of the pandemic.[9] By October 2020, guidelines issued by the Society of Family Planning,[10] the American College of Obstetricians and Gynecologists[10] and the National Abortion Federation[11] had been amended to endorse this no-test approach, providing abortion medications without ultrasonography or other facility-based tests.[12] Together, these changes enabled the emergence of several new online services that offered medication abortion entirely remotely using telemedicine and mail.[13,14]

Several studies, primarily in the UK and Canada, have concluded that history-based screening for medication abortion is safe and effective.[14-18] The largest, which included 18 435 medication abortions in the UK provided without screening ultrasonography, reported that 99% were complete without intervention, and serious adverse events occurred in 0.02%.[15] An analysis of data from 425 participants in the TelAbortion study,[19] a prospective multicenter study of medication abortions provided by telemedicine and mail conducted in the US, also found high effectiveness and safety in the subset screened by history alone, although these patients had lower effectiveness rates (94%) than those who had had pretreatment tests (98%). Another study among 141 patients of a new online service in California found an effectiveness rate of 95% and no major adverse events.[14]

Many people throughout the US face insurmountable financial, transportation, legal, and other barriers to reaching an abortion facility,[20] and access to abortion care is geographically inequitable.[21,22] Longer travel distance means increased logistical and emotional burdens and costs for gas or public transit fare, hotel stays, and loss of wages from time off work, as well as arranging for childcare. Access to patient-centered abortion care could be greatly improved if more primary care and other clinicians could prescribe abortion medications locally to their patients without specialized equipment and if abortion medications could be dispensed by brick-and-mortar and mail-order pharmacies.

We conducted a multicenter retrospective cohort study assessing the effectiveness and safety of using history-based screening alone for medication abortion care among a large sample of US patients from diverse clinics. This article summarizes the protocols that the clinics adopted, describes the characteristics of patients who had no-test abortions, and estimates the effectiveness and safety of no-test medication abortion. We also compare the effectiveness of abortions with medications dispensed in-person to those dispensed by mail to patients.

Key Points

Question What are the outcomes and safety of medication abortion care provided to patients screened for eligibility by history alone without ultrasonography or pelvic examination?

Findings In this multicenter cohort study of 3779 patients with eligible abortions, 95% of abortions were complete without additional medical intervention, and 0.54% were followed by a major abortion-related adverse event.

Meaning This study provides evidence that screening patients for medication abortion using history alone maintains high effectiveness and low risk; this screening approach may facilitate more equitable access to abortion care by enabling a wider variety of clinicians to offer this essential service.

Methods

Between May 2020 and January 2021, we recruited US clinics through webinars, professional email distribution lists, and personal contacts, inviting any facility that offered medication abortion using history-based screening for at least some patients to join the study. We included clinics that offered history-based screening through the TelAbortion study (NCT02513043 and NCT04599725).[23,24] Each clinic completed a survey on its medication abortion protocol, including eligibility criteria and screening procedures. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cohort studies. Allendale Institutional Review Board and University of California, San Francisco Institutional Review Board provided ethical approvals. Because this study was a retrospective medical record review, and thus presented no more than minimal risk, the institutional review boards waived the need for patient informed consent.

Staff at participating clinics abstracted medical records of all medication abortions in which both mifepristone and misoprostol were dispensed without pretreatment ultrasonography or pelvic examination during a defined subperiod between February 1, 2020, and January 31, 2021. Clinic staff were required to be familiar with their clinic's protocols and received a 1-hour training with 1 or 2 of the study coauthors (L.R.K. and sometimes E.G.R.). Staff entered data into a secure online REDCap database,[25,26] including patient age, race and ethnicity, abortion payment type, zip codes, details about mifepristone and misoprostol provision, and events after provision, such as timing of mifepristone and misoprostol administration, unscheduled clinical contacts, treatments, diagnosis and treatment of ectopic pregnancy, last known status of pregnancy (viable, nonviable, or unknown), and confirmatory test results. Race and ethnicity categories included Black, Latinx/Hispanic, White, multiracial and other, and unknown. The "other" category included Alaska Native, American Indian, Asian, Asian Indian, Filipino, Guyanian, Guamanian/Chamorro, Japanese, Middle Eastern, Native American, Native Hawaiian, Pacific Islander, and Turkish. We used 2010 Rural-Urban Commuting Area (RUCA) codes[27] to categorize participant zip codes into urban, suburban, and rural places.

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We asked site staff to report the final outcome as determined by a clinician and as recorded in the medical record. Although we collected data on test results that supported the diagnosis of complete medication abortion, we did not systematically collect information on the criteria clinicians used to diagnose abortions as complete by history. The first 3 authors (U.D.U., E.G.R., and L.R.K.) reviewed selected cases to clean data and flagged any inconsistencies within a specific medical record. These records were then rereviewed by clinic staff, who made any needed corrections. Additionally, 4 clinician coauthors with experience in abortion provision (B.K., L.C., C.M.B., and M.G.) reviewed selected cases to resolve analysis outcomes.

Outcomes

Effectiveness and safety were the primary outcomes of interest and were defined during a consensus meeting held in December 2020 with experts in medication abortion research and clinical care. We defined effectiveness as a binary measure of complete medication abortion after initial treatment without subsequent known intervention. Abortions that met any of the following 4 criteria were determined not to be complete: (1) the patient had an aspiration, dilation and evacuation, other procedure, or other surgical intervention; (2) the patient received greater than 200 mg of mifepristone, more than 1600 µg of misoprostol, or other uterotonic medications; (3) the patient received treatment for ectopic pregnancy; or (4) the patient had a viable pregnancy detected by ultrasonography at last contact and no known intervention.

Among abortions recorded as complete, we coded abortions as "complete by test" if the patient had a negative urine pregnancy test result, ultrasonography or pelvic examination showing no continuing pregnancy, an expected decline in serum beta human chorionic gonadotropin (β-hCG) level, a single posttreatment serum β-hCG value less than 500 mIU/mL at least 8 days after mifepristone dispensing,[28] or clinician examination of intact fetus or fetal parts. We coded abortions as "complete by history" if the site staff indicated that the abortion was complete based on a symptom checklist or patient report, if at the time of a subsequent pregnancy the patient reported that the prior pregnancy had ended in abortion, or if the patient reported expulsion of intact fetus or fetal parts. After reviewing preliminary results, including a lower proportion of known outcomes and a lower effectiveness rate among the group who received the medications by mail rather than in person, we reviewed 230 records for which the abortion outcome was originally coded as unknown but included text pertaining to the abortion outcome in the notes field. The clinician authors reviewed all 230 of these records and recoded 67 of them as "complete by history" based on notes in the study database indicating that the treating clinician had no concern that the abortion was incomplete after phone, text, or email follow-up contact with the patient. The results presented herein incorporate the recoded data.

We defined safety as a binary measure of abortions not followed by a known abortion-related major adverse event, which was defined as hospital admission, blood transfusion, major surgery, including laparotomy and laparoscopy for ectopic pregnancy, or death. The clinician authors determined the relation of adverse events to the abortion by consensus.

We assessed 2 secondary outcomes: ectopic pregnancy and retrospective determination that the initial medication abortion treatment had been provided at greater than 70 days of gestation. While some clinics routinely offered medication abortion up to 77 days, we sought to identify any abortion where it was discovered only at follow-up that the initial medication was dispensed beyond the gestational limit on the FDA-approved mifepristone label.

Statistical Analysis

We first described the characteristics of the clinics and their protocols. We then summarized patient and service delivery characteristics and compared the characteristics of patients for whom abortion outcomes were known and unknown.

We then used mixed-effects logistic regression models to produce effectiveness and safety rates using Stata's margins and mimrgns commands. After finding no evidence of differential clustering by TelAbortion participation or by multiple abortions from the same patient, these models included only 1 random intercept to account for clinic-level clustering.

To estimate effectiveness outcomes, we originally conducted complete case analyses, examining unadjusted and adjusted effectiveness rates overall and by patient and service delivery characteristics among only those abortions with recorded outcomes. However, based on editor suggestion, we then conducted an analysis using multiple imputation by chained equations to account for missing outcomes due to loss to follow-up. We assumed data to be missing at random and imputed missing data for covariates and effectiveness and safety outcomes in the multivariable models using Stata's mi impute command.[29] Imputation models included effectiveness and safety outcome variables and age, race and ethnicity, residence, prior medication abortion, participation in the TelAbortion Study, method of mifepristone provision, and pregnancy duration. We computed 200 imputations to facilitate reproducibility for rare outcomes and combined the imputed results using Stata's mi estimate command. We then used a multivariable mixed-effects logistic regression model adjusting for age, race and ethnicity, residence, prior medication abortion, participation in the TelAbortion Study, method of mifepristone provision, and pregnancy duration to estimate adjusted effectiveness rates. We also estimated rates of intervention and continuing pregnancy using multivariable mixed-effects logistic regression, adjusting for the same variables.

We performed 2 additional sensitivity analyses for the effectiveness outcomes. The first replicated the effectiveness analysis excluding patients whose outcomes were determined by history alone. The second sensitivity analysis was ad hoc, based on reviewer suggestion, among only those at 9 weeks or shorter gestation who initially received 800 µg of misoprostol. Both of these analyses were performed on the imputed data and adjusted for the same covariates as the primary efficacy analysis.

We then estimated the overall safety rate among all abortions with any follow-up information recorded, as well as the

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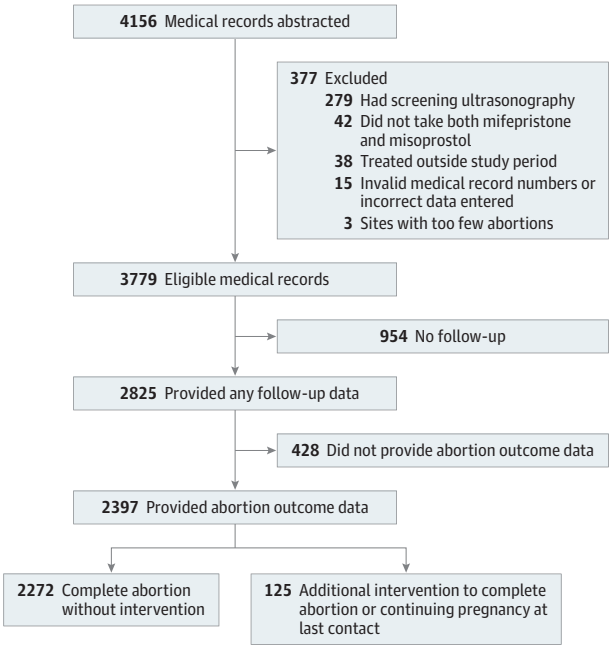
rates of each major adverse event type (blood transfusion, surgery, or hospital admission) without adjustment. Additionally, we estimated adjusted safety rates using the imputed data set, adjusting for the same covariates as in the effectiveness analysis. To facilitate model convergence for all rare outcomes (n < 9), the random intercept for clinic was omitted in the unadjusted analyses, and rates from the imputed data were calculated with random effects but without adjustment. We also described all ectopic pregnancies and the outcomes of cases found by posttreatment ultrasonography or examination of the fetus to have had pregnancy durations greater than 70 days at screening, but not identified at screening.

For both effectiveness and safety outcomes, we report both the unadjusted complete case analysis results and the adjusted multiple imputation analysis results. All rates reported in text are from the random-effects models calculated after imputation.

All analyses excluded patients who reported that they took neither mifepristone nor misoprostol. All analyses of patient data used the abortion, not patient, as the unit of analysis. All statistical tests were 2-tailed with significance set at .05. We used Stata, version 15.1 (StataCorp LLC).

Figure. Study Flow Diagram



Results

Participating Clinics

We received data from 15 clinics, representing independent, Planned Parenthood, academic-affiliated, and online-only clinics. We excluded 1 clinic that contributed only 3 abortions, leaving 14 clinics for analysis. Each clinic contributed a range of 11 to 981 eligible abortions; 5 provided no-test abortions both outside of and within the TelAbortion study, 1 provided them only within the study, and 8 only outside of the TelAbortion study. Most clinics generally followed a published protocol,[12] with modifications determined by each individual clinic. The clinical protocols are described in the eTable in the Supplement. Most (n = 9) clinics offered no-test medication abortion up to 77 days of gestation. Some clinics (n = 10) varied the number of misoprostol tablets dispensed by pregnancy duration or study participation; others routinely provided 8 tablets to all patients (n = 4). More than half of clinics (n = 9) offered multiple methods of mifepristone dispensing during the study period; 3 dispensed mifepristone to patients only in-person, and 2 dispensed only by mail, either directly from the clinic or via mail-order pharmacy. Among the 12 clinics that dispensed mifepristone in person, 4 offered a curbside pickup option that allowed patients to receive the medications without coming inside the facility. Four clinics did not require Rh factor testing for any patients. All but 1 clinic routinely called, texted, or emailed patients at 1 to 2 weeks and again at 4 weeks to determine patient outcomes, while 1 clinic offered an optional follow-up contact or visit and advised patients to take a pregnancy test at 4 to 5 weeks to confirm completion.

Description of the Sample

We received data on 4156 medication abortions. A total of 377 medical records were excluded because medical record data were invalid or incorrectly entered (n = 15), patients were treated outside the study period (n = 38), patients had screening ultrasonography (n = 279), patients did not take both mifepristone and misoprostol (n = 42), and patients were from the excluded clinic (n = 3). Some patients subsequently were entirely lost to follow-up and some provided incomplete follow-up data, for example, confirmation that they took the mifepristone and/or misoprostol but their medical records did not have sufficient data to determine whether their abortions were complete. Thus, of the remaining 3779 patients with abortions, 2825 (74.8%) had some follow-up data, and 2397 (63.4%) had abortion outcome data (**Figure**).

The sample was racially and ethnically diverse and included 870 (23.0%) Black patients, 533 (14.1%) Latinx/Hispanic patients, 1623 (42.9%) White patients, and 327 (8.7%) who identified as multiracial or with other racial or ethnic groups; race or ethnicity was unknown for 426 (11.3%) (**Table 1**). Half of the patients (1903 [50.4%]) paid for the abortion, at least in part, out of pocket. Patients lived in 34 states, and 2785 (73.7%) lived in urban areas. Nearly all abortions (3711 [98.2%]) were determined by patient history to be provided at 70 or less days of gestation. For 2511 (66.4%) abortions, the medications were dispensed in person, and for 1268 (33.6%), they were mailed to the patient. A total of 22 patients had more than 1 abortion at the same clinic and were represented more than once in the data set. Abortion outcomes were more likely to be known if the patient used private insurance to pay for the abortion, had lower pregnancy duration at treatment, received the abortion medications in person, or participated in the TelAbortion study. Among the 425 TelAbortion Study participants in this analysis, outcomes of 346 were reported in a previously published paper.[7] Additionally, we included

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Table 1. Characteristics of the Overall Sample and the Subgroup With Follow-up Data

Characteristic	No. (%)			*P* value
	Total eligible sample (n = 3779)	Sample with known abortion outcome (n = 2397)	Sample without known abortion outcome (n = 1382)	
Age at mifepristone provision, y				
≤24	1186 (31.4)	761 (31.7)	425 (30.8)	.23
25-34	1904 (50.4)	1206 (50.3)	698 (50.5)	
≥35	689 (18.2)	430 (17.9)	259 (18.7)	
Race and ethnicity				
Black	870 (23.0)	536 (22.4)	334 (24.2)	.008
Latinx/Hispanic	533 (14.1)	346 (14.4)	187 (13.5)	
White	1623 (42.9)	1034 (43.1)	589 (42.6)	
Multiracial or other[a]	327 (8.7)	223 (9.3)	104 (7.5)	
Unknown	426 (11.3)	258 (10.8)	168 (12.2)	
Residence[b]				
Urban	2785 (73.7)	1702 (71.0)	1083 (78.4)	.98
Suburban	243 (6.4)	153 (6.4)	90 (6.5)	
Rural	607 (16.1)	430 (17.9)	177 (12.8)	
Unknown	144 (3.8)	112 (4.7)	32 (2.3)	
Payment methods[c]				
Private insurance	769 (20.3)	546 (22.8)	223 (16.1)	<.001
Medicaid	881 (23.3)	581 (24.2)	300 (21.7)	.08
Abortion fund	212 (5.6)	140 (5.8)	72 (5.2)	.95
Patient	1903 (50.4)	1111 (46.3)	792 (57.3)	.10
Site subsidy	46 (1.2)	21 (0.9)	25 (1.8)	.13
Unknown	274 (7.3)	217 (9.1)	57 (4.1)	<.001
Previous medication abortion				
None	2626 (69.5)	1696 (70.8)	930 (67.3)	.002
Any	748 (19.8)	450 (18.8)	298 (21.6)	
Unknown	405 (10.7)	251 (10.5)	154 (11.1)	
Participated in the TelAbortion study				
No	3354 (88.8)	2031 (84.7)	1323 (95.7)	<.001
Yes	425 (11.2)	366 (15.3)	59 (4.3)	
Method of mifepristone provision				
In person	2511 (66.4)	1670 (69.7)	841 (60.9)	<.001
Mailed	1268 (33.6)	727 (30.3)	541 (39.1)	
No. of misoprostol tablets initially prescribed				
4 × 200 µg	2034 (53.8)	1267 (52.9)	767 (55.5)	<.001
8 × 200 µg	1745 (46.2)	1130 (47.1)	615 (44.5)	
Method of misoprostol provision				
Dispensed with mifepristone	3766 (99.7)	2386 (99.6)	1380 (99.9)	.85
Prescription	12 (0.3)	10 (0.4)	2 (0.1)	
Unknown	1 (0.0)	1 (0.0)	0 (0.0)	
Pregnancy duration by last menstrual period at mifepristone provision, d[d]				
<43	1400 (37.0)	904 (37.7)	496 (35.9)	<.001
43-56	1700 (45.0)	1080 (45.1)	620 (44.9)	
57-70	611 (16.2)	365 (15.2)	246 (17.8)	
>70	62 (1.6)	43 (1.8)	19 (1.4)	
Unknown	6 (0.2)	5 (0.2)	1 (0.1)	

[a] The "other" category included Alaska Native, American Indian, Asian, Asian Indian, Filipino, Guyanian, Guamanian/Chamorro, Japanese, Middle Eastern, Native American, Native Hawaiian, Pacific Islander, and Turkish.

[b] Estimated based on patient zip codes using Rural-Urban Commuting Area codes data.[27]

[c] Multiple payment options may apply.

[d] For the mailed group, pregnancy duration was calculated based on the date the medications were mailed.

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Table 2. Unadjusted and Adjusted Rate of Complete Medication Abortion by Characteristics of the Sample

Characteristic	Unadjusted complete case effectiveness rate, % (95% CI)	*P* value	Adjusted imputed effectiveness rate, % (95% CI)[a]	*P* value
No.	2397	NA	3779	NA
Overall	94.5 (92.9-96.1)	NA	94.8 (93.6-95.9)	NA
Age at mifepristone provision, y				
<24	96.4 (94.8-98.0)	[Reference]	96.6 (95.3-98.0)	[Reference]
25-34	94.1 (92.2-96.8)	.01	94.3 (92.8-95.9)	.02
≥35	92.8 (90.0-95.6)	.004	92.6 (89.9-95.3)	.002
Race and ethnicity				
Black	93.8 (91.2-96.5)	.88	93.9 (91.5-96.2)	.43
Latinx/Hispanic	96.4 (94.1-98.7)	.13	96.3 (94.1-98.6)	.31
White	94.0 (92.0-96.1)	[Reference]	94.9 (93.4-96.4)	[Reference]
Multiracial or other[b]	93.8 (90.1-97.5)	.90	93.7 (90.1-97.3)	.53
Residence				
Urban	94.0 (91.6-96.5)	[Reference]	94.2 (91.9-96.5)	[Reference]
Rural	94.7 (93.0-96.4)	.61	94.9 (93.6-96.2)	.57
Previous medication abortion				
None	94.6 (92.8-96.3)	[Reference]	94.7 (93.4-95.9)	[Reference]
Any	95.1 (92.6-97.5)	.69	95.1 (92.9-97.3)	.70
Participated in the TelAbortion study				
No	94.1 (92.1-96.0)	[Reference]	94.4 (93.2-95.8)	[Reference]
Yes	96.0 (93.9-98.2)	.14	96.3 (94.3-98.2)	.17
Method of mifepristone provision				
In person	94.9 (93.1-96.7)	[Reference]	95.4 (94.1-96.7)	[Reference]
Mailed	94.0 (91.8-96.3)	.54	93.3 (90.7-95.9)	.14
Pregnancy duration, d				
<43	95.2 (93.4-97.1)	[Reference]	95.5 (94.1-97.0)	[Reference]
43-56	95.2 (93.4-97.0)	.97	95.5 (94.1-96.9)	>.99
≥57	90.9 (87.1-94.6)	.004	90.9 (87.6-94.2)	.003

[a] Multivariable estimates are adjusted for all other covariates in the table. Both models are mixed-effects models estimated with clinic as a random intercept.

[b] The "other" category included Alaska Native, American Indian, Asian, Asian Indian, Filipino, Guyanian, Guamanian/Chamorro, Japanese, Middle Eastern, Native American, Native Hawaiian, Pacific Islander, and Turkish.

outcomes of 117 patients[14] and 111 patients[8] reported in previous articles.

Effectiveness

The overall adjusted effectiveness rate was 94.8% (95% CI, 93.6%-95.9%) (**Table 2**) and was not significantly different whether the patients picked up their medications (95.4%; 95% CI, 94.1%-96.7%) or received them by mail (93.3%; 95% CI, 90.7%-95.9%). Effectiveness rates were highest among patients who were younger than 24 years and among those with pregnancies of 56 days of gestation or less. The sensitivity analysis excluding cases in which the abortion was determined complete by history alone resulted in an adjusted effectiveness rate of 93.0% (95% CI, 91.2%-94.8%). The sensitivity analysis that included only those with a gestation of 9 weeks or less who initially received 800 µg misoprostol found an adjusted effectiveness rate of 95.7% (95% CI, 94.3%-97.2%). Among the sample, 46 abortions (1.7%; 95% CI, 1.1%-2.2%) were determined by ultrasonography to be continuing viable pregnancies after the initial medications were dispensed (**Table 3**). Among those, 36 were treated with a procedure or additional medication to complete the abortion, 1 had a complete abortion with 1600 µg of misoprostol, and 9 had no further known intervention, so the final outcome was recorded as continuing viable pregnancy.

Safety

The adjusted rate of major abortion-related adverse events was 0.54% (95% CI, 0.18%-0.90%) and was not statistically significantly different for patients who received medications in-person (0.46%; 95% CI, 0.09%-0.83%) and by mail (0.76%; 95% CI, 0.00%-1.57%). Among the patients with follow-up data, 12 major abortion-related adverse events occurred. These events included 8 blood transfusions, 3 major surgical procedures (including a possible but unconfirmed laparoscopic procedure for ectopic pregnancy), and 6 hospital admissions. Abortion-related hospital admissions included 1 due to pain that was treated with antibiotics and an unknown procedure to remove blood clots and residual tissue from the uterus; 2 for bleeding and pain that were treated with aspiration and transfusion; 1 for ongoing bleeding and kidney infection, which was treated with an unknown surgery, transfusion, and antibiotics; 1 for pain associated with endometritis that was treated with antibiotics; and 1 for major surgery (salpingectomy) to treat an ectopic pregnancy (Table 3). In total, 72 patients (2.6%; 95% CI, 1.9%-3.4%) were known to have visited emergency departments, including the 6 that resulted in hospital admissions described above.

We identified 4 ectopic pregnancies (0.22%; 95% CI, 0.00%-0.45%). One was detected 9 days after mifepristone ingestion after the patient contacted the clinic about unilateral

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Table 3. Medication Abortion Additional Interventions and Major Adverse Events

Intervention/adverse event	No.	% (95% CI)	
		Unadjusted rate	Adjusted imputed rate[a]
Effectiveness			
No.	NA	2397	3779
Complete abortion without known intervention[b]	2272	94.5 (92.9-96.1)	94.8 (93.6-95.9)
Intervention to complete abortion[c,d]	116	5.1 (3.7-6.5)	4.6 (3.7-5.5)
Aspiration, second trimester abortion procedure, or surgery[e]	88	3.8 (2.8-4.8)	3.6 (2.7-4.4)
Prescribed >1600 µg of misoprostol, mifepristone, or other medications	37	1.7 (0.7-2.8)	2.5 (1.5-3.6)
Treatment for ectopic pregnancy	4	0.17 (0.00-0.33)	0.22 (0.00-0.45)
Continuing viable pregnancy without known intervention	9	0.34 (0.00-0.74)	1.27 (0.00-2.64)
Safety			
No.	NA	2825	3779
No major abortion-related adverse events	2813	99.6 (99.3-99.8)	99.5 (99.1-99.8)
Major abortion-related adverse events[2]	12	0.42 (0.18-0.66)	0.54 (0.18-0.90)
Blood transfusion	8	0.28 (0.02-0.53)	0.40 (0.08-0.73)
Other major surgery, including treatment of ectopic pregnancy	3	0.11 (0.00-0.23)	0.23 (0.00-0.51)
Hospital admission	6	0.21 (0.04-0.38)	0.21 (0.04-0.38)

Abbreviation: NA, not applicable.

[a] Adjusted rates were calculated from mixed-effects logistic regression models fit to imputed data and adjusted for age, race and ethnicity, residence, prior medication abortion, participation in the TelAbortion Study, method of mifepristone provision, and pregnancy duration, with the exception of rare outcomes ($n \leq 9$), which were not adjusted to facilitate model convergence.

[b] Includes patients who received 800 µg of misoprostol initially followed by a single additional dose of 800 µg of misoprostol. One of these patients had a continuing viable pregnancy after the first dose and then aborted after the second.

[c] Includes 36 continuing viable pregnancies after initial treatment. In total, there were 46 (1.7%; 95% CI, 1.1%-2.2%) continuing viable pregnancies after initial medications were dispensed.

[d] Intervention and safety categories are not mutually exclusive because multiple interventions or treatments may have been provided for a single abortion.

[e] Includes 2 dilation and evacuation procedures and 1 salpingectomy.

Table 4. Patients Determined at Follow-up to Have Had Pregnancy Durations Greater Than 70 Days at Mifepristone Provision

Pregnancy duration documented at mifepristone provision, d	Corrected pregnancy duration at mifepristone provision based on pregnancy duration found at follow-up, d	Pregnancy duration at follow-up appointment, d	Abortion outcome
57	74	91	Procedure
53	80	88	Procedure
72	82	94	Procedure
60	85	92	Procedure
56	87	90	Lost to follow-up after ultrasonography
55	89	101	Procedure
70	90	93	Procedure
68	107	112	Complete abortion without intervention
42	230	231	Complete abortion without intervention

pelvic cramping; the patient was admitted that day to a hospital where a salpingectomy was performed. Two were diagnosed after rising serum β-hCG results and treated with methotrexate; 1 of these may have had a laparoscopic procedure in addition, but full documentation was unavailable. The fourth was reported by an outside physician, but the treatment was unknown and documentation was unavailable.

During follow-up, 9 (0.40%; 95% CI, 0.00%-0.84%) patients were found to have had pregnancy durations greater than 70 days at mifepristone dispensing although not identified at screening (**Table 4**). Of these patients, 6 had procedures to complete the abortion at 88 to 101 days of gestation, 2 had complete abortions without additional intervention at 16 and 33 weeks, and 1, who received mifepristone at 87 days, had a continuing viable pregnancy at last follow-up contact 3 days after screening. The patient who was estimated to be at 33 weeks of gestation delivered a stillborn fetus at home, brought the fetus to the clinic, and required no further medical care.

Discussion

In this retrospective cohort study of patients who obtained medication abortions with screening by history alone from 14 clinics across the US using a range of protocols, we found high effectiveness and safety rates. As the largest (to our knowledge) US study of this approach to date, it offers a generalizable picture of what medication abortion may look like as more primary care and other clinicians adopt history-based screening protocols in-person or remotely. The effectiveness rate of 95% is comparable to studies of medication abortion models with screening ultrasonography that found effectiveness rates of 93% to 98%.[24,30,31] The major adverse event rate of 0.5% (95% CI, 0.2%-0.9%) was slightly higher than previous studies finding rates of 0.2% to 0.3%[31,32] but not significantly different and still rare from a clinical perspective. This study found similarly high effectiveness and

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safety rates comparing patients who received medications in-person vs by mail.

Before the COVID-19 pandemic, the FDA-mandated Risk Evaluation and Mitigation Strategy required mifepristone to be dispensed only in physicians' offices, clinics, or hospitals. The FDA allowed mailing temporarily in mid-2020 and made this change permanent in December 2021.[33] This study adds support for these actions, as we found that mifepristone can be dispensed safely either in person or by mail. Additionally, the mifepristone label could be revised to explicitly state that ultrasonography or clinical examination is not required if pregnancy duration can be reasonably estimated by history and if no symptoms or risk factors for ectopic pregnancy are present.

One of the major obstacles to expanded provision of medication abortion with history-based screening alone is clinician concern about the ability to identify an ectopic pregnancy. In this study, the ectopic pregnancy rate of 2 per 1000 suggests that the screening procedures used by the participating clinics will not triage all patients with ectopic risks to ultrasonography before the abortion. However, the potential benefits of expanded access, increased convenience, and earlier treatment conferred by removing testing requirements may outweigh potential risks of delayed identification of ectopic pregnancies.[34-36]

The risk of inadvertently treating a patient with a pregnancy duration greater than the accepted limit for medication abortion (70 or 77 days) is another concern. In this study, 9 patients were found at follow-up to have been treated at a gestation of greater than 70 days. The true number may be larger, as some advanced gestations may not have been recognized among patients who had successful abortions. We observed 1 case for which pregnancy duration was substantially underestimated; this patient passed the pregnancy and had a complete abortion at 33 weeks of gestation without additional intervention, medical complications, or sequelae. Clinicians offering the no-test approach should counsel patients about the possibility of an unidentified advanced gestation and discuss options for further evaluation and care if the patient were to encounter this situation.

Limitations

The retrospective design of this study limited the precision and detail of the data. In particular, sites did not have uniform, validated criteria for confirming complete abortion using symptoms alone without ultrasonography, serum β-hCG, or urine pregnancy tests. However, the sensitivity analysis that excluded abortion outcomes determined without any tests found only slightly lower effectiveness rates than the full analysis. This study did not include a direct comparison group of patients who received pretreatment ultrasonography and other screening tests; however, given the similarity of our effectiveness and safety findings to those from multiple prior studies, we can be assured that there are not large differences in effectiveness and safety.

The follow-up rate of 75% was comparable to the 77% follow-up rates reported in previous research,[37,38] but we may have failed to identify some additional interventions and adverse events. We aimed to mitigate the loss to follow-up with multiple imputation methods. If patients who were lost to follow-up were more likely to require additional intervention, our analysis may overestimate effectiveness. However, much of the loss to follow-up may be explained by the ubiquity of urine pregnancy tests that allow patients to assess their own outcomes. As history-based screening, telehealth, and self-assessment of outcomes using urine pregnancy tests become more common, the percentage of patients who do not experience complications and who contact the original clinician to confirm abortion completion is likely to decline. The net effect may be an apparent decline in effectiveness rates among patients who complete follow-up.

Conclusions

Given the high effectiveness and very low risks associated with omitting in-person tests and using history-based screening alone, no-test medication abortion can offer substantial benefits to clinicians and patients and is consistent with the principle of patient-centered care. The use of history-based screening may appeal to primary care and other types of clinicians without access to ultrasonography technology or other tests. A shift toward history-based screening could expand the provision of abortion care to a variety of primary care clinicians, including nurse practitioners and physicians in family medicine, adolescent medicine, and internal medicine. Because many of these clinicians work in rural and low-income communities and with marginalized racial and ethnic groups and other historically marginalized communities, increasing the types of clinicians and locations offering abortion services could also lead to more equitable access to abortion care. This expansion could enhance patient-centered care and satisfaction, given that many patients would prefer to get their abortion from their primary care clinician.[39-41]

Combining history-based screening protocols with a pharmacy prescription or mailing of abortion medications to patients can support public health efforts and reduce the numerous logistical, distance, and cost barriers to abortion.[21,22,42,43] No-test medication abortion can lower costs, result in earlier treatment, increase convenience and privacy, and allow patients to avoid harassment at clinics.[17,35] These benefits have the potential to increase equitable access to abortion for all patients, particularly marginalized racial and ethnic groups, those with low incomes, who reside in rural locations, and who face greater barriers to abortion care. Clinicians should eliminate unnecessary tests to support patient-centered care.

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Author Contributions: Dr Upadhyay had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Upadhyay, Raymond, Gold, Kaneshiro, Winikoff.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Upadhyay, Raymond, Koenig, Coplon, Gold, Kaneshiro.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Upadhyay, Koenig.
Obtained funding: Upadhyay, Raymond, Winikoff.
Administrative, technical, or material support: All authors.
Supervision: Upadhyay, Raymond, Boraas, Winikoff.

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Invited Commentary

It Is Time to Change the Standard of Medication Abortion

Jennifer Karlin, MD, PhD; Jamila Perritt, MD, MPH

Before prescribing medication abortion, clinicians have been compelled to perform a pelvic examination or ultrasonography for gestational dating to adhere to the requirements of the US Food and Drug Administration (FDA) Risk Evaluation and Mitigation System (REMS) program for dispensing mifepristone. These examinations require an in-person clinic visit, which can be logistically burdensome and limit access to care. In this issue of *JAMA Internal Medicine*, Upadhyay et al[1] provide evidence that medication abortion using mifepristone and misoprostol is safe and effective for pregnancy termination without requiring an in-person clinical evaluation. These data should reassure clinicians and FDA evaluators that allowing history-based screening in lieu of in-person examinations is appropriate and evidence based.

Related articles pages 482 and 558

This report is particularly timely given the FDA's recently completed review of the Mifepristone REMS Program. On December 20, 2021, the FDA sent a letter to the plaintiffs in a case the American Civil Liberties Union filed in 2017 (*Chelius v Becerra*) on behalf of a Hawaiian doctor and health care associations, which argued that the FDA restricted access to abortion care with no medical basis by requiring in-person dispensing of mifepristone. Based on the available data, the FDA decided to remove the requirement for in-person dispensing of mifepristone.[2-5] This does not change current practice because the FDA had previously removed the in-person dispensing requirement during the COVID-19 public health emergency. While this decision eliminates the in-person dispensing requirement permanently, it does not adjust additional requirements for the patient agreement and the specialized clinician certification, which the FDA left in place. Moreover, the new rules added an additional restriction requiring certification of the pharmacies meant to dispense mifepristone. There are no data that we could find that these certifications of patients, clinicians, and pharmacies adds clinical benefit to an already safe and effective medication with limited contraindications and adverse effects. Moreover, the FDA's action will not affect existing state-level restrictions on access to medication abortion that are already in place. As a result, communities that already face difficulty accessing medication abortion remain vulnerable to medically unnecessary restrictions.

The study by Upadhyay et al[1] provides evidence collected before and during the COVID-19 pandemic in the US that supports a shift in the practice for initiating medication abortion to one that uses history-based screening and remote prescribing. The authors present data from a retrospective cohort study of 3779 medication abortions dispensed either in

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ORAL ABSTRACTS

O01
AN UPDATED ASSESSMENT OF CLINICAL OUTCOMES OF MEDICATION ABORTION WITHOUT PRETREATMENT ULTRASONOGRAPHY

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Objectives: Routine ultrasound before medication abortion may create an impediment to expanding abortion access. This study examines clinical outcomes among medication abortion patients without pretreatment ultrasound evaluation at Planned Parenthood health centers in multiple states.
Methods: We conducted a secondary analysis among 23 Planned Parenthood affiliates that provided medication abortion without pretreatment ultrasound for eligible patients from March 2020 to December 2021. Affiliates collected and aggregated electronic health record data from 19,041 medication abortion patients at <=77 days' gestation (based on self-report of last menstrual period) without a pretreatment ultrasound. Among patients with follow up (n=10,085, 53%), we calculated the incidence rates and 95% CI of the following outcomes: completed abortion, ongoing pregnancy, surgical intervention, emergency department and hospital admissions associated with medication abortion, and confirmed ectopic pregnancies.
Results: Among medication abortion patients with follow-up, 96.6% had a complete abortion (95% CI, 96.3–97.0%), and 2.0% had an ongoing pregnancy (95% CI, 1.7%–2.3%). Four percent of medication abortion patients had a subsequent surgical procedure (4.0%, 95% CI, 3.6%–4.4%), and 2.3% had a documented emergency department/hospital admission (95% CI, 2.0%–2.6%). About 2 in 1,000 had a confirmed ectopic pregnancy (1.7, 95% CI, 1.0–2.7 per 1,000).
Conclusions: Our calculated incidence rates of clinical outcomes align with rates from the previous literature on medication abortion with pretreatment ultrasonography and from the emerging literature on medication abortion without pretreatment ultrasonography. Findings from this analysis suggest that medication abortion without pretreatment ultrasound is safe and effective for eligible patients.

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O02
ABORTION PATIENTS' PRIORITIES AND TRADEOFFS DECIDING WHERE TO OBTAIN OUT-OF-STATE CARE FOLLOWING TEXAS 2021 ABORTION BAN

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Objectives: Explore pregnant Texans' decisions about where to obtain out-of-state abortion care following the September 2021 implementation of Senate Bill 8 (SB8), which prohibited abortions after embryonic cardiac activity.
Methods: To recruit Texans who obtained out-of-state abortion care after SB8, we provided flyers to abortion facilities in Arkansas, Colorado, Kansas, Louisiana, Mississippi, New Mexico, and Oklahoma. Between October 2021 and February 2022, we conducted in-depth telephone interviews with English-speaking participants ≥18 years of age who self-referred to the study to explore their experiences seeking care. We used inductive and deductive codes in our thematic analysis describing people's decisions about where to obtain care and how they evaluated available options.
Results: The 65 Texans who participated considered multiple factors when deciding where to obtain out-of-state care. Participants prioritized facility proximity and appointment availability. The majority called multiple facilities in surrounding states to find the earliest appointment, and were often told the next appointment was 2–4 weeks away. Some ultimately obtained care at a more distant location that had an earlier appointment, and others waited because they could not travel farther. Participants considered the economic hardships of caregiving responsibilities, lost wages, and travel expenses when weighing the tradeoffs between appointment availability and facility proximity, but few mentioned comparing abortion prices at different facilities. Informative facility websites and compassionate scheduling staff solidified participants' choice of care.
Conclusions: Pregnant Texans who could not get an in-state abortion after SB8 made difficult tradeoffs when deciding where to obtain out-of-state care that made seeking services burdensome.

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O03
SAFETY AND EFFECTIVENESS OF SYNCHRONOUS AND ASYNCHRONOUS TELEHEALTH MEDICATION ABORTION PROVIDED BY US VIRTUAL CLINICS

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Objectives: In 2021, new virtual clinics proliferated, offering remote-only telehealth abortion care with synchronous (phone or video) or asynchronous (messaging) communication and mailed pills. However, few large US studies have evaluated their safety and effectiveness.
Methods: We evaluated the safety and effectiveness of medication abortions provided by three virtual clinics operating in 21 states. We reviewed electronic health records for consecutive patients served between April 2021 and January 2022 and also invited the patients to participate in longitudinal surveys. We used multivariable mixed-effects models to estimate effectiveness and safety rates.
Results: Among the 6,134 included medication abortion patients, 73% received asynchronous services. Among the 5,036 (82%) abortion patients with follow-up data, 18 (0.44%, 95% CI: 0.36%-0.52%) had abortions that were followed by a serious adverse event. Abortion outcomes were confirmed for 4,106 (67%) cases, among whom 114 (2.8%, 95% CI: 2.3%-3.3%) required additional intervention to complete the abortion and 7 (0.21%, 95% CI: 0.06%-0.37%) were diagnosed with ectopic pregnancies. Rates of effectiveness (3.0% vs. 2.1%, p=0.187) and serious adverse events (0.44% vs. 0.44%, p=0.991) were similar between asynchronous and synchronous care. Among the 1,592 survey participants, 29 (2%) reported they would have had to continue the pregnancy had they not had access to telehealth abortion. Among survey participants, 47 received medications but did not take them, and among those, 36 still had the pills.

Conclusions: This real-world evidence shows that telehealth medication abortion care is safe and effective. Telehealth can increase access to this vital service while maintaining patient safety.

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O04

PREVALENT BUT NOT INEVITABLE: MAPPING CONTRACEPTION DESERTS ACROSS THE AMERICAN STATES

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Objectives: To provide a socio-spatial analysis of the allocation of Title X funding, the federal government's only program dedicated to reproductive healthcare; to systematically assess whether access to publicly-funded reproductive health resources are distributed in an equitable way across the US; to utilize an innovative measure of potential access that incorporates both spatial and aspatial variables to ascertain the size, scope, and demographic characteristics of geographies of concentrated disadvantage, which we refer to as "contraception deserts."
Methods: We employed methods that incorporated geographic information systems (GIS) and statistical/spatial analysis. We used the integrated two-step floating catchment area (I2SFCA) method, which incorporates both spatial (eg, distance, rurality/urbanicity) and aspatial (eg, poverty) variables, to more accurately develop a measure of potential access to Title X–funded clinics (FY2019). To map contraception deserts and to determine the demographic profile of these spaces of inequity, we used US Census data (at the tract level) and Title X–clinic location data from the Office of Population Affairs.
Results: GIS mapping techniques illustrate that significant proportions of the US can be characterized as contraception deserts, though with a great deal of variability in size across them. However, historically marginalized racial groups and those experiencing poverty are disproportionately represented in contraception deserts.
Conclusions: Given the various ways Title X can be implemented across states, results reveal that contraception deserts are prevalent but not inevitable. Speaking to policy implication, the results show that with strategic siting decisions, state-level Title X networks can mitigate inequitable access to federal resources.

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O05

CABERGOLINE FOR LACTATION INHIBITION AFTER SECOND-TRIMESTER ABORTION OR LOSS: A RANDOMIZED CONTROLLED TRIAL

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Objectives: To assess cabergoline's efficacy at decreasing lactation after second-trimester abortion or loss.
Methods: This is a double-blinded, block-randomized superiority trial (IRB approved, NCT04701333) comparing cabergoline 1mg once to placebo for preventing bothersome breast engorgement after second-trimester uterine evacuation. April 2021-June 2022, we enrolled pregnant people 18-28-weeks gestation, English- or Spanish-speaking, without contraindication to the study drug. Participants completed a validated, piloted, electronic survey at baseline and through two weeks post-procedure assessing breast symptoms, side-effects, and bother at each time point. Our primary outcome is breast symptoms on day 4; we planned to enroll 80 patients to show a 30% difference in breast symptoms (80% power, $\alpha = 0.049$). A sub-group of participants returned for serum prolactin levels.
Results: After screening 150 patients, we enrolled 73 participants. Baseline demographics were balanced between groups: median gestational age 21 weeks (range: 18-26), 56% nulliparous, 35% self-identified as Hispanic, 37% with public insurance. At baseline, reported breast symptoms were similar between groups. At day 4, significantly fewer participants receiving cabergoline reported any symptoms compared to placebo (27.8% vs 97.0%, $p<0.0001$) and fewer reported significant bother (2.8% vs 29.7%, $p=0.002$). These differences persisted through day 14. Reported side-effects ($p=0.31$) were similar between groups: most common were constipation (44%), fatigue (32%), and headache (29%). Serum prolactin was similar at baseline. On day 4, mean serum prolactin was 6.5ng/mL (std dev 2.2) for those receiving cabergoline and 18.0ng/mL (std dev 5.9) for placebo ($p=0.04$).
Conclusions: Cabergoline is an effective strategy to prevent breast symptoms following second-trimester abortion or loss.

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O06

SELF-MANAGED ABORTION OUTCOMES FOR PREGNANCIES OF 9–22 WEEKS' GESTATION: RESULTS FROM A PROSPECTIVE, OBSERVATIONAL STUDY IN THREE COUNTRIES

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Objectives: The literature on self-managed abortion at later gestations is sparse, and more information is urgently needed in the US and elsewhere where this practice may become increasingly common. This analysis offers novel results on the effectiveness of self-managed medication abortion among people with pregnancies >9 weeks.
Methods: In 2019–2020, as a part of The Studying Accompaniment Model Feasibility and Effectiveness (SAFE) Study, we recruited callers to safe-abortion hotlines in Argentina, Nigeria, and Southeast Asia who were seeking support for self-managed medication abortion. Via phone, participants completed a baseline survey prior to taking the medications, and up to three follow-up surveys over four weeks to ascertain abortion outcomes.
Results: We recruited 1,351 participants, of which 264 self-managed an abortion for a pregnancy that was 9–22 weeks' gestation; 149 (56%) respondents used mifepristone and misoprostol, while 115 (44%) used misoprostol alone. One week after taking the pills, 222 (91%) participants had a complete abortion — 87% with pills alone, and 4% with additional intervention. At last follow-up, 95% of participants had had a complete abortion (89% with pills alone, 5% with additional intervention; 93% of combined regimen users, and 97% of misoprostol-alone users). A minority of participants sought healthcare at a clinic or hospital at any point (30% of combined regimen users, 15% of misoprostol-alone users). Among those seeking care, most (60%) did so to confirm abortion completion, and a small minority (1.5%) received treatment indicative of a serious complication (blood transfusion).
Conclusions: Self-managed medication abortion can be a safe and effective option for ending a pregnancy at 9+ weeks' gestation.

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O07

THE IMPACT OF THE TEXAS ABORTION BAN ON GESTATIONAL AGE AT TIME OF ABORTION IN A LARGE-VOLUME COLORADO CLINIC

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Objectives: To assess changes in the proportion of Texas residents, gestational age at time of abortion, and rates of second-trimester abortion, at a university-affiliated abortion clinic in Colorado after Texas passed Senate Bill 8 (SB8), which prohibits abortions >6 weeks' gestation.
Methods: We focused on all patients obtaining an abortion ≤22 weeks' gestation at a university-affiliated clinic between January 2018 and mid-April 2022. We created two time periods: before SB8 (January 2018–August 2021) and after SB8 (September 2021–April 2022). We compared the proportion of Texas residents obtaining care and gestational age categories before and after SB8 using chi-square tests. We determined the adjusted odds of a second-trimester abortion (≥13 weeks) after SB8 using logistic regression models adjusted for gravida, parity, age, and the proportion of Texas residents.
Results: We assessed 4,358 abortions; 3,630 before and 728 after SB8. After SB8, the proportion of patients who were Texas residents increased from 1% to 17%, $p<0.001$. Among all patients, abortions ≥15 weeks increased from 11% to 21%, $p<0.01$, and surgical abortions at 6–10 weeks decreased from 46% to 33%, $p<0.001$. There was no change in abortions at 11–14 weeks. The proportion of second-trimester abortions increased from 17% to 27%, $p<0.001$ and the odds nearly doubled after SB8 (aOR1.9, 95% CI, 1.6–2.3). Although higher among Texas residents (aOR, 2.6, 95% CI,1.1–6.9), the odds of a second-trimester abortion also increased among Colorado residents (aOR,1.8, 95% CI, 1.4–2.2).
Conclusions: Post-*Roe* abortion bans will likely delay care not only for people forced to seek care out of state, but for residents of states maintaining abortion access.

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Research Letter | Obstetrics and Gynecology

Safety and Efficacy of Telehealth Medication Abortions in the US During the COVID-19 Pandemic

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Introduction

Early in the COVID-19 pandemic, medication abortion, which typically includes mifepristone (ie, progesterone receptor antagonist) and misoprostol (ie, prostaglandin), gained prominence because it can be provided without physical contact. The American College of Obstetricians and Gynecologists and other professional organizations quickly endorsed telehealth and no-test abortion care.[1] These protocols omit Rh testing[2] and use patient history, rather than routine ultrasonography, to assess pregnancy duration and screen for ectopic pregnancy risks.[3,4]

To mitigate potential risk of complications, US Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategy (REMS) require that mifepristone be dispensed in a medical office, clinic, or hospital, prohibiting dispensing from pharmacies. Between a federal judge's ruling that suspended enforcement of this requirement in July 2020 and a reversal by the Supreme Court in January 2021, clinicians could offer medication abortion via telehealth and dispense from mail-order pharmacies where not prohibited by state law. During this period, a virtual clinic called Choix began providing medication abortions in California. We assessed safety and efficacy outcomes of a telehealth medication abortion model, which could inform the FDA's decision regarding removal of the REMS.

Methods

This retrospective cohort study was approved by the institutional review board at the University of California, San Francisco, and informed consent was waived because the research presented no more than minimal risk. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

We examined the safety and efficacy of fully remote, asynchronous medication abortion care using a published protocol.[3] Eligibility criteria, assessed using an online form, included pregnancy duration of less than 70 days (by history, including date of last menstrual period, or by ultrasonography) and no contraindications to mifepristone or misoprostol. Nurse practitioners reviewed the form within 24 hours and referred patients with unknown last menstrual period date or ectopic pregnancy risk factors for ultrasonography to confirm eligibility. A mail-order pharmacy delivered medications to eligible patients. The protocol involved 3 follow-up contacts: confirmation of medication administration, a 3-day assessment of expulsion and pregnancy symptoms, and a 4-week home pregnancy test. Follow-up interactions were conducted by text, secure messaging, or telephone. At each scheduled follow-up, clinicians made up to 4 attempts to contact patients.

In accordance with Choix's privacy policy, the service shared deidentified health record data for all patients with our research team. Efficacy was assessed as complete abortion without additional intervention (aspiration or other procedure, surgery, >1600 µg of misoprostol, or continuing pregnancy) among those with a known abortion outcome from the 3-day or 4-week follow-up. Safety was assessed by any major adverse event, including blood transfusion, abdominal surgery, hospital admission, or death. We estimated outcomes as percentages and calculated 95% CIs for key rates in Stata version 15.1 (StataCorp).

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Results

The service provided abortion care for 141 patients between October 2020 and January 2021. Mean (SD) participant age was 29 (7) years, 81 (57%) had pregnancy durations 42 days or less, and 24 (17%) had screening ultrasonography (**Table 1**). At least 1 follow-up contact was made for 128 patients (91%), and abortion outcomes were collected for 110 patients (86%). Among the 110 patients with outcome data, 105 (95%) had a complete abortion without intervention. Five patients (5%) required medical care to complete the abortion, 2 of whom were treated in emergency departments. No patients reported any major adverse events (**Table 2**).

Discussion

These results represent some of the earliest data on new telehealth abortion clinics in the US. This 95% efficacy rate is similar to in-person provision[5] and recent international studies of telehealth for medication abortion.[6]

In April 2021, the FDA paused enforcement of the REMS for the duration of the COVID-19 pandemic, allowing clinics and pharmacies to mail mifepristone once again. The FDA is now considering permanently removing the REMS. This study is small with some loss to follow-up, and thus some adverse events and ongoing pregnancies may have been undetected. However, it reflects real-world data, which increases generalizability. This study provides preliminary evidence that suggests medication abortion care, administered by telehealth and delivered via mail, is feasible, safe, and efficacious.

Table 1. Description of Patient Characteristics

Characteristic	Total, No. (%), (n = 141)
Age, mean (SD)	28.5 (6.7)
Had ultrasonography before abortion	24 (17.0)
Pregnancy duration, d	
≤42	81 (57.4)
43-56	43 (30.5)
57-70	17 (12.1)
Rh type	
Positive	67 (47.5)
Unknown	60 (42.6)
Negative	14 (9.9)
Received Rh immune globulin	0
Any follow-up information collected	128 (90.8)

Table 2. Abortion Safety and Efficacy Outcomes

Follow-up data	Total, No./total No. (%), [n = 128]
Efficacy	
Outcome unknown[a]	18/128 (14.1)
Outcome known	110/128 (85.9)
Complete, No./total No. (% [95% CI])	105/110 (95.5 [91.6-99.3])
Complete by test[b]	88/110 (80.8)
Complete by history[c]	17/110 (15.5)
Required additional medical intervention for completion, No./total No. (% [95% CI])[d]	5/110 (4.5 [0.7-8.4])
Safety, No./total No. (% [95% CI])	
Confirmed or suspected ectopic pregnancy	0/128 (0 [0.0-2.3])
Any major adverse event[e]	0/128 (0 [0.0-2.3])

[a] Ten patients confirmed initial administration of medications and were subsequently lost to follow-up. Eight patients had inconclusive symptoms or test results and were subsequently lost to follow-up.

[b] Confirmed complete by 4-week urine pregnancy test.

[c] Presumed complete by symptom assessment 3 days after medications.

[d] Overall, 3 patients had an aspiration or dilation and curettage (2 treated in emergency department), and 2 patients required 2400 µg of misoprostol.

[e] No patients had a major adverse event defined as blood transfusion, surgery, hospital admission, or death.

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Author Contributions: Dr Upadhyay had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: Upadhyay, Koenig.

Drafting of the manuscript: Upadhyay, Koenig.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Koenig.

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Conflict of Interest Disclosures: Dr Meckstroth reported receiving personal fees from Danco, Inc, a distributor of mifepristone, for staffing a US Food and Drug Administration–mandated expert hotline. The mifepristone used in this care was purchased from GenBioPro, not Danco. No other disclosures were reported.

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Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomised controlled equivalence trial in Nepal

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Summary

Background Medical abortion is under-used in developing countries. We assessed whether early first-trimester medical abortion provided by midlevel providers (government-trained, certified nurses and auxiliary nurse midwives) was as safe and effective as that provided by doctors in Nepal.

Methods This multicentre randomised controlled equivalence trial was done in five rural district hospitals in Nepal. Women were eligible for medical abortion if their pregnancy was of less than 9 weeks (63 days) and if they resided less than 90 min journey away from the study clinic. Women were ineligible if they had any contraindication to medical abortion. We used a computer-generated randomisation scheme stratified by study centre with a block size of six. Women were randomly assigned to a doctor or a midlevel provider for oral administration of 200 mg mifepristone followed by 800 µg misoprostol vaginally 2 days later, and followed up 10–14 days later. The primary endpoint was complete abortion without manual vacuum aspiration within 30 days of treatment. The study was not masked. Abortions were recorded as complete, incomplete, or failed (continuing pregnancy). Analyses for primary and secondary endpoints were by intention to treat, supplemented by per-protocol analysis of the primary endpoint. This trial is registered with ClinicalTrials.gov, NCT01186302.

Findings Of 1295 women screened, 535 were randomly assigned to a doctor and 542 to a midlevel provider. 514 and 518, respectively, were included in the analyses of the primary endpoint. Abortions were judged complete in 504 (97·3%) women assigned to midlevel providers and in 494 (96·1%) assigned to physicians. The risk difference for complete abortion was 1·24% (95% CI –0·53 to 3·02), which falls within the predefined equivalence range (–5% to 5%). Five cases (1%) were recorded as failed abortion in the doctor cohort and none in the midlevel provider cohort; the remaining cases were recorded as incomplete abortions. No serious complications were noted.

Interpretation The provision of medical abortion up to 9 weeks' gestation by midlevel providers and doctors was similar in safety and effectiveness. Where permitted by law, appropriately trained midlevel health-care providers can provide safe, low-technology medical abortion services for women independently from doctors.

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Introduction

Each year, 210 million women throughout the world become pregnant and nearly one in five chooses to terminate the pregnancy.[1] About 22 million pregnancies are terminated unsafely, and nearly all (98%) of these unsafe abortions take place in developing countries.[2] In many countries where abortion is not restricted by law, access to safe abortion is poor because of a shortage of skilled medical staff and surgical facilities. Early first-trimester medical abortion, by administration of an antiprogestagen (mifepristone) followed by a prostaglandin analogue (usually misoprostol), has provided millions of women worldwide with a safe, effective, and acceptable alternative to surgical abortion, which is usually done by manual vacuum aspiration. More than 20 years ago, medical abortion was recognised as likely to have particular application in those low-resource countries where skilled medical and surgical experience were in short supply.[3] Most medical abortions do not require the health-care infrastructure needed for manual vacuum aspiration, although back-up vacuum aspiration is needed for a small percentage of women.

Medical abortion remains under-used and inaccessible for many women in developing countries because almost all national regulations restrict its prescription and supervision to doctors.[4] However, the safety record of medical abortion makes it amenable to provision by midlevel health-care providers (non-physician health-care workers such as midwives and nurses) in regions where doctors are unavailable. Training of midlevel health-care providers in medical abortion with appropriate referral systems would expand access to safe abortion services and would be consistent with the global trend towards task-shifting in places where doctors are costly and scarce.[5,6] These providers have the potential to provide accessible, low-cost, and safe abortion services in developing countries in which abortion is not restricted by law. Results from a previous randomised trial[7] in

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South Africa and Vietnam showed that midlevel providers can perform first-trimester abortions by vacuum aspiration as safely as doctors do. Nonetheless, questions remain about the standard of care and safety of medical abortion provided by midlevel health-care providers.[4,8]

In Nepal, unsafe abortion is the third largest cause of maternal mortality.[9] Surgical termination of pregnancy on request up to 12 completed weeks of gestation has been provided by certified doctors at registered government sites since 2004. Midlevel providers (staff nurses) were permitted to do surgical abortions up to 8 weeks' gestation in these sites. Since 2009, medical abortion has been available for pregnancies of less than 9 completed weeks of gestation (≤63 days). At the time of the study, the provision of medical abortion services by nurses was limited to government facilities in which a doctor was present; nurses did not provide medical abortion independently from physicians' oversight. The aim of this study was to assess whether early first trimester medical abortion provided by midlevel health-care providers was as safe and effective as that provided by doctors in Nepal.

Methods

Participants and study design

Women met eligibility criteria if their pregnancy was less than 9 weeks (≤63 days) of gestation according to date of last menstrual period and as estimated by bimanual pelvic examination, if they were older than 16 years, resided no more than 90 min journey from the study clinic, and were willing to be randomly assigned to a provider, to return to the clinic 10–14 days after the start of treatment, and to provide written informed consent. A woman was ineligible if she had any contraindication to medical abortion: previous allergic reaction to any of the drugs in the medical abortion regimen; known or suspected ectopic pregnancy or undiagnosed adnexal mass; inherited porphyria; chronic adrenal failure; long-term corticosteroid therapy; haemorrhagic disorder or anticoagulant therapy; or an intrauterine device that could not be removed before administration of mifepristone.

This study was a multicentre, randomised, controlled equivalence trial to assess outcomes of medical abortion services provided by midlevel health-care providers and doctors in settings with low health-care resources. Women seeking termination of early first-trimester pregnancy were randomly assigned to medical abortion managed by doctors or by midlevel health-care providers and followed up for completeness of abortion and any complications. Data were collected between April 15, 2009, and March 17, 2010, in five district hospitals in hilly (Bhaktapur, Baglung, Dhading) and lowland regions (Rupendehi, Chitwan) in Nepal. The feasibility of the study was tested on a sample of 53 women in a pilot phase from Jan 7, to Feb 26, 2009. District hospitals are small government health facilities equipped to provide emergency obstetric services with less than 25 beds in rural and peri-urban areas. The hospitals had sufficient staff to establish a group of doctors and a group of midlevel health-care providers for implementation of the study. As a surrogate for how providers would manage in an independent setting and to reduce interactions between the two groups, each study site established separate waiting areas and examination rooms for midlevel health-care providers and doctors.

The study was developed, coordinated, and funded by the UNDP/UNFPA/WHO/World Bank Special Programme of Research Development and Research Training in Human Reproduction (HRP) at WHO, Geneva, Switzerland. A coordinating centre was established at the Centre for Research on Environment Health and Population Activities (CREHPA) in Kathmandu, Nepal. Reporting of the trial follows CONSORT reporting guidelines.[10,11] The study was approved by the Scientific and Ethical Review Group of the Reproductive Health and Research Department (RHR) and the Research Ethics Review Committee of WHO in Geneva, Switzerland, the National Health Research Council (NHRC) of Nepal, and was endorsed by the Department of Health Services, Ministry of Health and Population, Nepal.

Randomisation and masking

We used a computer-generated randomisation scheme stratified by study centre with a block size of six generated at RHR, WHO in Geneva, Switzerland. Sealed opaque envelopes containing the random allocation were consecutively numbered and were opened and assigned sequentially to women by a research assistant once written informed consent had been obtained. The random allocation sequence was generated by use of SAS software (SAS Institute, Cary, NC, USA).

Procedures

Only providers trained in manual vacuum aspiration were eligible for medical abortion training. All 25 eligible providers in the study hospitals participated in the study. Midlevel health-care providers consisted of eight staff nurses (3-year degree) and three auxiliary nurse midwives (18 months of training). The doctors were six obstetricians and gynaecologists, three general practitioners, and five doctors (with a Bachelor of Medicine and Bachelor of Surgery Degree). Participating providers underwent a 3-day training course in medical abortion and were certified by the National Health Training Centre. Table 1 summarises the characteristics of the providers. Female research assistants with backgrounds in nursing, health, and social science were employed to take part in the study. They did screening interviews for study eligibility and for provisional eligibility for medical abortion, implemented randomisation procedures, and collected data at admission, before misoprostol insertion, and at scheduled and unscheduled follow-up visits. They tracked women who

did not attend scheduled visits. Providers reviewed the forms completed by the research assistants and had full responsibility for clinical management of each case; they made the final decision on eligibility for the study and for medical abortion after physical examination, and recorded clinical data on physical examinations, administration of the drug, case management, and abortion outcome.

Clinical procedures for medical abortion followed the Nepalese medical abortion protocol and no changes were made in the procedures for the purposes of the study. Ultrasonography is not part of the Nepalese protocol for medical abortion but machines were available and used at the providers' discretion; such use was recorded for the study. Oral antibiotics were not routinely prescribed, and pregnancy tests were not done. Use of pregnancy tests and ultrasound is not routine for medical abortions in Nepal. Testing and treatment for sexually transmitted infections followed national syndromic protocols. All women were offered 400 mg ibuprofen for pain relief. Assigned providers gave counselling, and undertook vaginal and cervical inspection and abdominal and pelvic bimanual examination to establish duration of gestation.

The regimen consisted of one 200 mg tablet of mifepristone and four 200 µg tablets of misoprostol packaged in a single blister pack (Medabon, Sun Pharmaceutical Industries Ltd, Mumbai, India). The assigned provider gave the woman the mifepristone tablet orally on day 1 and administered the misoprostol tablets vaginally on day 3. After misoprostol insertion, the woman was monitored in hospital for 3 h; her assigned provider examined her bimanually to assess the status of the abortion before she left the hospital. 10–14 days after the administration of mifepristone, the woman returned for a follow-up visit to the same assigned provider for a clinical assessment of the outcome of the abortion. Additional follow-up visits were scheduled with the assigned provider if needed, and women were encouraged to return at any time for unscheduled visits.

The primary endpoint was complete abortion without manual vacuum aspiration within 30 days of treatment. Incomplete abortion was defined as products of conception remaining in the uterus with continued bleeding, bulky uterus, and open cervix at examination, possibly necessitating surgical evacuation at the discretion of the provider or at the woman's request. Failed abortion (continuing pregnancy) was recorded when clinical examination indicated continuing symptoms of pregnancy and manual vacuum aspiration was needed to terminate the pregnancy.

The secondary endpoint measured case-management decisions by recording case-management discussions and referrals between providers to assess the extent to which each group provided medical abortion services independently. Serious adverse events (haemorrhage necessitating blood transfusion, conditions necessitating hospitalisation) were recorded. The completeness of the abortion and any complications were identified by an interview with the woman and by clinical examination. Women were also asked whether they had visited any non-study hospital, clinic, or provider during the study.

Data management was organised locally by data entry personnel at CREHPA and at RHR, WHO in Geneva. Research assistants sent case record forms weekly to CREHPA and retained copies in their clinics. Data were entered at CREHPA by use of the OpenClinica clinical trial software, checked for accuracy, and corrected after consultation of clinical records and research assistants. Data were reviewed monthly by the Study Coordinator at WHO with further checking and review of clinic records as necessary.

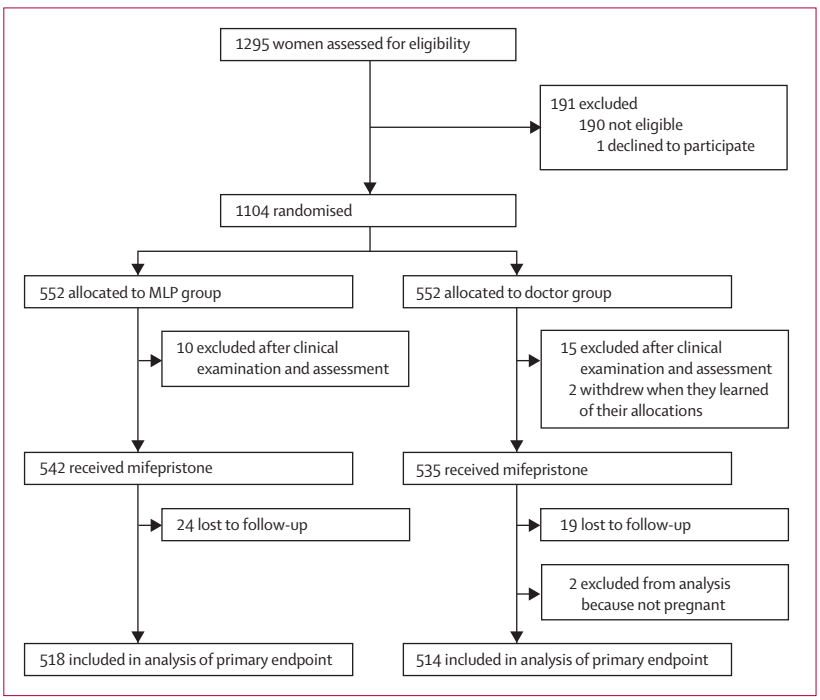

Figure 1: **Trial profile**
MLP=midlevel health-care providers.

	MLP (n=11)	Doctors (n=14)	Total (n=25)
Age (years)			
Mean (SD)	41·9 (6·8)	42·4 (11·0)	42·2 (9·2)
Median (IQR)	44·0 (36·0–46·0)	45·5 (30·0–52·0)	44·0 (34·0–50·0)
Range	30·0–50·0	27·0–56·0	27·0–56·0
Sex			
Female	11 (100%)	3 (21%)	14 (56%)
Male	0 (0%)	11 (79%)	11 (44%)
Years of professional medical practice			
Mean (SD)	21·8 (7·3)	14·1 (10·8)	17·5 (10·0)
Median (IQR)	25·0 (16·0–27·0)	15·0 (2·5–20·0)	18·0 (10·0–26·0)
Range	9·0–30·0	2·0–34·0	2·0–34·0

MLP=midlevel health-care providers. IQR=interquartile range.

Table 1: **Background characteristics of providers**

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	MLP (n=542)	Doctors (n=535)	Total (n=1077)
Age (years)			
Mean (SD)	28·1 (6·0)	28·0 (5·8)	28·0 (5·9)
≤19	32 (6%)	28 (5%)	60 (6%)
20–29	296 (55%)	310 (58%)	606 (56%)
30–39	186 (34%)	170 (32%)	356 (33%)
≥40	28 (5%)	27 (5%)	55 (5%)
Marital status			
Married or cohabiting	530 (98%)	528 (99%)	1058 (98%)
Separated, divorced, widowed	3 (<1%)	1 (<1%)	4 (<1%)
Single	9 (2%)	6 (1%)	15 (1%)
Education			
Never attended or not completed primary school	169 (31%)	154 (29%)	323 (30%)
Primary school	103 (19%)	86 (16%)	189 (18%)
Lower secondary school	75 (14%)	70 (13%)	145 (13%)
Secondary school	114 (21%)	138 (26%)	252 (23%)
Higher than secondary school	81 (15%)	87 (16%)	168 (16%)
Height (cm)			
Mean (SD)	151·5 (5·4)	151·8 (5·3)	151·6 (5·4)
Weight (kg)			
Mean (SD)	48·8 (8·0)	49·5 (8·4)	49·2 (8·2)
Livebirths			
Mean (SD)	2·3 (1·1)	2·2 (1·1)	2·3 (1·1)
No data	51 (9%)	47 (9%)	98 (9%)
0	2 (<1%)	4 (<1%)	6 (<1%)
1–2	323 (60%)	322 (60%)	645 (60%)
3–8	166 (30%)	162 (30%)	328 (30%)
Previous induced surgical abortions			
Mean (SD)	0·2 (0·7)	0·3 (0·7)	0·2 (0·7)
No data	51 (9%)	47 (9%)	98 (9%)
0	365 (67%)	342 (64%)	707 (66%)
1	87 (16%)	108 (20%)	195 (18%)
2–5	39 (7%)	38 (7%)	77 (7%)

MLP=midlevel health-care providers.

Table 2: **Characteristics of women undergoing early medical abortion by type of provider**

Statistical analysis

This equivalence trial was designed to assess the similarity between two types of providers of medical abortion with a potential cluster effect on the primary endpoint among service providers. The margin of equivalence, Δ, was 5% and the range –5% to 5% was predefined as an acceptable range of completion rates between the two types of providers. The margin was based on clinically and statistically important differences as well as ethical criteria, cost, and feasibility.[12,13]

The sample size of 1086 women was calculated to be sufficient (with a two-sided 95% CI and 80% power) to establish equivalence.[14] The sample size calculation allowed for 10% loss to follow-up and for a potential cluster effect among service providers with an estimated intraclass correlation coefficient of 0·001 from a previous study.[7] The cluster effect could occur because some service providers might provide better medical abortion services than others due to individual variations in, for example, years of medical practice or individual aptitude.

To assess the equivalence between midlevel health-care providers and doctors, the risk difference between the two provider types together with their 95% CI was derived by use of a generalised estimating equation (GEE) model with treatment as the fixed effect and service provider as a random effect as implemented in the PROC GENMOD procedure of SAS version 9.2 (SAS Institute, Cary, NC, USA). The CI gives an interval estimate of the true population difference Δ. If the CI of the risk difference between the two groups falls within the predetermined margin of equivalence (–5% to 5%), the two types of providers can be considered equivalent. In addition, covariate-adjusted analyses were done on six prespecified baseline characteristics of participants (centre, age, duration of gestation, parity, number of previous induced abortions, and body-mass index). The number and percentage of women with each side-effect from the medical abortion were calculated and compared by use of a χ^2 test. The analyses for the primary and secondary endpoints were on an intention-to-treat basis, supplemented by per-protocol analysis of the primary endpoint.

This trial is registered with ClinicalTrials.gov, NCT01186302.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study. The corresponding author had the final responsibility for the decision to submit for publication.

Results

Of 1295 women screened for eligibility, 190 were ineligible for medical, geographical, or follow-up scheduling reasons, and one woman declined to take part in the study (figure 1). 1104 women were randomised. After clinical examination, in the midlevel health-care providers' group ten women were excluded: in eight, the duration of gestation was longer than 9 weeks; one had signs of ectopic or adnexal mass; and one was diagnosed with cervical polyps. In the doctors' group 15 women were excluded: in 12, the duration of gestation was longer than 9 weeks; one had signs of ectopic or adnexal mass; one was not pregnant; and one had a miscarriage before receiving any drugs. Additionally, two women withdrew from the study before physical examination when they were told of their group allocation.

Loss to follow-up of women receiving treatment was 24 of 542 (4%) in the midlevel health-care providers' group and 19 of 535 (4%) in the doctors' group. Women lost to follow-up were, on average, less educated than those

followed up. Two women in the doctors' group were excluded from the analysis because at follow-up they were shown not to have been pregnant: one was a long-time user of a 3-monthly injectable contraceptive, and the other one had had a manual vacuum aspiration 37 days before.

Participating doctors had, on average, fewer years of professional medical practice than midlevel health-care providers and a higher proportion were men (table 1). Baseline characteristics of women included in the analysis were similar by type of provider (table 2). On average, women were 28 years old and married with two children. More than 25% had had an induced abortion previously and about 30% had never attended school or had not completed primary school. Overall mean duration of gestation was 6·6 weeks as reported by the date of the last menstrual period and 6·8 weeks by clinical examination and did not differ by type of provider (table 3). In women reporting the date of their last menstrual period (84%), there was a high level of congruence between duration of gestation based on that date and that based on clinical examination. No important difference was noted between the two types of provider (data not shown). Doctors were more likely to use ultrasonography (23 cases) than were midlevel health-care providers (two cases).

The clinical outcomes of medical abortion from intention-to-treat and per-protocol analyses were similar by type of provider (table 4). For women with a recorded outcome, the overall intention-to-treat complete abortion rate was 96·7%, the incomplete abortion rate 2·8%, and continuing pregnancy rate 0·5% at 30 days from start of treatment. The risk difference for complete abortion rates between midlevel providers and doctors was 1·24% (95% CI –0·53 to 3·02), and the estimated 95% CI was well within the equivalence range for both intention-to-treat and per-protocol analyses (table 4, figure 2). Therefore, equivalence between midlevel health-care workers and doctors can be established for the primary endpoint. For the covariate-adjusted analyses, the GEE model did not converge when all six covariates were entered simultaneously. With a stepwise approach, only woman's age and duration of gestation produced converging GEE models for both the intention-to-treat and per-protocol populations (table 4, figure 2). The webappendix shows the rate of complete abortion by gestational age (see webappendix p 1).

All 34 incomplete and continuing pregnancies were terminated by manual vacuum aspiration by the assigned provider. No serious adverse events were recorded. Women reported typical side-effects such as nausea, vomiting, diarrhoea, abdominal pain, chills, and fever with no difference by type of provider (data not shown). 12 cases with midlevel health-care providers and 13 cases with physicians were discussed with another provider or referred (data not shown). Midlevel health-care providers reported discussing less than 2% of cases with doctors and referred less than 1% of cases to a doctor, a pattern similar to that of doctors.

	MLP (n=542)	Doctors (n=535)	Total (n=1077)
Number of women reporting LMP	456 (84%)	450 (84%)	906 (84%)
Duration of gestation from LMP (weeks)			
Mean (SD)	6·6 (1·1)	6·6 (1·1)	6·6 (1·1)
Median (IQR)	6·4 (5·9–7·4)	6·4 (5·7–7·4)	6·4 (5·7–7·4)
Range	4·0–9·1	4·3–9·0	4·0–9·1
Number of women clinically examined	542 (100%)	535 (100%)	1077 (100%)
Duration of gestation by clinical examination (weeks)			
Mean (SD)	6·9 (1·0)	6·6 (1·0)	6·8 (1·0)
Median (IQR)	7·0 (6·0–8·0)	6·0 (6·0–8·0)	6·0 (6·0–8·0)
Range	5·0–9·0	5·0–9·0	5·0–9·0
Ultrasonography used to assess duration of gestation	2 (0·4%)	23 (4·3%)	25 (2·3%)

MLP=midlevel health-care providers. LMP=date of last menstrual period. IQR=interquartile range.

Table 3: **Assessment of duration of gestation by provider**

	MLP	Doctors	Risk difference for the primary endpoint* (95% CI)	Risk difference for the primary endpoint-adjusted analysis† (95% CI)
ITT analysis				
Number of women	518	514	..	..
Complete abortion	504 (97·3%)	494 (96·1%)	1·24% (–0·53% to 3·02%)	1·49% (–0·17% to 3·14%)
Incomplete abortion	14 (2·7%)	15 (2·9%)	..	..
Continuing pregnancy	0	5 (1·0%)	..	..
PP analysis				
Number of women	504	472	..	..
Complete abortion	490 (97·2%)	455 (96·4%)	0·89% (–1·11% to 2·88%)	1·12% (–0·70% to 2·93%)
Incomplete abortion	14 (2·8%)	12 (2·5%)	..	..
Continuing pregnancy	0	5 (1·1%)	..	..

MLP=midlevel health-care providers. ITT=intention to treat. PP=per protocol. *Estimated from a generalised estimating equation model with treatment as the fixed effect and service provider as a random effect. †Adjusted for woman's age and duration of gestation.

Table 4: **Outcomes of medical abortion by type of provider**

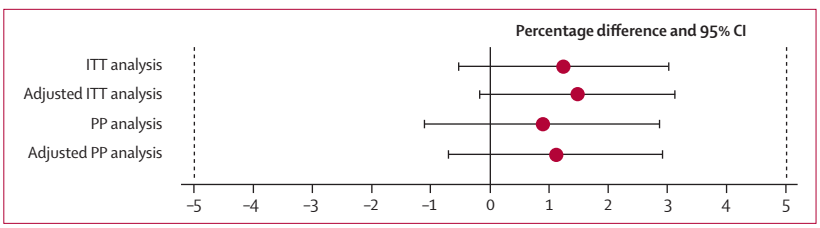

Figure 2: **Percentage difference and 95% CI of complete abortion by midlevel health-care providers compared with doctors**
ITT=intention to treat. PP=per protocol.

Discussion

This randomised controlled equivalence trial assessed clinical outcomes, safety, and case management of early medical abortion provided by nurses and auxiliary nurse midwives compared with doctors. These findings provide evidence that midlevel providers with previous training in abortion care can, after additional training in medical abortion, independently administer medical abortion

See Online for webappendix

***Panel*: Research in context**

Systematic review

When developing the study protocol, we searched PubMed and Popline for relevant articles with the keywords "abortion", "medical abortion", "nurse-midwives", "midwife", "mid-level provider", "nurse practitioner", "non-physician clinician", and "physician assistant". Given the paucity of research in this area, we reviewed all studies and reports about midlevel providers of medical abortion and manual vacuum aspiration in developed and developing countries.

Interpretation

Findings from our study showed that midlevel providers of medical abortion can administer medical abortion as safely as doctors in a low-resource setting in which ultrasonography and pregnancy tests are rarely used. These results build on one previous randomised controlled trial of midlevel providers and manual vacuum aspiration that showed equivalence in safety between midlevel providers and doctors in developing countries. Several observational studies lend support to the competency of midlevel health-care providers as providers of medical abortion. Taken together, these studies show that appropriately trained and government certified midlevel providers of both medical abortion and manual vacuum aspiration can provide safe and effective abortion services independently from physicians.

safely and effectively in a low-resource setting where pregnancy tests, antibiotics, and ultrasonography are available but rarely used. These equivalence results are robust irrespective of the analysis population.

Midlevel health-care providers have been trained in medical abortion in several countries but assessments have been limited to those of in-house training. The role of these care providers in the introduction of medical abortion has been examined in India,[15] Vietnam,[16] Nepal,[8] and the USA.[17,18] Two papers reviewed the evidence on midlevel health-care providers of abortion but did not specifically address safety or acceptability by doctors and these providers (panel).[4,19]

The overall complete abortion rate of 96·7% was comparable with rates in other studies that used the same regimen (93·5% to 97·7%).[20–22] Previous studies of medical abortion in Nepal showed completion rates of 91·3%[23] with oral administration of 400 μg misoprostol and 96%[24] with vaginal administration of 800 μg misoprostol. In gestations of up to 63 days' amenorrhoea, the rate of continuation of pregnancies with the regimen used here was less than 1%,[25] in line with our results. The numbers of incomplete abortions for both types of providers were similar, 14 cases for midlevel health-care providers and 15 cases for doctors, with no difference in propensity to evacuate cases of incomplete abortion that might have become complete over time.

Despite its availability, ultrasonography was rarely used by any provider to assess duration of gestation or completeness of the abortion at follow-up. This study supports guidelines that emphasise the safety of medical abortion without the routine use of ultrasonography before or after abortion.[26] The study was designed to maximise the generalisability of the findings for the public sector in Nepal and other developing countries. It was conducted in public-sector district hospitals and all 25 full-time public-sector providers received the same government-certified training in medical abortion. The clinical procedures for medical abortion did not deviate from the national protocol. The sociodemographic characteristics of women included in our study were very similar to those of a national sample of women seeking induced abortion in Nepal done in 2006.[27]

Some issues might affect the external validity and applicability of the findings. In this study, midlevel health-care providers had more years of professional experience than did the doctors. In ad-hoc multivariate analyses, years of professional experience did not have any effect on equivalence results (data not shown). Although the socioeconomic and demographic characteristics of study participants are typical of women seeking abortions throughout Nepal, they might not be representative of women living in underserved rural areas of this country. District hospitals are also not representative of the small health facilities located in remote areas of Nepal, which are staffed exclusively by midlevel health-care providers.

A limitation of the findings is that the study was part of the first wave of medical abortion training in Nepal, and the initial training curriculum has since been revised. Future medical abortion outcomes might differ as the national protocol is adapted to follow women's needs and new regimens. A further limitation of the study is that although separate waiting and examination rooms for the two groups were set up for the duration of the study, both types of providers worked in the same hospital and in the same environment. Although this controlled environment optimised comparison, it might have led to a convergence of outcomes that would not have happened if the women had been assigned to providers at different clinics.

The Nepalese medical abortion protocol at the time of the study was rather burdensome with three clinic visits and physical examinations. Testing home use or omitting the follow-up visit are important topics for future research of medical abortion in Nepal. However, 96·3% of women reported that they would prefer having a medical abortion at the clinic and 3·7% at home, which suggests that visits to the clinic were acceptable for these women.

In conclusion, nurses and auxiliary nurse midwives could have an important role in making life-saving abortion methods accessible to women living in remote areas of developing countries, as long as timely back-up manual vacuum aspiration is accessible if providers themselves are not trained in this technique. In areas with shortages of physicians, decentralisation of medical abortion services to include government-certified midlevel health-care providers who work independently from doctors would greatly increase women's access to safe abortion services. Appropriately trained providers can administer safe, low-technology medical abortion services for women who might otherwise turn to unsafe abortion, exposing themselves to the risks of disabilities and death.

Contributors

IKW developed the protocol and study design, directed the study and the data analysis, and was the lead author of the report. DW was the statistician for the study and participated in the study design, data analysis, data interpretation, and writing of the report. NTMH was the study coordinator and participated in data collection, management, and analysis, and writing of the report. KT was the principal investigator and was responsible for the overall supervision of the trial and participated in the implementation of study, data analysis, and the writing of the report. AT was responsible for the coordination and implementation of the study in Nepal and participated in the data management, data analysis, and the writing of the report. IS participated in the development of the protocol, data analysis, and the writing of the report. DTB and OM participated in the development of the protocol and the writing of the report. All authors had access to the data, commented on subsequent drafts, and approved the final submitted version.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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Comparing telemedicine to in-clinic medication abortions induced with mifepristone and misoprostol

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ABSTRACT

Objective: The objective was to compare the practical aspects of providing medication abortions through telemedicine and in-person clinic visits so that clinics can use this information when planning to add this service.
Study design: We conducted a comparative retrospective chart review comparing telemedicine medication abortions to a control group matched for date seen. We extracted and compared demographics, use of dating ultrasound, outcomes and unscheduled visits or communications with staff and physicians.
Results: During the study period, we provided 4340 medication abortions, of which 182 (4.2%) were provided through by telemedicine; 199 patients met the criteria to be in the control group. The mean age was 28.7 years for telemedicine patients and 28.1 years for in-person patients ($p = .38$). The mean gestational ages were also similar, 48.2 days for telemedicine patients and 46.5 days for in-person patients ($p = .03$). Only 33 (18.1%) of telemedicine patients had dating ultrasounds compared to 199 (100%) of in-clinic patients ($p < .001$). The proportions of documented completed abortions (164/182, 90.1% and 179/199, 89.9%, $p = .76$) were similar, as were the proportions of aspirations for completion (6/182, 3.3% and 9/199, 4.5%, $p = .54$) and the proportions lost to follow-up (5.5% and 6.6%, $p = .66$). There were 10 complications in each group (5.5% of telemedicine patients and 5.0% of in-clinic patients) ($p > 0.5$). Unscheduled communications with office assistants were greater in the telemedicine patients than the in-person patients (84/182, 46.2% vs. 43/199, 21.6% in-person, $p < .001$).
Conclusion: We found that telemedicine patients required more unscheduled communications and received ultrasounds far less often compared to in-clinic patients.
Implications: We could provide telemedicine without the need for ultrasound to most women. Larger studies without routine ultrasound use are needed to validate our findings. Unscheduled communication with clinic staff was more frequent with telemedicine medication abortion patients. This information may help clinics when planning to add this service.
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1. Introduction

At Willow Clinic in Vancouver, British Columbia (BC), we have been offering medication abortions by telemedicine since 2012 [1]. Initially, we were using methotrexate 50 mg/m^2 and misoprostol 800 mcg repeated twice to induce abortions up to 7 weeks' gestation. In January 2017, mifepristone became available in Canada. At that point, Willow Women's Clinic started offering medication abortions with mifepristone and misoprostol by telemedicine up to 10 weeks' gestation, and there was a much greater uptake. We followed the Society of Obstetricians and Gynecologists of Canada (SOGC) Clinical Practice Guidelines recommending that mifepristone 200 mg with misoprostol 800 mcg be used up to 10 weeks' gestation [2].

Previous literature demonstrates that telemedicine is safe, effective and feasible [3]. In response to the high mortality and morbidity from unsafe abortions (i.e., the termination of a pregnancy by individuals lacking the necessary skills, or in an environment lacking minimal medical standards, or both) worldwide, various providers have offered telemedicine abortions using different protocols and in different settings [4–9]. Routine care of medication abortion patients in North America involves ultrasound before the procedure to determine gestational age and exclude ectopic pregnancies, home use of misoprostol and ultrasound after the procedure to evaluate for completion of the abortion [10,11]. Alternatives to routine ultrasound have been investigated to increase accessibility, including human chorionic gonadotropin (hCG) testing or phone follow-up [12–16].

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We performed this study to evaluate our use of telemedicine for medication abortion in which women did not receive routine ultrasound for evaluation or follow-up. We wished to gain information that could help other clinics when planning to add this service.

2. Methods

We performed a retrospective chart review of all telemedicine abortions between January 31, 2017, and January 31, 2019, and a similar group of controls seen in the clinic during the same time frame (i.e., matched consecutively by date of initial appointment). We used a billing log to identify both the telemedicine and in-clinic patients. One or two in-clinic patients seen on the same day were selected for each telemedicine abortion patient so that the two groups were similar in regards to the staff that cared for them. We also compared the sample of women included in this study to all 4340 medication abortions done at our clinic during the same time period to check the representativeness of the sample.

The Willow Clinic provides telemedicine medical abortion to individuals who live >2 h from the clinic, have access to video chat programs on a computer or smart phone, have access to a laboratory, can get an ultrasound if necessary and are able to travel to Willow Clinic or to another community for surgical completion if necessary. The physician sees the patient by telemedicine and uses the patient's history (last normal menstrual period, regularity of menses, onset of pregnancy symptoms) to decide whether an ultrasound is necessary to assess if the gestational age was greater than 70 days. The patient has the tests done, including a hemoglobin, Rh status and ultrasound if necessary. At a second telemedicine visit, the physician reviews the results and signs the prescription for the mifepristone and misoprostol. There is not a specific hCG level cutoff, and each physician uses clinical judgment to determine that the patient is less than 10 weeks' gestation and therefore eligible for the medication abortion. The patient and a counselor then have a telemedicine visit to discuss the details of taking the medications. The patient reads the consent form and gives verbal consent witnessed by the counselor. The medications are couriered to her, or a prescription is faxed to her pharmacy Depending on the clinic scheduling, there are usually three hCG levels done: the initial one, one within 2 days of mifepristone ingestion and one a week later. The physicians at Willow Clinic have a follow-up by telemedicine to discuss the woman's reaction to the medications and her blood test results. If the quantitative hCG has fallen by 80% in 1 week, the physician tells her that the abortion is completed and that she needs no further follow-up [17]. If she needs more misoprostol, surgery or further blood tests, the physician and office assistant will arrange these. Using the SOGC and National Abortion Federation (NAF) guidelines, we tested for Rh status in pregnancies over 8 weeks' gestation in the clinic [2,18]. Since we often did not have confirmation of the exact gestational age, we were very conservative and obtained Rh status in most telemedicine patients. We accepted an HCG of under 2000 to indicate that they were <8 weeks' gestation.

In-clinic abortion patients see the physician and counselor in the clinic and receive the medication at the pharmacy to use at home. They are assessed before and after the abortion by endovaginal ultrasound. If the pregnancy is not seen by ultrasound prior to medication, the women are monitored by measuring serum quantitative hCG. Some in-clinic patients choose to have telemedicine follow-up with serial hCGs, but these were not eligible to be in the control group.

We extracted patient demographics, including age and gestational age, distance from our clinic, use of dating ultrasound, outcome, complications and unscheduled communication with clinic staff and physicians, from the charts of all evaluated patients. Our primary outcomes were the differences that matter to a clinic planning to add telemedicine care. We coded communications about appointments or lab tests as nonclinical and all other communications as clinical. Phone calls to assistants about clinical issues would have been passed to physicians, so one patient could have had unscheduled communication with both the assistant and physician for the same issue. To assess complications, we used the data required by the NAF for quality assurance [18]. We entered the data into a Statistical Package for the Social Sciences database. We compared the two groups using t tests for continuous variables and χ^2 for discontinuous variables.

3. Results

During the 2 years, we saw 4340 individuals requesting medication abortion, of whom 182 (4.2%) were seen only by telemedicine. We reviewed all their charts and a group of 199 in-clinic patients. Table 1 shows the patient characteristics. The in-clinic patients lived an average of 0.66 h (range 0–15 h) and the telemedicine patients lived an average of 5.5 h (range 1.4–21.4 h) away from the clinic ($p < .001$). We did not record the proportion of the entire population that lived >2 h from the clinic. There were 33 (18.1%) individuals who had dating ultrasounds in the telemedicine group compared to 100% of the in-clinic group.

Table 2 shows that the proportions of documented completed abortions (164/182, 90.1% and 179/199, 89.9%, $p = .76$) were similar, as were the proportions of aspirations for completion (6/182, 3.3% and 9/199, 4.5%, $p = .54$) and the proportions lost to follow-up (5.5% and 6.6%, $p = .66$). Table 2 also shows complications. Unscheduled communication with physicians or office assistants includes all phone calls patients made to the clinic after registering. These were handled by office assistants who might pass them on to physicians during clinic hours or by the after-hours emergency service that passed all calls to the physicians. There were no significant differences in the unscheduled communication with physicians (13/182, 7.3% telemedicine and 22/199, 11.1% in clinic, $p = .12$), but fewer telemedicine patients were seen by phyisicians for unscheduled in-person follow-up visits (10/182, 5.6% and 21/199, 10.6%).Unscheduled communications with office assistants were greater in the telemedicine patients than the in-person patients (84/182, 46.2% vs. 43/199, 21.6% in-person, $p < .001$), with much of this being nonclinical (27/182, 14.6% clinical vs. 57/182, 31.3% unclinical) ($p < .001$). For the in-clinic patients, 107 (53.8%) were not tested for Rh status because they were under 8 weeks' gestation by ultrasound and the five who were Rh negative were given anti-D immunoglobulin in the clinic. Only 17 (9.4%) of telemedicine patients were not tested, and there were 31 (17.0%) who were Rh negative. Eight declined anti-D because they planned no further pregnancies, four were told that they did not need anti-D on the basis of a low hCG, and 18 received anti-D at the closest hospital or clinic (one was unknown).

4. Discussion

The most important addition this study provides to the literature is the difference in the practical aspects of clinic care between telemedicine and in-clinic medication abortions; specifically, telemedicine patients required more unscheduled communications and received ultrasounds far less often compared to in-clinic patients. This information may help providers plan services. The results from this study

Table 1
Demographics of in-clinic and telemedicine patients requesting abortion at one clinic in BC in 2017–2018

	In-clinic ($n = 199$)	Telemedicine ($n = 182$)	p value
Age (years)	28.1 ± 6.0	28.7 ± 6.3	.38[a]
Gestational age by LMP[b] (days)	46.5 ± 8.8	48.2 ± 9.6	.03[a]
Distance to clinic (hours)[c]	0.7 ± 1.2	5.1 ± 3.0	<.001[a]
Received dating ultrasound	199 (100%)	33 (18.1%)	<.001[d]

[a] t test.
[b] Last menstrual period.
[c] Driving distance calculated using Google Maps.
[d] χ^2 test.

Table 2
Outcome and complications of in-clinic and telemedicine abortions at one clinic in BC in 2017–2018

		In-clinic (n = 199)	Telemedicine (n = 182)	p value[a]
Outcome	Documented complete medication abortion	179 (89.9%)	164 (90.1%)	.76
	Continuing pregnancy	0	0	
	Aspiration for completion	9 (4.5%)	6 (3.3%)	
	Lost to follow-up	11 (5.5%)	12 (6.6%)	
				.54
				.66
Complications[b]	Infection requiring intravenous antibiotics	0	1 (0.5%)	.30
	Extra misoprostol for incomplete expulsion	7 (3.5%)	2 (1.1%)	.18
	Hemorrhage	0	1 (0.5%)	.30
	Emergency room visit	3 (1.5%)	6 (3.3%)	.25

[a] χ^2.
[b] One person could have multiple complications.

show that it is feasible to provide medication abortions using telemedicine. These results are similar to the results of the studies with other models of telemedicine abortion care using clinic-to-clinic video or email consultations [9,14–17]. One strength of our study was the low loss-to-follow-up rates for all our patients.

This study did not have a large enough sample size to provide evidence of the safety of telemedicine abortions because the complications rates are so low [21]. It does add to the literature about safety in a variety of settings. Women on Web set up a telemedicine medication abortion service in 2006 and uses an online questionnaire and email support to provide abortions with mifepristone and misoprostol to women in situations where safe abortions are not available [4–7]. Using a different model, Planned Parenthood clinics in Iowa offer abortions in which the patients see a counselor and nurse in the clinic but then see a doctor by videoconferencing [8]. The study showed no difference in outcomes or patient satisfaction when comparing women obtaining medication abortion by telemedicine or face-to-face with a physician. More recently, there is a report of direct-to-patient abortions with 248 women receiving medication by mail, and the authors found the service "safe, effective, efficient, and satisfactory" [9].

Canadians often need to travel long distances for abortion care because there are few providers outside of major cities. Many individuals prefer medication abortions to surgical abortions and cannot access these in their communities. Telemedicine is less expensive and more convenient for those who would need to travel long distances to an abortion clinic. The government insurance in BC pays physicians to see their patients by video-conferencing similar amounts to in-office visits. The regulators permit the use of various video platforms that are easy to access on smart phones with appropriate consents [19,20]. These factors help improve access to medication abortions in BC. Some other jurisdictions in Canada do not have billing codes for telemedicine visits between doctors and patients (only medical professionals for consults), some restrict the platforms allowed, and some jurisdictions in the United States prohibit telemedicine abortions completely.

This study highlights the differences for a clinic providing both in-clinic and telemedicine abortions. Standard in-clinic medication abortions would include one booking telephone call and two in-person visits to the clinic, while the standard telemedicine abortion includes at least two telephone calls and three video visits. In clinic, the necessary blood tests are done in the same building, and those patients getting serial hCGs receive paper requisitions with the address of the lab close to their homes. The pharmacy dispensing the mifepristone is also in the building. For telemedicine abortions, the addresses and fax numbers of the labs and pharmacies in the many different communities must be found. Not all pharmacies will dispense mifepristone; when this occurs, another pharmacy must be found or the medications must be couriered. Finding anti-D for Rh negative women was sometimes a challenge. These logistics increased the number of nonclinical communications between patients and office assistants, both scheduled and unscheduled. The unscheduled communications with physicians were not different between the two groups. This would indicate that the information provided by the clinic counselors about what to expect was adequate for telemedicine patients. One of the trade-offs in not having ultrasound dating was that we tested more individuals for Rh status.

One limitation of our study was that we gathered only the limited demographic data required for clinical care and so could not do a detailed comparison between the two groups. Our rate of emergency room (ER) visits (3.3%) was lower than that of Raymond et al. (7%) [9]. We speculate that when counselors prepare individuals to cope with the pain and side effects of medication abortions, they are less likely to go to an ER for pain and bleeding. Our loss-to-follow-up rate of 6.6% was lower than the 23.0% rate in Raymond et al., and this may have been due to the effort by staff to contact them [9]. More research is needed on using different protocols and in different settings.

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Extending Outpatient Medical Abortion Services Through 70 Days of Gestational Age

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OBJECTIVE: To estimate the efficacy and acceptability of medical abortion at 64–70 days from last menstrual period (LMP) and to compare it with the already proven 57–63 days from LMP gestational age range.

METHODS: This prospective, comparative, open-label trial enrolled 729 women with pregnancies 57–70 days from LMP requesting abortion at six U.S. clinics. Medical abortions were managed with 200 mg mifepristone and 800 micrograms buccal misoprostol and sites' service delivery protocols. Follow-up visits occurred 7–14 days after mifepristone, with an abortion considered complete if surgical intervention was not performed. Success, ongoing pregnancy, and acceptability rates were compared.

RESULTS: A total of 629 cases were analyzable for efficacy. Success rates were similar in the two groups (57–63 days group: 93.5%, 95% confidence interval [CI] 90–96; 64–70 days group: 92.8%, 95% CI 89–95). Ongoing pregnancy rates also did not differ significantly (57–63 days: 3.1%, 95% CI 1.6–5.8; 64–70 days: 3.0%, 95% CI 1.5–5.7). Acceptability was high and similar in both arms, with most women (57–63 days: 87.4%; 64–70 days: 88.3%) reporting that their experience was either very satisfactory or satisfactory.

CONCLUSION: Medical abortion with mifepristone and misoprostol in current outpatient settings is an efficacious and acceptable method of ending pregnancies 64–70 days from LMP and can be offered without alteration of existing services.

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LEVEL OF EVIDENCE: II

When medical abortion with mifepristone and misoprostol was approved by the U.S. Food and Drug Administration (FDA) in 2000, the regimen was recommended for outpatient use through 49 days from the last menstrual period (LMP).[1] Extensive research and more than 11 years of experience in the United States with approximately 1.75 million uses have established that medical abortion is safe and effective through 63 days from LMP when used by women at home (May 2011, Danco Laboratories, personal communication).[2–6]

Generally, women in the United States whose first-trimester pregnancies are beyond 63 days from LMP are not offered medical abortion with mifepristone and misoprostol. Medical abortion after 63 days from LMP is occasionally available outside the United States, but only on an inpatient basis using complex regimens.[7–9] Inpatient protocols typically involve redosing of medications, vaginal speculum examination, and an overnight stay, and are burdensome for women, providers, and health care systems. Data supporting use of medical abortion past 63 days from

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LMP in outpatient services are limited to one small trial, but results were not available when this study began.[10] Our study sought to estimate the efficacy and acceptability of the most common outpatient medical abortion regimen in the United States (200 mg mifepristone and 800 micrograms buccal misoprostol) through 70 days from LMP and to compare outcomes between women with pregnancies of 64–70 days' duration and women with pregnancies in the range of 57–63 days. The gestational age limit of 70 days extends the usual gestational age cutoff of 63 days by 1 week.

MATERIALS AND METHODS

The study was performed at six facilities: Family Planning Associates Medical Group (Chicago, IL), Planned Parenthood League of Massachusetts (Boston, MA), Planned Parenthood of New York City (New York, NY), Planned Parenthood of Waco (Waco, TX), Presidential Women's Center (West Palm Beach, FL), and Planned Parenthood of Minnesota, North Dakota, South Dakota (St. Paul, MN). The Quorum Review Institutional Review Board approved the protocol.

Women seeking pregnancy termination were invited to participate in the study if they were eligible for medical abortion, were at least 18 years old, and had a confirmed intrauterine pregnancy 57 through 70 days from LMP, based on routine ultrasound practices of the respective study sites (crown-rump length+42 was most commonly used). Participants had to be willing and able to provide informed consent, have access to a telephone and emergency transportation, be able to speak and read English or Spanish, and agree to follow study protocols. Screening and enrollment generally occurred during the same visit, except when a state-mandated 24-hour waiting period after informed consent required a second visit.

On day 1, participants swallowed mifepristone 200 mg (Mifeprex) in the clinic and then were provided with misoprostol 800 micrograms to take 24–48 hours later at home. Women were instructed to hold the misoprostol buccally for 30 minutes before swallowing any remains. Analgesics and antinausea medications were dispensed or prescribed according to local standards at each facility, and participants were counseled to call the clinic with questions or concerns. Participants maintained a diary for up to 15 days to record time of misoprostol administration, bleeding, expulsion time (if recognized), pain medications used, and days of missed work or school.

Participants returned to the study site 7 to 14 days after using mifepristone (according to clinic practice) for clinical assessment, which included ultrasonography. Uterine suction curettage was recommended for women with ongoing pregnancies. Women with nonviable pregnancies (eg, empty sac or static size with absent cardiac activity on ultrasonography) could opt for suction curettage, expectant management, or a second misoprostol dose. If either of the latter two options was chosen, then women were asked to return to the clinic in 1 week for further follow-up. If a persistent nonviable pregnancy was diagnosed at the extended follow-up visit, suction curettage was recommended. Providers also intervened surgically if they deemed it medically necessary or at the patient's request. After expulsion of uterine contents was confirmed, women responded to a semi-structured interview about their experiences with the medical abortion overall, the incidence of side effects and their severity (based on their own definitions of mild, moderate, and severe), and the acceptability of the procedure. If a participant failed to return for a follow-up visit, then assessment of abortion status and the interview could be conducted by telephone. Study sites were required to document at least three attempts to contact women who were lost to follow-up.

The study's primary objective was to assure that an outpatient medical abortion regimen could be used in gestations 64–70 days from LMP and achieve a success rate of at least 90%, which would characterize a clinically acceptable regimen. A cohort of women with gestations 57–63 days from LMP was also enrolled to serve as a comparison; 334 women per group were needed to detect a 5% or greater lower efficacy than the hypothesized 95% success rate in the 57–63 days group, based on previously published reports ($\alpha=0.05$, $1-\beta=0.8$, using a one-tailed test) and would allow us to estimate a success rate of 90% with a confidence interval (CI) of $\pm 3.2\%$.[2–3,11] Data were analyzed using SPSS 15.0. An independent data and safety monitoring committee reviewed the interim results for safety and efficacy after 50% of the data were available.

The primary outcome of the trial was complete abortion without surgical intervention at any point, regardless of the number of misoprostol doses used. Secondary outcomes included side effects, patient satisfaction and acceptability, days of heavy bleeding, days of missed work or school, and number of calls and unscheduled visits to the clinic. One-tailed $P<.05$ was considered to indicate statistical significance. We chose to use one-tailed P values because our objective was to determine whether use of medical abortion in

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the gestational age range of 64–70 days would result in worse outcomes than its current use in the 57- to 63-day age range. Binomial proportion CIs for efficacy rates were calculated. We used Fisher's exact test to determine differences in proportions, and for continuous variables we used the Student *t* test to determine differences in means.

RESULTS

Between August 2009 and February 2011, the study sites enrolled 729 women; 379 women in the 57–63 days group and 350 women in the 64–70 days group. Fifty-three (14%) women in the earlier and 45 (13%) in the later gestational age group were lost to follow-up, and two women, one from each group, withdrew before using mifepristone. Enrollment was continued to 729 women to compensate for loss to follow-up. Six-hundred twenty-nine cases had outcome data, short of the estimated sample size of 668. Analysis of the outcomes at that time were conducted to determine the utility of continuing the study and whether a statistically significant difference in success would be possible if the study were to continue and the remaining 39 analyzable case records were available. We analyzed the hypothetical scenario that maximized the possible difference in efficacy between the two groups by adding all 39 hypothetical additional cases to the 57–63 days group (because it had the higher efficacy rate) and assuming that every woman had a successful abortion (to model the maximum mathematical differences possible between the groups). This model improved the efficacy rate in the 57–63 days study group by 0.7 percentage points and doubled the difference in efficacy between the two gestational age groups from 0.7% to 1.4%. Comparing the projected success rates of the two gestational age groups resulted in $P=0.2$. It was therefore determined that enrolling all 688 women would not show a statistically significant or a clinically meaningful difference in success rates. The study would have required an additional 13,120 women with follow-up in each study group (total 26,240 analyzable cases) to be able to find a statistically significant difference between the observed success rates. Therefore, a total of 629 medical abortions, 325 in the 57–63 days group and 304 in the 64–70 days group, were analyzed for efficacy in the final analysis. Baseline characteristics of women in the two groups were similar for mean age, education level, gravidity, and previous abortions (Table 1).

Efficacy of the outpatient medical abortion regimen in the 57–63 days group was 93.5% (95% CI 90.1–95.9) and 92.8% (95% CI 89.1–95.3; $P=.41$) in the 64–70 days group (Table 2). Three percent of women in both groups had a surgical intervention because of ongoing pregnancy (57–63 days: 3.1%, 95% CI 1.6–5.8; 64–70 days: 3.0%, 95% CI 1.5–5.7; $P=.62$). Rates of surgical intervention attributable to persistent nonviable pregnancy or sac ($P=.33$), substantial uterine debris ($P=.29$), excessive prolonged bleeding ($P=.75$), or woman's request ($P=.86$) were comparable between study groups. There was no significant difference in efficacy by study site ($P=.137$).

Approximately 5.2% of women in the 57–63 days group and 5.3% of women in the 64–70 days group had incomplete abortion diagnosed (ie, persistent gestational sac or substantial debris) at their first follow-up visits ($P=.56$). The majority were treated with a second dose of misoprostol, with those in the 57–63 days group receiving a second dose at a higher rate than those in the 64–70 days group (76.5% compared with 56.3%; $P=.195$). Of those who received a second dose of misoprostol and underwent an extended follow-up evaluation, 91% (10 of 11) in the earlier and 66.7% (6 of 9) in the later gestational age group were determined to have a complete abortion ($P=.974$).

Almost 70% of participants in each group reported a time of expulsion at follow-up. Among women who reported a time of expulsion, those in

Table 1. Participant Demographic Characteristics

	57–63 d (n=325)	64–70 d (n=304)	*P* (Two-Tailed)
Age (y)	26 (18–42)	26 (18–42)	.66
Primigravid woman	32 (103)	31 (94)	.86
Previous abortion	47 (154)	48 (146)	.87
Previous medical abortion	21 (67)	24 (72)	.39
Education level	322	303	4 unknowns
Less than high school	8 (24)	9 (26)	.71
High school	59 (191)	60 (183)	.85
University	27 (87)	27 (83)	.99
Postgraduate	6 (20)	4 (11)	.19

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Table 2. Efficacy and Major Adverse Events by Gestational Age Group

	57–63 d (n=325)	64–70 d (n=304)	*P* (One-Sided)
Success	93.5 (304; 90–96)	92.8 (282; 89–95)	.41
Interventions	6.5 (21)	7.2 (22)	
Ongoing pregnancies	3.1 (10)	3.0 (9)	.62
Persistent nonviable sac	0.92 (3)	1.6 (5)	.33
Substantial debris in uterus	0.31 (1)	1.0 (3)	.29
Excessive prolonged bleeding	1.2 (4)	1.0 (3)	.75
Woman's request	0.61 (2)	0.33 (1)	.86
Other	0.31 (1)	0.33 (1)	.73
Major adverse events			
Went to emergency department	3.7 (12)	4.6 (14)	.36
Received blood transfusion	0.6 (2)	0.3 (1)	.52
Admitted to hospital	0.9 (3)	0.7 (2)	.53

Data are % (n; 95% confidence interval) or % (n) unless otherwise specified.

the earlier gestational age group were significantly more likely than those in the later gestational age group to expel sooner (Fig. 1; log-rank test *P*=.005). This difference in reported expulsion time was most notably seen at 3 hours after using misoprostol (37.7% in week 9 compared with 22.5% in week 10; *P*=.001), but equal numbers (93.1% compared with 92.1%, respectively; *P*=.43) reported expulsion by 24 hours (Fig. 1).

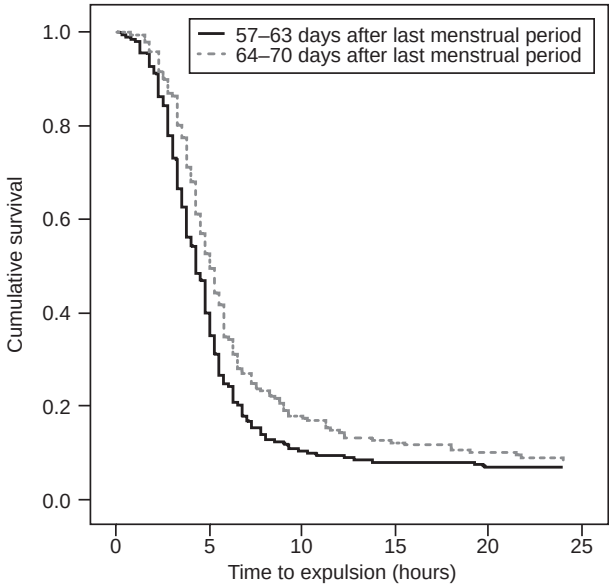

Fig. 1. Time from misoprostol administration to pregnancy expulsion. Survival curves of the number of hours since misoprostol administration until pregnancy expulsion for women 57–63 days from last menstrual period or 64–70 days from last menstrual period. Includes women who reported a time of expulsion, excluding those with ongoing pregnancies or persistent nonviable sac at follow-up. Log-rank test *P*=.005.

Winikoff. Medical Abortion Through 70 Days From LMP. Obstet Gynecol 2012.

Twenty-nine women made visits to an emergency department, primarily for pain and bleeding during the study period (3.7% from the earlier gestational age group and 4.6% from the later group (*P*=.35) (Table 2). Three women received blood transfusions, two in the 57–63 days group and one in the 64–70 days group (*P*=.52). One woman in the 57–63 days group was admitted to the hospital and was successfully treated for *Escherichia coli* sepsis, and one woman in the 57–63 days group with a history of chronic pancreatitis was admitted to the hospital for recurrence of her disease.

Eighty-five percent of participants completed and submitted the diaries they maintained for up to 15 days. Mean duration of heavy bleeding did not differ significantly by group (Table 3). There was no significant difference in mean days of work or school missed by women because of the abortion (1.85 in 57–63 days group compared with 1.80 in 64–70 days group; *P*=.81).

The side effect profiles of each study group were similar, with no significant differences except for vomiting (Table 3). A minority of women in each group experienced this side effect, but fewer in the earlier gestational age group (36% compared with 46%; *P*=.01). However, severe vomiting was no different in the two groups (10.7% for 57–63 days compared with 12.0% for 64–70 days; *P*=.35). Opiates were reportedly used more often for pain relief by women in the 64–70 days group (76% in the 57–63 days group compared with 84%; *P*=.003), but nonsteroidal anti-inflammatory drug use did not differ. Mean days of any analgesic use were the same in both groups. Fewer women in the 57–63 days group reported use of antiemetic medication (34% compared with 46%; *P*=.002). The study participants requested relatively little clinic staff time beyond the scheduled study visits. Only 20%

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Table 3. Side Effect and Bleeding Profile

Side Effects	57–63 d (n=318)	64–70 d (n=300)	*P* (One-Sided)
None	22.6 (72)	17.0 (51)	.05
Chills	24.2 (77)	22.7 (68)	.36
Fever	11.9 (38)	10.3 (31)	.31
Vomiting	35.8 (114)	45.7 (137)	.008
Nausea	50.0 (159)	51.7 (155)	.37
Diarrhea	17.9 (57)	17.3 (52)	.47
Heavy bleeding	319	298	
Days of heavy bleeding	2.5±2.06 (0–14)	2.3±1.86 (0–11)	.09
Median days of heavy bleeding	2	2	

Data are % (n), n, or mean±standard deviation (range) unless otherwise specified.

of women in both groups made phone calls because of concerns related to their abortion, and 4% of women in the earlier and 3% of women in the later gestational age groups made unanticipated clinic visits.

The majority of women in both groups (57–63 days: 87.4%; 64–70 days: 88.3%) reported being either satisfied or very satisfied with the medical abortion method, and 78% and 79% of women in the two groups, respectively, reported that they would choose medical abortion again instead of surgery. Women in the earlier gestational age group were as likely to report seeing the pregnancy or some part of it as those in the later gestational age group (64% compared with 69.3%; *P*=.10). There were no significant differences in women's reported reactions to what they saw, with the exception that women in the earlier gestational age group were more likely to report "nothing or no feeling" (13.9% compared with 8.2%; *P*=.04) and those in the later group were more likely to report that they were "relieved" (7.4% compared with 13.9%; *P*=.02).

DISCUSSION

The results show that medical abortion with an outpatient regimen of 200 mg mifepristone followed 24 to 48 hours later by 800 micrograms buccal misoprostol self-administered at home is efficacious and acceptable in women 64 to 70 days from LMP and is not statistically or clinically different from a current outpatient medical abortion protocol used with women 57–63 days from LMP. In 2000, the FDA approved mifepristone based on an efficacy of 92% for gestations up to 49 days from LMP.[12] The success rate achieved in this study during week 10 of gestation (92.8%) is similar to that rate and clinically acceptable. Based on this evidence, medical abortion using the study protocol can be extended from 63 days from LMP to 70 days from LMP without reconfiguration of existing outpatient clinical services. Our findings are consistent with those of Boersma et al,[10] who offered the same outpatient medical abortion regimen as in the current study to 26 women with gestational ages 64–70 days from LMP, but with an interval of 24–36 hours between the mifepristone and misoprostol doses. That study found 96% success in those women but was too small to provide reliable point estimates of success rates.

The study cannot reject the null hypothesis that there is no difference between the success rates of medical abortion among women with pregnancies of 9 and 10 weeks of gestation. Although the inability to reject the null hypothesis theoretically could be attributable to early cessation of the study, the observed differences between study groups are much smaller than those originally hypothesized and are not clinically meaningful. The additional analyses conducted also suggest that continuing enrollment to include 668 analyzable cases would not have affected the study conclusions.

The overall high efficacy of the medical abortion regimen used in this study through 63 days from LMP is well-documented, and only a very minimal decline in efficacy as gestational age increases has been noted.[2,13] The trend observed in the two point estimates for success in weeks 9 and 10 in this study is consistent with such a small decline (Fig. 2), alleviating concern of an abrupt decline in efficacy of the method beyond 63 days from LMP.

The study was not powered to detect a difference in safety outcomes because major adverse events attributable to medical abortion (eg, hospitalizations, emergency department visits, and blood transfusions) are rare. No medical abortion studies (including the pilot studies on which FDA approval was based) were powered to detect rates of rare occurrences such as transfusion or hospitalization. Similar to those studies, the occurrence of major adverse events in this study was very infrequent.

Many studies have explored women's experiences with outpatient medical abortion in the first trimester,[14]

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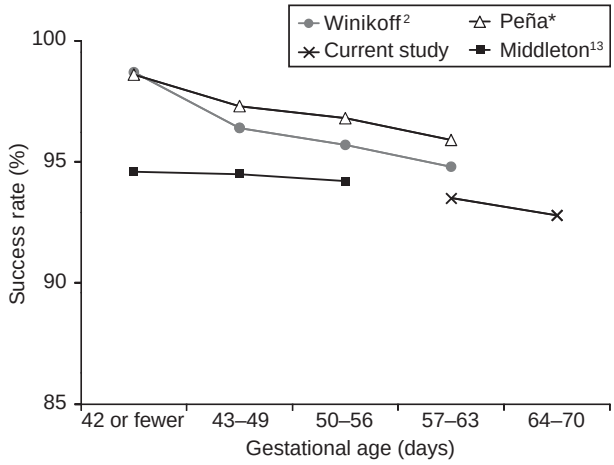

Fig. 2. Efficacy of mifepristone medical abortion with 800 micrograms buccal misoprostol from 49 to 70 days from last menstrual period. Illustration of success rates by gestational age from different studies that used the same medical abortion regimen as in this study. *Peña M. Medicamentos para la interrupción legal del embarazo: La experiencia de la Secretaría de Salud del Districto Federal (Mexico). 20th Congress of the Latin American Federation of Obstetrics and Gynecology (FLASOG) 2011; Managua, Nicaragua.

Winikoff. Medical Abortion Through 70 Days From LMP. Obstet Gynecol 2012.

but often the information is not disaggregated by week. Although our findings do not show any differences between the two study groups in such aspects as bleeding profiles, days of school or work missed, and reports of seeing the expulsion, women's experiences at these later weeks of gestational age may differ in some ways from women with earlier first-trimester pregnancies. The results from this study may help clinicians who provide medical abortion to women with pregnancies 57–70 days of gestational age to tailor counseling messages to prepare women for what to expect. For example, more than two-thirds of women reported witnessing uterine expulsion, so women should be counseled on that likelihood. Women with gestations in week 10 may expel their pregnancies less quickly after using misoprostol, but perhaps this is not surprising given the slightly larger size of the gestational sac at the later gestational age The fact that more women in week 10 expressed relief after their medical abortions could be an artifact of participating in the test group of a research trial.

Some women may have been misclassified into study groups based on usual variability in gestational age dating by ultrasonography. To be sure that such misclassification would not have affected study results, reanalysis of success among women with pregnancies at the opposite extremes of the gestational age spectrum considered in this study (ie, a comparison of the earlier half of the early age range with the latter half of the later age range), as well as by standardizing gestational age assessment, did not affect our outcomes or our conclusions (data not shown).

The content of counseling was not dictated by the study protocol and was based on usual counseling provided. Possible assumptions that pain, bleeding, and the size of the expelled fetus in week 10 may be more than at earlier weeks of gestation could have had an effect on women's perceptions. It is also possible that there were slight differences in counseling messages as a result of the counselors' knowledge of gestational age in each woman. Similarly, observations and experience amassed during the course of the study may have resulted in adjustments in counseling messages to later enrollees, better-preparing women with pregnancies in week 10 for what they might experience.

The study sites already were highly experienced at providing medical abortion and were accustomed to administering the specific regimen used in this study. Therefore, the observed efficacy rates may not be generalizable to clinics that are less experienced. Results also are not generalizable to regimens other than the one studied, for either efficacy or the side effects of misoprostol, which are known to vary by route and dose. Last, because adverse events were so rare in our study, the sample size was not sufficient to characterize adequately the occurrence of adverse events for women who terminate their pregnancies medically during the ninth or tenth week other than to say that serious events are infrequent and side effects are tolerable.

In conclusion, the regimen of 200 mg mifepristone and 800 micrograms buccal misoprostol is efficacious and acceptable for women seeking medical abortion with pregnancies of 70 days or less. The findings of this research are important for expanding the availability of this nonsurgical option to women seeking termination of pregnancy in the first trimester.

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Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion

A Randomized Controlled Trial

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OBJECTIVE: To study the efficacy, safety, and acceptability of oral immediately swallowed and buccal misoprostol 800 mcg after mifepristone 200 mg for terminating pregnancy through 63 days since the last menstrual period (LMP).

METHODS: This seven-site study randomly assigned 966 women seeking abortions to oral or buccal misoprostol 800 mcg 24–36 hours after mifepristone 200 mg with 7–14-day follow-up.

RESULTS: Success rates in the oral and buccal groups were 91.3% (389 of 426) and 96.2% (405 of 421), respectively (*P*=.003; relative risk [RR] 0.95, 95% confidence interval [CI] 0.92–0.98). Ongoing pregnancy occurred in 3.5% (15 of 426) of women who took oral misoprostol compared with 1.0% (4 of 421) of women in the buccal group (*P*=.012; RR 3.71, 95% CI 1.24–11.07). Through 49 days since the LMP, oral and buccal regimens performed similarly, but success with oral misoprostol decreased as pregnancy advanced. In pregnancies of 57–63 days since the LMP, success with oral misoprostol fell below 90%, whereas that with buccal remained high (oral 85.1% [97 of 114], buccal 94.8% [109 of 115], *P*=.015, RR 0.90, 95% CI 0.82–0.98). Furthermore, in this gestational age group, there were significantly more ongoing pregnancies among women who took misoprostol orally (7.9% [9 of 114]) compared with buccally (1.7% [2 of 115]; *P*=.029, RR 4.54, 95% CI 1.0–20.55). Adverse effect profiles were similar, although fever and chills were reported approximately 10% more often among women who took buccal misoprostol. Satisfaction and acceptability were high for both methods.

CONCLUSION: Buccal misoprostol 800 mcg after mifepristone 200 mg is a good option for medical abortion through 63 days since the LMP. Oral misoprostol 800 mcg is also a safe and effective alternative, although success rates diminish with increasing gestational age.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00386867

(Obstet Gynecol 2008;112:1303–10)

LEVEL OF EVIDENCE: I

From the Gynuity Health Projects, New York, New York; Magee Womens Hospital/University of Pittsburgh, Pittsburgh, Pennsylvania; Planned Parenthood of Waco, Waco, Texas; Planned Parenthood League of Massachusetts, Boston, Massachusetts; Whole Woman's Health, Austin, Texas; Family Planning Associates Medical Group, Chicago, Illinois; Parkmed, New York, New York; and Institute for Urban Family Health, New York, New York.

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Financial Disclosure

Dr. Winkoff, Ms. Dzuba, and Ms. Shannon are all with Gynuity Health Projects (New York, NY), who had a contract with Danco Laboratories, the distributor of mifepristone in the United States, to carry out Phase IV studies that are a part of Danco's responsibility to the U.S. Food and Drug Administration. Dr. Creinin has received compensation from Danco Laboratories, LLC, for providing third-party telephone consultations to clinicians who seek expert advice on mifepristone. The other authors have no potential conflicts of interest to disclose.

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After mifepristone was approved by the United States Food and Drug Administration in 2000, vaginal use of misoprostol 800 mcg became almost a standard of care in early medical abortion.[1–3] However, nonvaginal routes of misoprostol administration are now of increasing interest to women and providers because of 1) lower acceptability of vaginal administration[4,5]; 2) legal peril to women where abortion is clandestine and pill remnants may remain in the vagina; and 3) concern about infection, specifically,

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very rare but fatal clostridial infections[6,7] (although no association between such infections and use of vaginal misoprostol has been found). In March 2006, Planned Parenthood Federation of America changed its national guidelines to avoid vaginal administration of misoprostol, but the scanty evidence supporting a nonvaginal regimen through 63 days since the last menstrual period (LMP) meant that medical abortion was no longer an option for women with pregnancies of more than 56 days since the LMP.

Oral (immediately swallowing pills), buccal (holding pills in the cheek) and sublingual (holding pills under the tongue) misoprostol administration after mifepristone has been studied as an alternative to vaginal administration in early medical abortion. Encouraging but equivocal findings of studies on 800 mcg oral misoprostol[8–10] and unpublished claims of high clinical success and tolerance of adverse effects with this regimen in a large United Kingdom system (January 2006, Dr. Kate Worsley, personal communication) suggested the need for a more definitive trial. Similarly, because an 800 mcg buccal regimen had been shown to be as effective as a 800 mcg vaginal regimen through 56 days since the LMP[11] and the pharmacokinetic profiles and effect on uterine contractility were similar,[12,13] we decided that buccal administration was also a likely candidate for use through 63 days since the LMP. We conducted a randomized trial to explore whether 800 mcg oral and buccal misoprostol 24–36 hours after mifepristone 200 mg are effective regimens for routine clinical use in medical abortion through 63 days since the LMP.

MATERIALS AND METHODS

We report an open-label, randomized trial to characterize oral and buccal misoprostol administration after mifepristone in women with pregnancies through 63 days since the LMP. The study was implemented in seven facilities in the United States: Family Planning Associates Medical Group (Chicago); Institute of Urban Family Health (New York); Magee Womens Hospital/University of Pittsburgh (Pittsburgh); Parkmed (New York); Planned Parenthood League of Massachusetts (Boston); Planned Parenthood of Waco (Waco); and Whole Woman's Health (Austin). The Western Institutional Review Board and the institutional review boards at the University of Pittsburgh and the Institute for Urban Family Health approved the protocol.

Women seeking medical abortion were eligible if they did not have U.S. Food and Drug Administration–labeled contraindications to the method, were at least 18 years old, and had an intrauterine pregnancy not exceeding 63 days since the LMP on the day of the medical abortion. Gestational age was determined by LMP, clinical examination, and/or ultrasonography, as needed. Participants had to be willing and able to sign consent forms, have access to a telephone and emergency transportation, speak and read English or Spanish, and agree to comply with the study procedures. Screening and enrollment generally occurred during the same visit, except when state-mandated 24-hour waiting periods after informed consent required a second visit.

On day 1, participants swallowed mifepristone 200 mg (Mifeprex; Danco Laboratories, New York, NY) in the clinic and then were provided with misoprostol 800 mcg (Ivax Pharmaceuticals, Miami, FL) to take 24–36 hours later at home, either orally or buccally according to random assignment. Women assigned to take misoprostol buccally were instructed to hold two 200-mcg pills in each cheek pouch for 30 minutes and then to swallow any remnants. Women were offered prescriptions for oral narcotics to manage pain and antidiarrheal and antinausea medications, according to local standards at each facility. Participants maintained a diary for up to 15 days to record misoprostol administration, pain, bleeding, adverse effects and medications taken.

Participants returned to the study site 7 to14 days after taking mifepristone for clinical assessment, including transvaginal ultrasonography, except at one site where ß-hCG levels were routinely monitored and ultrasonography was employed only when needed. Women with ongoing pregnancies were recommended suction aspiration. Women with nonviable pregnancies (eg, sac or other evidence of products of conception, but no gestational growth and no cardiac activity on ultrasonography) could opt for suction aspiration, expectant management, or a second misoprostol dose administered by the same route as the initial dose. If either of the latter two options was chosen, women were asked to return 7 days later. If a persistent nonviable pregnancy was diagnosed at the extended follow-up visit, a suction aspiration was recommended. Providers also could intervene surgically if deemed medically necessary (eg, for excessive bleeding) or at the participant's request. After expulsion was confirmed, women responded to a semi-structured interview about the experience overall, the acceptability of the procedure, and adverse effects.

Allocation to study group was determined by computer-generated assignment concealed in sealed opaque envelopes. Randomization sequence (using random blocks of eight and stratified by study center) and envelopes were prepared by Gynuity Health Projects staff unrelated to the clinical conduct of the

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study. Envelopes were assigned to study participants in numerical sequence. Both providers and participants became aware of group assignment when the envelopes were opened.

The primary objective of the study was twofold: 1) to estimate the effectiveness of each regimen among women with gestations 57 to 63 days since the LMP and 2) to compare their effectiveness among all women. In determining the sample size, recruitment of women in the 57–63 day gestational age group was a limiting factor, and therefore the sample size calculation was based on the first stated objective. We determined that a sample of 105 women in the gestational age range of 57–63 days was required in each study arm to be able to estimate efficacy at 93% with a 95% confidence interval (CI) of ±5% (assuming a 5% rate of loss to follow-up). Based on U.S. abortion clinic statistics, we estimated that 15–20% of all participants would fall in the 57–63 day gestational age group, and anticipated enrolling a total of 1,200 women. With at least 425 women per arm, and assuming a 95% efficacy for the buccal regimen,[11] we would be able to detect a 5% difference between the study arms with 80% statistical power at the 95% confidence level—a difference we considered clinically important for formulating practice guidelines.

Data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL). An interim analysis was conducted when approximately 50% of the study sample completed participation to assess safety. Baseline demographic variables were compared according to treatment group to test randomization, using the Student *t* test or the Mann-Whitney *U* test for continuous variables and χ^2; or Fisher exact test (where cell sizes were 5 or less) for categorical variables. Normality of continuous variables was assessed by graphic display.

The primary outcome variable—treatment success—was assessed both by per-protocol and intention-to-treat analyses; because no significant differences were found using the χ^2 test, only the per-protocol analysis is presented. Per-protocol analysis has been deemed more appropriate for an exploratory efficacy trial[14] and more valuable to clinicians and clinic managers who want to understand the true efficacy of the two regimens; moreover, it is commonly presented in medical abortion trials.[10] In both analyses, we included in-clinic or telephone follow-up adequate to determine that a woman's pregnancy had been terminated; for per-protocol analysis, adherence to the regimen was determined according to information provided at the follow-up visit. Successful medical abortion was defined as a complete abortion without surgical intervention at any point, regardless of the number of doses of misoprostol taken. For the final analysis of the primary outcome variable, the alpha was reduced to 0.0479, as a result of the interim analysis and according to the O'Brien and Fleming method.[15]

Secondary outcome variables were the effect of a second dose of misoprostol, adverse effects, patient satisfaction and acceptability of each of the regimens, adverse effects, and pain; these outcomes were assessed according to treatment group using χ^2 test or Fisher exact test. Finally, the effect of gestational age on primary and secondary outcome variables was assessed by χ^2 test for trend, and post-hoc, pair-wise comparisons were conducted using the Tukey HSD test, where results were significant. Efficacy within groups by site was assessed using χ^2 test or Fisher exact test. For secondary analyses, two-tailed values of $P<.05$ were considered significant.

RESULTS

Between September 2006 and May 2007, the study sites enrolled 966 participants (Fig. 1). Enrollment was discontinued after 265 women with pregnancies between 57 and 63 days since the LMP were randomly assigned, ensuring at least 210 analyzable cases. The two treatment groups were similar with respect to education level, marital status, gravidity, gestational age, and previous abortions, but there was a statistically significant difference in mean age (25.8 years for oral compared with 26.7 years for buccal $P=.02$) (Table 1).

Five participants (0.5%) withdrew from the study after randomization and 92 (9.5%) were lost-to-follow-up. The experiences of 847 women were analyzed for efficacy (Fig. 1). Overall the efficacy after buccal misoprostol administration was greater than that of oral administration (96.2% compared with 91.3%, $P=.003$) (Table 2). An intention-to-treat analysis was also conducted, which yielded no difference in conclusions (96.1%, buccal compared with 91.0%, oral, $P=.003$, RR 1.06, 95% CI 1.02–1.09). One percent of the women assigned to buccal misoprostol and 3.5% of the women assigned to oral misoprostol had a surgical intervention due to ongoing pregnancy (RR 3.71; $P=.012$). Other reasons for surgical intervention included persistent nonviable pregnancy or sac (n=14), medical indications (n=19), or woman's request (n=1), none of which varied significantly by study group. Efficacy did not vary significantly by study group among all women with gestations 56 days since the LMP or less, but among women with pregnancies 57–63 days since the LMP, efficacy was higher after buccal administration (85.1% compared with 94.8%, RR 0.90; $P=.015$). Fur-

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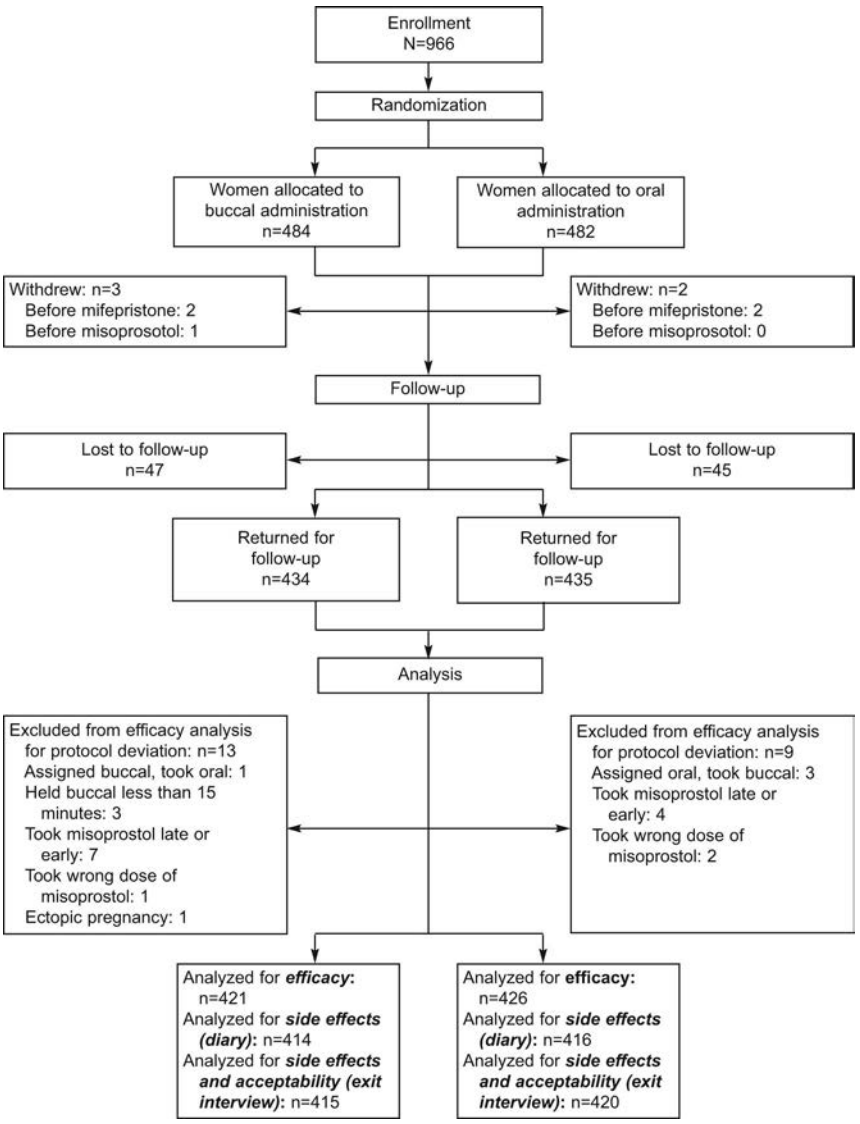

Fig. 1. Illustration of the flow and numbers of study participants through each phase of the study (enrollment, randomization, follow-up and analysis). *Winikoff. Misoprostol by Mouth in Medical Abortion. Obstet Gynecol 2008.*

ther, the frequency of ongoing pregnancy was significantly higher in that gestational age group among women administering misoprostol orally (7.9% compared with 1.7%, RR 4.54; P=.029). The success of buccal administration did not vary significantly with gestational age (χ^2 for trend 1.776; P=.183), although there was some decline in success with advancing gestational age (Fig. 2). Success after oral administration, however, was high (96.1%) among women with gestations 49 days since the LMP or less, but declined to 85.1% among those 57–63 days (P<.001).

The frequency of use of a second dose of misoprostol at follow-up to treat women with persistent nonviable pregnancies or uncertain outcomes did not vary between women in the buccal (n=14) and oral (n=12) groups (P=.668). Nonetheless, more women in the buccal group who took a second dose achieved a successful outcome (92.9% compared with 50.0%, P=.026). After a second dose of misoprostol, the success rate among women using misoprostol buccally increased by 3.1%, whereas the success rate was improved by only 1.5% for women in the oral group. This difference in improved outcome was not statistically significant.

Women reported adverse effects in diaries and in semistructured interviews at the follow-up visit (Table 3). The differences between what women recorded in diaries and what they reported in interviews were less than 10% for all effects except weakness, and approximately 80% of women's responses were consistent between the two sources (data not shown). Regardless of the source of report, the adverse effect profiles of

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Table 1. Participant Characteristics by Study Group

	Oral (n=435)	Buccal (n=434)
Age (y)*	25.8 (±5.8)	26.7 (±6.1)
Educational level		
Less than high school	7.6 (33)	7.4 (32)
High school graduate	53.1 (231)	52.3 (227)
University graduate	33.8 (147)	32.0 (139)
Postgraduate degree†	3.9 (17)	6.9 (30)
Unknown	1.6 (7)	1.4 (6)
Currently married	14.1 (61)	16.8 (73)
Gravidity	3 (1–13)	3 (1–11)
Previous abortions	50.5 (219)	46.4 (201)
Gestational age (d)	49.7 (±8.3)	49.9 (±8.1)

Data are mean (±standard deviation), % (n), or median (1st quartile–3rd quartile).
* P=.02.
† P=.05.

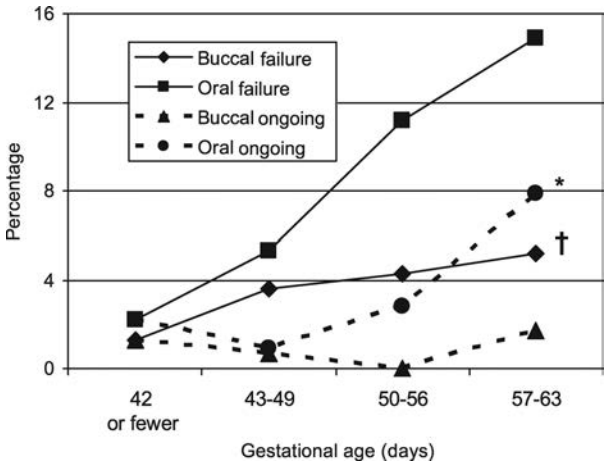

Fig. 2. Illustration of how failure rates and, more specifically, ongoing pregnancy rates increased with gestational age, particularly in the group of women that took oral misoprostol. * Difference between ongoing pregnancy rates by regimen is statistically significant at 57–63 days since the LMP (P=.029). † Difference between failure rates by regimen is statistically significant at 57–63 days since the LMP (P=.015).

Winikoff. Misoprostol by Mouth in Medical Abortion. Obstet Gynecol 2008.

each study group were similar. Nausea vomiting, and diarrhea were reported equally frequently by women in each group. Fever/chills were also reported about 10% more frequently among women who took misoprostol buccally, whether reported in the diary (47.6 compared with 36.1, P=.001) or during the exit interview (41.4% compared with 33.3%, P=.020).

Twenty-six (3.0%) women made visits to an emergency room during the study period (14 from the oral group and 12 from the buccal group), 21 of whom were not admitted, primarily for pain and bleeding. Three participants from the buccal group were hospitalized during the study period for reasons that were unrelated to the study protocol (pulmonary embolus, ruptured ectopic pregnancy, and right hip pain).

Participants were highly satisfied with the procedure, regardless of the route by which they administered misoprostol: 91.9% of women were either satisfied or very satisfied (Table 4). Satisfaction decreased significantly with increasing gestational age in the oral

Table 2. Treatment Outcomes by Study Group and Gestational Age (Days)

Gestational Age (d)	Oral	Buccal	RR (95% CI)
Success*	91.3* (389/426) (88.2–93.8)	96.2* (405/421) (93.9–97.8)	0.95 (0.92–0.98)
42 or less	97.8 (90/92) (92.4–99.7)	98.7 (75/76) (92.9–100.0)	0.99 (0.93–1.03)
43–49	94.7 (107/113) (88.8–98.0)	96.4 (132/137) (91.7–98.8)	0.93 (0.86–1.00)
50–56	88.8† (95/107) (81.2–94.1)	95.7† (89/93) (89.4–98.8)	0.69 (0.56–1.04)
57–63	85.1* (97/114) (77.2–91.1)	94.8* (109/115) (89.0–98.1)	0.90 (0.82–0.98)
Failure	8.7* (37/426) (6.2–11.8)	3.8* (16/421) (2.2–6.1)	2.29 (1.29–4.04)
Ongoing pregnancy	3.5* (15/426) (2.0–5.7)	1.0* (4/421) (0.3–2.4)	3.71 (1.24–11.07)
42 or less	2.2 (2/92) (0.3–7.6)	1.3 (1/76) (0.0–7.1)	1.65 (0.15–17.87)
43–49	0.9 (1/113) (0.0–4.8)	0.7 (1/137) (0.0–4.0)	1.21 (0.08–19.17)
50–56	2.8 (3/107) (0.6–8.0)	0.0 (0/93) (0.0–3.2)	–
57–63	7.9* (9/114) (3.7–14.5)	1.7* (2/115) (0.2–6.1)	4.54 (1.0–20.55)
Medically necessary	2.6 (11/426) (1.3–4.6)	1.9 (8/421) (0.8–3.7)	1.36 (0.55–3.34)
Persistent sac	2.3 (10/426) (1.1–4.3)	1.0 (4/421) (0.3–2.4)	2.47 (0.78–7.82)
Patient request	0.2 (1/426) (0.0–1.3)	0.0 (0/421) (0.0–0.7)	–

RR, relative risk; CI, confidence interval.
Data are %, (n/N), or (95% confidence interval), unless otherwise specified.
* P<.048, comparing oral and buccal groups.
† P<.10, comparing oral and buccal groups.

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Table 3. Adverse Effects (% Reporting Ever Experiencing)*

	Reported on Diary				Reported During Exit Interview			
Adverse Effect	Oral (n=416)	Buccal (n=414)	RR (95% CI)	*P*	Oral (n=420)	Buccal (n=415)	RR (95% CI)	*P*
None	2.6 (11)	4.9 (21)	1.67 (0.99–2.83)	.132	7.1 (30)	8.0 (33)	0.90 (0.56–1.46)	.680
Nausea	68.5 (285)	75.1 (311)	0.92 (0.84–1.01)	.067	63.6 (267)	66.0 (274)	0.97 (0.88–1.07)	.559
Vomiting	43.5 (181)	47.6 (197)	0.92 (0.79–1.07)	.228	39.5 (166)	40.2 (167)	0.99 (0.84–1.17)	.901
Diarrhea	38.7 (161)	43.0 (178)	0.91 (0.77–1.07)	.257	35.0 (147)	33.7 (140)	1.05 (0.87–1.26)	.646
Fever/chills	36.1 (150)	47.6 (197)	0.76 (065–0.90)	.001	33.3 (140)	41.4 (172)	0.81 (0.68–0.97)	.020
Headache	38.5 (160)	41.1 (170)	0.95 (0.80–1.12)	.517	31.0 (130)	34.0 (141)	0.92 (0.75–1.12)	.393
Dizziness	37.5 (156)	39.4 (163)	0.96 (0.81–1.14)	.658	29.8 (125)	32.8 (136)	0.91 (0.75–1.12)	.389
Weakness	53.6 (223)	58.0 (240)	0.93 (0.83–1.06)	.274	42.9 (180)	45.1 (187)	0.96 (0.82–1.12)	.588

RR, relative risk; CI, confidence interval.
Data are % (n) unless otherwise specified.
* Responses were consistent between reports on diaries and in exit interviews for 83% of women reporting nausea, 87% reporting diarrhea, 83% reporting dizziness, 83% reporting headache, 79% reporting weakness, and 85% reporting fever/chills.

group (χ^2 for trend 8.708, P=.003) but not in the buccal group (χ^2 for trend 3.495, P=.062). Participant satisfaction was significantly related to success, regardless of study group (χ^2 136.8, P<.001, oral; χ^2 50.1, P<.001, buccal).

Of women having successful abortions, overall satisfaction was higher among those who took misoprostol orally (96.9% compared with 92.8%, P=.009). Among women whose abortions were successful, the difference in the acceptability of adverse effects between the study groups was statistically significant, with more women in the oral group finding the effects acceptable (78.5% compared with 72.1%, P=.037). In both study groups, pain, the time to completion, and adverse effects were considered acceptable or very acceptable to the majority of women (Table 4). In general, women's expectations of the procedure were similar to their experiences, with the majority of women experiencing the same or less pain (70.7%) and bleeding (72.5%) than expected. There was no difference between study groups in expectations of bleeding, but women were more likely to have less pain than expected with oral than with buccal administration (38.6% compared with 29.6%, P=.006). When asked about regimen preference for a future medical abortion, 93.6% of women in the oral group responded that they preferred to take misoprostol orally, whereas only 34.0% of women in the buccal group would prefer buccal administration. The primary complaint about the buccal route was a bitter

Table 4. Women's Experience With the Procedure and Its Acceptability*

	All Women		Successes	
	Oral (n=420)	Buccal (n=415)	Oral (n=386)	Buccal (n=401)
Satisfaction with procedure	92.6 (389)	91.1 (378)	96.9† (374)	92.8† (372)
Procedure not/slightly difficult	71.2 (299)	70.4 (292)	72.8 (281)	71.3 (286)
Amount bleeding				
Less than expected	28.3 (119)	28.9 (120)	25.9 (100)	27.4 (110)
Same as expected	44.0 (185)	43.6 (181)	45.9 (177)	45.1 (181)
More than expected	26.0 (109)	25.3 (105)	26.4 (102)	25.7 (103)
Amount pain				
Less than expected	38.6† (162)	29.6† (123)	37.3† (144)	29.2† (117)
Same as expected	34.3 (144)	38.8 (161)	34.7 (134)	39.2 (157)
More than expected	25.7 (108)	29.9 (124)	26.4 (102)	30.2 (121)
Pain acceptable	68.3 (287)	64.8 (269)	68.4 (264)	65.3 (262)
Adverse effects acceptable	76.4 (321)	71.3 (296)	78.5† (303)	72.1† (289)
Time acceptable	83.3 (350)	82.7 (343)	85.5 (330)	84.0 (337)

Data are % (n).
* Satisfied means responded that procedure was either very satisfactory or satisfactory; acceptable means that women reported adverse effects, pain, or time of procedure was either acceptable or very acceptable.
† P<.05 comparing oral and buccal groups.

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and chalky taste of the misoprostol, mentioned by 24% of women who administered it that way.

DISCUSSION

Our study demonstrates that, after 200 mg mifepristone, a dose of 800 mcg buccal misoprostol is more effective at terminating pregnancy than an 800 mcg oral dose. The buccal regimen is superior to the oral regimen between 57 days and 63 days since the LMP, with a trend over the entire gestational age range toward superiority between 49 days and 56 days since the LMP. Our results on the performance of the 800 mcg oral misoprostol regimen corroborate previous research that demonstrates a total efficacy of 90% or greater using oral regimens through 63 days since the LMP[8,10,16–20] and also corroborates that with increasing gestational age, success decreases and ongoing pregnancies rise significantly.[9,16,17,21] However, of the studies of 800 mcg oral misoprostol, one was terminated early due to low tolerance of adverse effects and reported outcomes in only 27 women.[9] In the other study, the failure rate among women 57–63 days since the LMP who took misoprostol orally was only two percentage points higher than among those who administered it vaginally (9.8% compared with 7.8%; RR 2.8, 95% CI 1.3–5.8),[10] a difference that may not be clinically relevant.

Our data also show that efficacy with buccal administration also decreases slightly with increasing gestational age (Table 2). Similar declines in efficacy may be observable regardless of route in early medical abortion.[9,10,16,22,23] There are three published trials using buccal misoprostol for pregnancy termination,[11,24,25] one of which used methotrexate, not mifepristone,[25] another was a pilot, noncomparative trial,[24] and the last of which tested the regimen only through 56 days since the LMP.[11] Our study demonstrates clearly that buccal misoprostol 800 mcg after mifepristone 200 mg is appropriate for use between 57–63 days since the LMP, whereas oral misoprostol 800 mcg is not as effective.

Differences in pharmacokinetics between oral and buccal routes offer one possible explanation for the different success rates, because the rapid peak in serum levels after oral use has been observed to result in increased uterine tone but not sustained uterine contractions. In contrast, regular and sustained uterine contractility has been documented after buccal as well as vaginal administration.[13]

Several large randomized clinical trials suggest that a repeated misoprostol dose may have a "leveling" effect on success among regimens.[10,16] A leveling effect was not observed in our study where use of additional misoprostol doses did not differ between study groups. In fact, the effect of a second dose among women who received it was a 1.5% increment in success for the oral regimen and 3.1% increment for the buccal route, widening the difference in efficacy between the routes.

Adverse effects were acceptable to women in both study groups and did not seem to affect overall satisfaction with the method, which was very high. Moreover, adverse effects did not vary significantly by study group, with the exception of more reports of fever/chills among those who took misoprostol buccally, but which were not judged clinically important. The adverse-effects profile in the buccal group was quite similar to that published by Middleton et al.[11] Despite claims that oral misoprostol leads to more gastrointestinal adverse effects (vomiting and diarrhea)[9,26] and the fact that our oral dose was higher than that used in some studies, we observed no differences in such effects between oral and buccal administration.

Clinical practices, including the timing and length of follow-up and propensity to intervene, have an important effect on observed differences in success rates in the published literature as well as in practice. A published meta-analysis and another case series have confirmed that provider practice may affect method success.[27,28] Clinicians in our study were aware of a woman's assigned regimen, and it is possible that this knowledge inadvertently influenced patient management. However, the overall differences in the reasons for surgical intervention were neither large nor significant, with the exception of ongoing pregnancies, the diagnosis of which is not as subject to provider bias.

The consideration of provider practice is particularly relevant because most of the mifepristone–misoprostol regimens tested in randomized trials are highly effective (greater than 90% overall efficacy). Moreover, management disparities may help to explain inconsistencies among randomized controlled trials, especially those done in one or only a few sites. The effect of provider practices may be unavoidable, costly to measure, and difficult to interpret, but if trial results should guide real-world practice, there is benefit to a protocol that does not overregulate clinical management.

In addition to oral and buccal, sublingual administration is another possible nonvaginal route of drug administration in medical abortion. The two randomized trials that had reported on the sublingual route through 63 days since the LMP at the time we initiated our study[22,23] examined use in a total of only

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169 women. These data were insufficient to assume that sublingual administration was a more promising route than buccal misoprostol, which had already been demonstrated to be at least as effective as vaginal misoprostol through 56 days since the LMP.[11] The sublingual route remains an alternative that warrants further investigation.

The findings of our research are important for expanding the availability of medical abortion to women with pregnancies beyond 56 days of gestation where providers or women are reluctant to use vaginal misoprostol. Our results support the offer of a highly effective, safe, and acceptable nonvaginal regimen for early termination of pregnancy.

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Dear Drs. Phipps and Grobman,

In your letter of April 20, 2020, to former Commissioner Stephen Hahn, you expressed concerns about the in-person dispensing requirements for certain prescription drugs during the current public health emergency. In my letter to you of March 19, 2021, I indicated that staff in the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) were evaluating the issues you raised.

Following up on my March 19, 2021, letter I am writing to report the results of CDER's review and analysis.

CDER conducted a literature search for studies pertinent to the in-person dispensing requirement in the Mifepristone REMS Program during the COVID-19 pandemic. Based on this literature search, CDER identified four publications that included relevant clinical outcome data.[1] CDER

[1] Chong E, et al. Expansion of a Direct-to-Patient Telemedicine Abortion Service in the United States and Experience during the COVID-19 Pandemic. Contraception 2021 (accepted manuscript). https://www.sciencedirect.com/science/article/pii/S0010782421000913; Kerestes C, et al. Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models. Contraception 2021 (accepted manuscript). https://doi.org/10.1016/j.contraception.2021.03.025; Aiken A et al. Effectiveness, Safety and Acceptability of No-test Medical Abortion Provided Via Telemedicine: a National Cohort Study. British J Obstet Gynecol 2021. https://obgyn.onlinelibrary.wiley.com/doi/10.1111/1471-0528.16668; Reynolds-Wright JJ et al. Telemedicine medical abortion at home under 12 weeks' gestation: a prospective observational cohort study during the COVID-19 pandemic. BMJ Sex Reprod Health 2021. https://srh.bmj.com/content/early/2021/02/04/bmjsrh-2020-200976

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found that although there are limitations to the study designs, the overall findings from these studies do not appear to show increases in serious safety concerns (such as hemorrhage, ectopic pregnancy, or surgical interventions) occurring with medical abortion as a result of modifying the in-person dispensing requirement during the COVID-19 pandemic.

CDER also reviewed postmarketing adverse events that reportedly occurred from January 27, 2020 - January 12, 2021, with mifepristone use for medical termination of early pregnancy, along with available information about deviations or noncompliance events associated with the Mifepristone REMS Program.[2] CDER found that the small number of adverse events reported to FDA during the COVID-19 public health emergency (PHE) provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to the reported adverse events.

In summary, provided the other requirements of the Mifepristone REMS Program are met, and given that the in-person dispensing of mifepristone for medical termination of early pregnancy may present additional COVID-related risks to patients and healthcare personnel because it may involve a clinic visit solely for this purpose, CDER intends to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form. Further, to the extent all of the other requirements of the Mifepristone REMS Program are met, CDER intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of mifepristone through the mail either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

CDER is communicating this decision to the approved application holders subject to the Mifepristone REMS Program.

Sincerely yours,

Janet Woodcock, M.D.
Acting Commissioner of Food and Drugs

[2] See Mifepristone REMS Program at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390. CDER's analysis covers both products that are subject to the Mifepristone REMS Program (Mifeprex and the approved generic, Mifepristone Tablets, 200 mg).

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Abortion care guideline

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Abortion care guideline

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Supplementary materials and web annexes available online https://www.who.int/publications/i/item/9789240039483:

- Web annex A. Key international human rights standards on abortion
- Web annex B. Technical meetings during guideline development
- Supplementary material 1. Evidence-to-Decision frameworks for the law and policy recommendations
- Supplementary material 2. Evidence-to-Decision frameworks for the clinical service recommendations
- Supplementary material 3. Evidence-to-Decision frameworks for the service delivery recommendations and best practice statements

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Acronyms and abbreviations

AAAQ	availability, accessibility, acceptability and quality
AN	auxiliary nurse
ANM	auxiliary nurse midwife
CEDAW	Convention on the Elimination of All Forms of Discrimination against Women
CESCR	United Nations Committee on Economic, Social and Cultural Rights
CRC	United Nations Convention on the Rights of the Child
CRVS	civil registration and vital statistics
CSE	comprehensive sexuality education
D&C	dilatation and (sharp) curettage
D&E	dilatation and evacuation
EML	WHO Model List of Essential Medicines (or Essential Medicines List)
EmOC	emergency obstetric care
ERG	External Review Group
ERRG	Evidence and Recommendation Review Group
EST	Evidence Synthesis Team
EtD	Evidence to Decision
EVA	electric vacuum aspiration
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	Guidelines Review Committee
HMIS	Health management information systems
IUD	intrauterine device
IUFD	intrauterine fetal demise
IV	intravenous
LMIS	logistics management information systems
LMP	last menstrual period
MVA	manual vacuum aspiration
NEML	national essential medicines list
NGO	nongovernmental organization
NMRA	national medicines regulatory authorities
NSAID	non-steroidal anti-inflammatory drug
OCP	oral contraceptive pill
PCB	paracervical block
PHC	primary health care
PICO	population, intervention, comparator, outcome(s)
Rh	Rhesus (blood group)
SDG	Sustainable Development Goal
SRH	sexual and reproductive health
STI	sexually transmitted infection
UHC	universal health coverage
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
USA	United States of America
VAS	visual analogue scale
WHO	World Health Organization

Glossary

For the sake of mutual understanding and consistency, below follows a list of how key terms and concepts are used throughout the guideline:

- **Community-based care**: Services delivered by a broadly defined community health workforce, according to their training and capacity, encompassing a range of health workers, lay and professional, formal and informal, paid and unpaid, as well as facility-based personnel who support and supervise them and provide outreach services and campaigns *(1)*.
- **Comprehensive abortion care (CAC)**: Provision of information, abortion management (including induced abortion and care related to pregnancy loss), and post-abortion care.
- **Concluding observations**: Following submission of a State report and a constructive dialogue with the State party to the particular convention, treaty monitoring bodies issue concluding observations to the reporting State, which are compiled in an annual report and sent to the United Nations General Assembly *(2)*.
- **Conscious sedation**: The use of a combination of medicines – a sedative to relax and an anaesthetic to block pain – to induce a depressed level of consciousness during a medical procedure.
- **Conscientious objection or conscientious refusal**: The practice of health-care professionals refusing to provide abortion care on the basis of personal conscience or religious belief.
- **Decriminalization**: Removing abortion from all penal/criminal laws, not applying other criminal offences (e.g. murder, manslaughter) to abortion, and ensuring there are no criminal penalties for having, assisting with, providing information about, or providing abortion, for all relevant actors.
- **Dilatation and evacuation (D&E)**: D&E is used after 12–14 weeks of pregnancy. It is the safest and most effective surgical technique for later abortion, where skilled, experienced practitioners are available. D&E requires preparation of the cervix using osmotic dilators and/or pharmacological agents, and evacuating the uterus primarily with forceps, using vacuum aspiration (refer to entry in this list) to remove to remove any remaining blood or tissue.

- **Gestational age (duration of pregnancy)**: The number of days or weeks since the first day of the woman's last normal menstrual period (LMP) in women with regular cycles (see Table 1). For women with irregular cycles or when LMP is unknown, gestational age is the size of the uterus, estimated in weeks, based on clinical examination or ultrasound, that corresponds to a pregnant uterus of the same gestational age dated by LMP.

Table 1. Equivalent gestational ages in weeks and days during early pregnancy

Weeks of gestation	Days of gestation
0	0–6
1	7–13
2	14–20
3	21–27
4	28–34
5	35–41
6	42–48
7	49–55
8	56–62
9	63–69
10	70–76
11	77–83
12	84–90
13	91–97
14	98–104

Note: Day 0 is the first day of the last menstrual period (LMP), and is also the first day of Week 0 of gestation (*not* Week 1).

Source: Adapted from 2012 *Safe abortion* guidance *(2)* based on International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10), 2004 *(3)*.

- **General comments/recommendations**: A treaty monitoring body's interpretation of the content and operation of human rights conventions. General comments seek to clarify the reporting duties of States Parties with respect to certain provisions, and suggest approaches to implementing treaty provisions *(2)*.
- **Health**: A state of complete physical, mental and social well-being and not merely the absence of disease or infirmity *(4)*.
- **Health system:** A health system consists of all organizations, people and actions whose primary intent is to promote, restore or maintain health *(5)*.
- **Health workers**: All people engaged in actions whose primary intent is to enhance health. While, strictly speaking, this includes unpaid carers (e.g. parents caring for sick children, and self-carers), the data available on health worker numbers are generally limited to people engaged in paid activities *(6; Chapter 1: Health workers)*.
- **Human rights standards**: The meaning and scope of human rights as provided for in international human rights treaties and as interpreted and applied by the human rights bodies tasked with this work, which can include international, regional and national courts, and human rights committees *(2)*.
- **Incomplete abortion**: Clinical presence of an open cervical os and bleeding, whereby all products of conception have not been expelled from the uterus, or the expelled products are not consistent with the estimated duration of pregnancy. Common symptoms include vaginal bleeding and abdominal pain. Uncomplicated incomplete abortion can result after an induced or spontaneous abortion (i.e. miscarriage).
- **International human rights treaty** (also sometimes called a covenant or a convention): An international legal instrument adopted by the international community of States, normally at the United Nations General Assembly. Each treaty sets out a range of human rights and corresponding obligations which are legally binding on States that have ratified the treaty *(2)* (Annex 2 includes a list of relevant treaties).

- **Intrauterine fetal demise (IUFD; fetal death)**: The intrauterine death of a fetus at any point in time during the pregnancy *(7)*.
- **Mandatory waiting period**: A requirement imposed by law or policy, or in practice, to wait a specified amount of time between requesting and receiving abortion care.
- **Medical methods of abortion (medical abortion)**: Use of pharmacological agents to terminate a pregnancy *(2)*.
- **Mental health**: A state of well-being in which every individual realizes their own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to their community *(8)*.
- **Miscarriage (spontaneous abortion)**: Spontaneous loss of a pregnancy prior to 24 weeks' gestation, that is, before the fetus is usually viable outside the uterus. The clinical signs of miscarriage are vaginal bleeding, usually with abdominal pain and cramping. If the pregnancy has been expelled, the miscarriage is termed "complete" or "incomplete" depending on whether or not tissues are retained in the uterus *(9)*.
- **Missed abortion**: Arrest of pregnancy development where the embryo/fetus/embryonic tissue or empty gestational sac remains in the uterus and the cervical os is closed. Symptoms may include pain and/or bleeding, or there may be no symptoms at all *(10)*.
- **Osmotic dilators**: Short, thin rods made of seaweed (laminaria) or synthetic material. After placement in the cervical os, the dilators absorb moisture and expand, gradually dilating the cervix *(2)*.
- **Policy**: A law, regulation, procedure, administrative action, incentive or voluntary practice of governments and other institutions *(11)*.
- **Post-abortion care**: Provision of services after an abortion, such as contraceptive services and linkage to other needed services in the community or beyond. It can also include management of complications after an abortion.
- **Primary health care (PHC)**: A whole-of-society approach to health that aims at ensuring the highest possible level of health and well-being and their equitable distribution by focusing on people's needs and preferences as early as possible along the continuum from health promotion and disease prevention to treatment, rehabilitation and palliative care, and as close as feasible to people's everyday environment *(12)*.
- **Quality of care**: QOC encompasses six areas or dimensions of quality that are required in relation to health care:
    - *effective*, delivering health care that is adherent to an evidence base and results in improved health outcomes for individuals and communities, based on need;
    - *efficient*, delivering health care in a manner which optimizes resource use and avoids waste;
    - *accessible*, delivering health care that is timely, geographically reachable, and provided in a setting where skills and resources are appropriate to medical need;
    - *acceptable/person-centred*, delivering health care that takes into account the preferences and aspirations of individual service users and the cultures of their communities;
    - *equitable*, delivering health care that does not vary in quality because of personal characteristics such as gender, race, ethnicity, geographical location or socioeconomic status;
    - *safe*, delivering health care that minimizes risks and harm to service users *(13; p. 9)*.
- **Regulation of abortion**: All formalized laws, policies and other instruments (e.g. facility-level protocol) that regulate pregnancy and abortion.
- **Self-care**: The ability of individuals, families and communities to promote health, prevent disease, maintain health, and cope with illness and disability with or without the support of a health worker. The scope of self-care thus includes health promotion, disease prevention and control, self-medication, providing care to dependent people, seeking hospital/specialist/primary care if necessary, and rehabilitation, including palliative care. It includes a range of self-care practices and approaches *(14)*.

- **Self-management of abortion**: Self-management of the entire process of medical abortion or one or more of its component steps, such as self-assessment of eligibility for medical abortion, self-administration of medicines without the direct supervision of a health worker, and self-assessment of the success of the abortion process.
- **Social enterprise (social business)**: Defined as a business that has specific social objectives that serve its primary purpose. Social enterprises seek to maximize profits while maximizing benefits to society and the environment. Their profits are principally used to fund social programmes *(15)*.
- **Social franchising**: Defined as a system of contractual relationships usually run by a nongovernmental organization which uses the structure of a commercial franchise to achieve social goals. The overarching difference between social and commercial franchising is that social franchising seeks to fulfil a social benefit whereas commercial franchising is driven by profit *(16, 17)*.
- **Social marketing**: Broadly defined as the application of marketing techniques to social problems. Aims to persuade or motivate people to adopt specific courses of action or behaviour which are generally accepted as being beneficial. It is the design, implementation and control of programmes seeking to increase acceptability of a social idea or practice in a target group(s). It cannot create the behaviour, it can only help to gain acceptance and a willingness to adopt the behaviour. Its strategy is predominately preventive *(18)*.
- **Surgical methods of abortion (surgical abortion)**: Use of transcervical procedures for terminating pregnancy, including vacuum aspiration, and dilatation and evacuation (D&E). (See definitions in this list) *(2)*.
- **Telemedicine (or Telehealth)**: A mode of health service delivery where providers and clients, or providers and consultants, are separated by distance *(19)*. That interaction may take place in real time (synchronously), e.g. by telephone or video link. But it may also take place asynchronously (store-and-forward), when a query is submitted and an answer provided later, e.g. by email or text/voice/audio message.
    - **Client-to-provider telemedicine**: Provision of health services at a distance; delivery of health services where clients/patients and health workers are separated by distance (e.g. consultations between remote client/patient and health worker; clients/patients transmit medical data [images, notes, videos] to health worker) *(20)*.
- **Third-party authorization**: A requirement imposed by law or policy, or in practice, that a party other than the woman, girl or other pregnant person (typically a parent, guardian, spouse, partner, health worker, health authority or judicial authority) must authorize an abortion where other applicable legal requirements for lawful abortion have been met.
- **Treaty monitoring body**: Each of the international human rights treaties (see above) is monitored by a designated treaty monitoring body (see Annex 2). The treaty monitoring bodies are committees composed of independent experts. Their main function is to monitor the States' compliance with the treaty in question, including through the examination of State reports *(2)*.
- **Universal health coverage (UHC)**: Ensuring that all people have access to needed promotive, preventive, curative, rehabilitative, and palliative health services, of sufficient quality to be effective, while also ensuring that the use of these services does not expose any users to financial hardship *(12)*.
- **Vacuum aspiration (electrical or manual; EVA or MVA)**: Vacuum aspiration involves evacuation of the contents of the uterus through a plastic or metal cannula, attached to a vacuum source. Electric vacuum aspiration (EVA) employs an electric vacuum pump. With manual vacuum aspiration (MVA), the vacuum is created using a hand-held, hand-activated, plastic 60 ml aspirator (also called a syringe). MVA aspirators accommodate 4–12 mm cannulae. Suction tubing for EVA can be used with cannulae up to 16 mm in diameter, permitting VA to be used up to 15–16 weeks of pregnancy or for post-abortion care cases presenting with dilated cervix where a higher number of cannulae is required for effective vacuum.

References

See Annex 3 for all references for this glossary.

Executive summary

Sexual and reproductive health is fundamental to individuals, couples and families, and to the social and economic development of communities and nations. As provided in the Constitution of the World Health Organization (WHO), the organization's objective is "the attainment by all peoples of the highest possible level of health", and to fulfil that objective, WHO's functions include providing technical assistance to countries in the field of health. Universal access to sexual and reproductive health (SRH) information and services is central to both individual and community health, as well as the realization of human rights. In the wake of the COVID-19 pandemic and based on lessons learnt from previous disease outbreaks – when SRH services have been severely disrupted, causing individuals to feel disempowered and be exposed to preventable health risks – WHO has included comprehensive abortion care in the list of essential health services in certain recent technical publications.[1]

Comprehensive abortion care includes the provision of information, abortion management (including induced abortion, and care related to pregnancy loss/spontaneous abortion and post-abortion care. Strengthening access to comprehensive abortion care within the health system is fundamental to meeting the Sustainable Development Goals (SDGs) relating to good health and well-being (SDG3) and gender equality (SDG5). WHO's Global Reproductive Health Strategy, which seeks to accelerate progress towards achievement of international development goals, identifies elimination of unsafe abortion[2] as a priority mandate. The importance of quality abortion care to health is similarly underscored by the United Nations Global Strategy for Women's, Children's and Adolescents' Health, which includes evidence-based interventions for abortion and post-abortion care as one effective way to help individuals thrive and communities transform.

Quality of abortion care is foundational to this abortion care guideline. Quality of care (see Glossary) encompasses multiple components. It is defined as care that is: effective, efficient, accessible, acceptable/patient centred, equitable and safe. Effective care includes the delivery of evidence-based care that improves the health of individuals and communities, and is responsive to their needs. Efficient care optimizes resource use and minimizes waste. Quality abortion care must also be both accessible (timely, affordable, geographically reachable, and provided in a setting where skills and resources are appropriate to medical need) and acceptable (incorporating the preferences and values of individual service users and the cultures of their communities). It is imperative that access to abortion care is equitable, and that the quality of care does not vary based on the personal characteristics of the person seeking care, such as their gender, race, religion, ethnicity, socioeconomic status, education, if they are living with a disability, or based on their geographic location within a country. And finally, quality abortion care implies that it is safely delivered and minimizes any risks and harms to service users.

1 When considering the concept of "essential health services", it is important to note that different areas, even within the same country, may require different approaches to designate essential health services and to reorient health system components to maintain these services. Please refer to: *Maintaining essential health services: operational guidance for the COVID-19 context, interim guidance, 1 June 2020* (https://www.who.int/publications/i/item/WHO-2019-nCoV-essential-health-services-2020.1). For additional relevant references, see Chapter 1, section 1.1.

2 "Unsafe abortion" refers to abortion when it is carried out by a person lacking the necessary skills or in an environment that does not conform to minimal medical standards, or both.

Abortion is a safe and non-complex health-care intervention that can be effectively managed using medication or a surgical procedure in a variety of settings. Complications are rare with both medical and surgical abortion, when abortions are safe – meaning that they are carried out using a method recommended by WHO, appropriate to the gestational age, and by someone with the necessary skills. Globally, abortion is a common procedure, with 6 out of 10 unintended pregnancies and 3 out of 10 of all pregnancies ending in induced abortion. However, global estimates demonstrate that 45% of all abortions are unsafe. This is a critical public health and human rights issue; unsafe abortion is increasingly concentrated in developing countries (97% of unsafe abortions) and among groups in vulnerable and marginalized situations. Legal restrictions and other barriers mean many women find it difficult or impossible to access quality abortion care and they may induce abortion themselves using unsafe methods or seek abortion from unskilled providers. The legal status of abortion makes no difference to a woman's need for an abortion, but it dramatically affects her access to safe abortion. Between 4.7% and 13.2% of all maternal deaths are attributed to unsafe abortions, which equates to between 13 865 and 38 940 deaths caused annually by the failure to provide safe abortion.

Medical abortion has revolutionized access to quality abortion care globally. Medicines for abortion can be safely and effectively administered at a health-care facility or self-administered outside of a facility (e.g. at home) by individuals with a source of accurate information and quality-assured medicines. Those managing their abortions safely at home in the first 12 weeks of gestation may still need or want support from a trained health worker at some stage of the process. Service delivery with minimal medical supervision can significantly improve access to – and privacy, convenience and acceptability of – the abortion process, without compromising safety or effectiveness.

Multiple actions are needed at the legal, health system and community levels so that everyone who needs it has access to comprehensive abortion care. A person's environment plays a crucial role in shaping their access to care and influencing their health outcomes. An enabling environment is the foundation of quality comprehensive abortion care. The three cornerstones of an enabling environment for abortion care are:

1. respect for human rights including a supportive framework of law and policy
2. availability and accessibility of information, and
3. a supportive, universally accessible, affordable and well functioning health system.

Abortion is lawful in almost all countries, although there is variation in the specific circumstances under which an individual may access abortion. In addition, almost all countries where abortion is lawfully available regulate abortion differently to other forms of health care. Unlike other health services, abortion is commonly regulated to varying degrees through the criminal law in addition to regulation under health-care law. This has an impact on the rights of pregnant individuals, and can have a chilling effect (e.g. suppression of actions due to fear of reprisals or penalties) on the provision of quality care. This is why clear, accessible and rights-based law and policy is part of ensuring an enabling environment.

Objectives, scope and conceptual structure of the guideline

Guidelines are the fundamental means through which WHO fulfils its technical leadership in health. WHO guidelines are subject to a rigorous quality assurance process that generates recommendations for clinical practice or public health policy with the aim of achieving the best possible individual or collective health outcomes. Towards this aim, WHO has made a commitment to integrate human rights into health-care programmes and policies at national and regional levels by looking at underlying determinants of health as part of a comprehensive approach to health and human rights.

The objective of this guideline is to present the complete set of all WHO recommendations and best practice statements relating to abortion. While legal, regulatory, policy and service-delivery contexts may vary from country to country, the recommendations and best practices described in this document aim to enable evidence-based decision-making with respect to quality abortion care.

This guideline updates and replaces the recommendations in the following previous WHO guidelines:

- *Safe abortion: technical and policy guidance for health systems, second edition* (2012)
- *Health worker roles in providing safe abortion care and post-abortion contraception* (previously known as the "task sharing" guidance) (2015), and
- *Medical management of abortion* (2018).

This guidance contains new recommendations consolidated here in an integrated manner with existing recommendations that remain unchanged and those that have been updated after re-assessment using the same rigorous methods for both new and updated recommendations (see more information in the "Guideline development methods" section below).

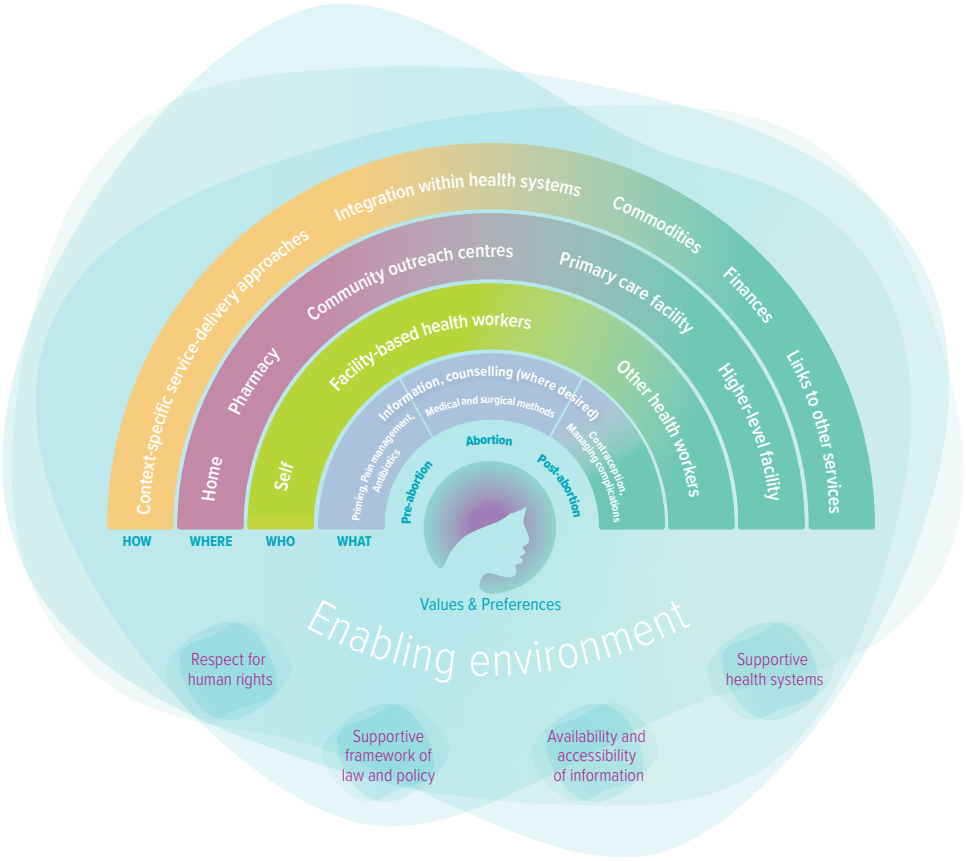
In this guideline, recommendations are presented across three domains that are essential to the provision of abortion care: Law and policy, Clinical services and Service delivery. The recommendations concerning the laws and policies that should or should not be in place in order to fully implement and sustain quality abortion care cover seven areas: criminalization of abortion, grounds-based approaches to permitting abortion, gestational age limits set for abortion, mandatory waiting periods before receiving a requested abortion, third-party authorization for abortion, restrictions on which health workers can provide abortion services, and conscientious objection/refusal by providers.[3] Clinical service recommendations address methods of abortion and related clinical care – from provision of information, counselling and pain management to methods and regimens for abortion (including for different clinical indications) – and provision of post-abortion care, including all methods of contraception.[4] Service delivery recommendations include those relating to which categories of health workers can provide the relevant clinical services. Self-management recommendations are also presented relating to tasks that can be managed by the woman herself: medical abortion in early gestation and use of many contraceptives, including self-administration of injectable contraceptives. A recommendation relating to telemedicine to facilitate early medical abortion has also been formulated, alongside best practice statements on other service-delivery approaches for abortion care. Together, the guidance presented in this document reflects recent changes in all these aspects of abortion care. Research gaps and priorities and emerging areas of interest are identified in the final chapter.

As indicated by the arrangement of the guidance in this document, as a woman, girl or other pregnant person moves through the abortion care pathway – pre-abortion, abortion and post-abortion care – health services must be integrated within the health system to ensure that service delivery meets their needs equitably and without discrimination. The conceptual framework for abortion care in this guideline (see Figure 1) recognizes and acknowledges the needs of all individuals with respect to abortion and is centred on the values and preferences of abortion seekers, considering them as active participants in – as well as beneficiaries of – health services. Individual health preferences may vary; no one model of abortion care will meet the needs of everyone seeking abortion care. However, the core values of dignity, autonomy, equality, confidentiality, communication, social support, supportive care and trust are foundational to abortion care and are reflected throughout this guidance. Important work is still needed to incorporate linkages to quality abortion care throughout the health system, and the focus on human rights and gender equality must be applied in all contexts providing services to people seeking health care.

3 The previous edition of the *Safe abortion* guidance (WHO, 2012) addressed these issues and related interventions and provided a composite recommendation. In this guideline, these have each been addressed separately as seven individual recommendations (Recommendations 1,2,3,6,7,21,22).

4 A full consideration of all contraceptive methods is beyond the scope of this guideline, but all contraceptive methods can be considered after an abortion, including a range of self-administered methods.

Figure 1: Conceptual framework for abortion care



Target audience and inclusivity

This guidance seeks to provide recommendations for national and subnational policy-makers, implementers and managers of sexual and reproductive health (SRH) programmes, members of nongovernmental organizations and other civil society organizations and professional societies, as well as health workers and other stakeholders in the field of sexual and reproductive health and rights (SRHR), to support them in ensuring that evidence-based, quality abortion care is available and accessible globally.

All individuals have the right to non-discrimination and equality in accessing SRH services. The right to be free from discrimination is stated in the Universal Declaration of Human Rights and in other universal human rights treaties and regional human rights instruments. It has been affirmed that the right to non-discrimination guaranteed by the International Covenant on Economic, Social and Cultural Rights (ICESCR) includes sexual orientation, gender identity and sex characteristics. As stated in the 2018 report of the Independent Expert on protection against violence and discrimination based on sexual orientation and gender identity to the United Nations General Assembly, "the right to effective recognition of one's gender identity is linked to the right to equal recognition before the law".

In this guideline, we recognize that most of the available evidence on abortion can be assumed to be derived from research among study populations of cisgender women, and we also recognize that cisgender women, transgender men, nonbinary, gender-fluid and intersex individuals with a female reproductive system and capable of becoming pregnant may require abortion care. To be concise and facilitate readability of this guideline, when referring to all gender diverse people who may require abortion care, we use the word "women" most often, although we also variously use the terms "individual", "person" and "abortion seeker". Providers of SRH services, including abortion care, must consider the needs of – and provide equal care to – all individuals; gender identity or its expression must not lead to discrimination.

Guideline development methods

The WHO Guideline Steering Group and wider WHO Secretariat, including staff members from both WHO headquarters and regional offices, led a wide-ranging guideline development process involving a vast range of expert contributors and support personnel. The process began in September 2018 with an online survey on the subject of updating WHO guidance on safe abortion, followed by scoping meetings between November 2018 and June 2019 to determine the key topic areas and to formulate key questions to be assessed through searches and analysis of the evidence base, for each of the three domains: Law and policy, Clinical services and Service delivery. In order to ensure broad representation, the following meetings were convened to further inform our guideline: (i) Implementation considerations for abortion care in humanitarian settings, (ii) Global values and preferences relating to abortion care, and (iii) Youth and safe abortion.

Global experts were invited by the Steering Group to convene three expert panels – the Evidence and Recommendation Review Groups (ERRGs) for each domain – involving active participation in a series of two-day meetings to discuss and draft the new and updated recommendations, based on the evidence provided by the Evidence Synthesis Teams (ESTs). The Guideline Development Group (GDG) members were selected and invited by the Steering Group from among the ERRG members for each domain, to bring together a single multidisciplinary group, including a youth representative and a human rights adviser, to finalize the recommendations.

In accordance with the WHO guideline development process, the formulation and refinement of recommendations by the ERRGs and the GDG was based on the available evidence (with quality of evidence ranging from high to very low), using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to recommendation development, with reference to the Evidence-to-Decision (EtD) tables prepared by the ESTs, and also guided by the participants' own expertise and experience. The WHO-INTEGRATE framework was used as a basis for deciding on the direction and strength of each recommendation (see notes accompanying the summary table below). For the law and policy recommendations, this same framework was used but an innovative approach was developed to evaluate the evidence in a manner that effectively integrated human rights protection and enjoyment as part of health outcomes and analysis.

After the conclusion of the ERRG and GDG meetings, the revised draft recommendations and full draft guideline were reviewed by GDG members and members of the External Review Group of peer reviewers. The GDG meeting observers and individual reviewers from several implementing organizations were also invited to comment on the same draft. Further revisions were made and the guideline was submitted to and approved by the WHO Guidelines Review Committee, followed by final revisions from the Office of the United Nations High Commissioner for Human Rights (OHCHR), final editing and planning for publication and launch. The full guideline development methods are presented in Annex 4.

Summary table of recommendations presented in this guideline

Important notes:

i. Each recommendation and its direction (for or against) and strength (strong or weak) has been determined by the panels of experts convened by WHO for this purpose. The determinations were based on the six substantive criteria of the WHO-INTEGRATE framework as applied to each intervention for the specified population – balance of health benefits and harms; human rights and sociocultural acceptability; health equity, equality and non-discrimination; societal implications; financial and economic considerations; and feasibility and health system considerations – while also taking into account the meta-criterion, quality of evidence (i.e. type, size and limitations of the available studies used as evidence). Wording used is as follows:

- **Recommend** – a strong recommendation in favour of the intervention
- **Suggest** – a weak recommendation in favour of the intervention
- **Recommend against** – a strong recommendation against the intervention/in favour of the comparison.

ii. Most of the recommendations are labelled as LP for "Law and policy", CS for "Clinical services" or SD for "Service delivery", referring to the broad domain under which the evidence for these recommendations was reviewed and evaluated by the respective expert panels (ERRGs). In addition, five recommendations are labelled as SELF-MANAGEMENT.

iii. The SD recommendations that refer to health worker categories assume that the people working within the categories mentioned have the skills and competencies required for the intervention specified. The roles, skills and competencies of each type of health worker mentioned in these recommendations are described in the table on health worker categories and roles in Annex 5, and further information can be found in WHO's 2011 publication, *Sexual and reproductive health: core competencies in primary care*, which describes the competencies (including skills and knowledge) required for each task.

iv. Recommendations were considered "new" (as labelled in this table and in Chapter 3) if no recommendation existed in a previous WHO guideline on the specific topic or intervention in question. In particular it should be noted that the 2012 *Safe abortion* guidance provided a composite recommendation related to law and policy; in this guideline, this has been developed this into seven separate recommendations, but they are not considered to be "new" (i.e. Recommendations 1,2,3,6,7,21,22).

SECTION **Topic area** Recommendation or best practice statement number and type	**Recommendation or best practice statement**	**Page number**
ABORTION REGULATION		
Criminalization		
1 (LAW & POLICY; LP)	**Recommend** the full decriminalization of abortion. **Remarks:** • Decriminalization means removing abortion from all penal/criminal laws, not applying other criminal offences (e.g. murder, manslaughter) to abortion, and ensuring there are no criminal penalties for having, assisting with, providing information about, or providing abortion, for all relevant actors. • Decriminalization would ensure that anyone who has experienced pregnancy loss does not come under suspicion of illegal abortion when they seek care. • Decriminalization of abortion does not make women, girls or other pregnant persons vulnerable to forced or coerced abortion. Forced or coerced abortion would constitute serious assaults as these would be non-consensual interventions.	24
Grounds-based approaches		
2 (LP)	**a. Recommend against** laws and other regulations that restrict abortion by grounds. **b. Recommend** that abortion be available on the request of the woman, girl or other pregnant person. **Remarks:** • Grounds-based approaches to restricting access to abortion should be revised in favour of making abortion available on the request of the woman, girl or other pregnant person. • Until they are replaced with abortion on request, any existing grounds should be formulated and applied in a manner consistent with international human rights law. This means that the content, interpretation and application of grounds-based law and policy should be revised to ensure human rights compliance. This requires that: i. existing grounds are defined, interpreted and applied in a human rights-compliant way; ii. abortion is available when carrying a pregnancy to term would cause the woman, girl or other pregnant person substantial pain or suffering, including but not limited to situations where the pregnancy is the result of rape or incest or the pregnancy is not viable; iii. abortion is available where the life and health of the woman, girl or other pregnant person is at risk; iv. health grounds reflect WHO's definitions of health and mental health (see Glossary); and v. there are no procedural requirements to "prove" or "establish" satisfaction of grounds, such as requiring judicial orders or police reports in cases of rape or sexual assault (for sources to support this information, refer to Web annex A: Key international human rights standards on abortion).	26
Gestational age limits		
3 (LP)	**Recommend against** laws and other regulations that prohibit abortion based on gestational age limits.	28
SERVICES ACROSS THE CONTINUUM OF CARE		
Provision of information on abortion care		
4 (SERVICE DELIVERY; SD)	Across the continuum of abortion care: **a. Recommend** provision of information on abortion care by community health workers, pharmacists, traditional and complementary medicine professionals, auxiliary nurses/auxiliary nurse midwives (ANMs), nurses, midwives, associate/advanced associate clinicians, generalist medical practitioners and specialist medical practitioners. **b. Suggest** provision of information on abortion care by pharmacy workers. • Condition: In contexts where the pharmacy worker is under the direct supervision of a pharmacist and there is access or referral to appropriate health services.	35
Provision of counselling		
5 (SD)	Across the continuum of abortion care: **a. Recommend** provision of counselling by community health workers, traditional and complementary medicine professionals, auxiliary nurses/ANMs, nurses, midwives, associate/advanced associate clinicians, generalist medical practitioners and specialist medical practitioners. **b. Suggest** provision of counselling by pharmacy workers and pharmacists. • Condition: Balanced counselling is provided (i.e. about both medical and surgical methods) and there is access or referral to appropriate health services should the woman choose a surgical method.	38

SECTION **Topic area** Recommendation or best practice statement number and type	**Recommendation or best practice statement**	**Page number**
PRE-ABORTION		
Mandatory waiting periods		
6 (LP)	**Recommend against** mandatory waiting periods for abortion.	41
Third-party authorization		
7 (LP)	**Recommend** that abortion be available on the request of the woman, girl or other pregnant person without the authorization of any other individual, body or institution. **Remark:** • While parental or partner involvement in abortion decision-making can support and assist women, girls or other pregnant persons, this must be based on the values and preferences of the person availing of abortion and not imposed by third-party authorization requirements.	43
Rh isoimmunization for abortion at gestational ages < 12 weeks		
8 (CLINICAL SERVICES; CS) (NEW)	For both medical and surgical abortion at < 12 weeks: **Recommend against** anti-D immunoglobulin administration. **Remark:** • Standard of care applies for anti-D administration at gestational ages ≥ 12 weeks.	44
Antibiotic prophylaxis for surgical and medical abortion		
9 (CS)	**a.** For surgical abortion, regardless of the individual's risk of pelvic inflammatory infection: **Recommend** appropriate prophylactic antibiotics pre- or perioperatively. **b.** For medical abortion: **Recommend against** the use of prophylactic antibiotics. **Remark:** • Lack of antibiotics should not limit access to abortion services.	46
Determining gestational age of pregnancy: pre-abortion ultrasound scanning		
10 (CS)	For both medical and surgical abortion: **Recommend against** the use of ultrasound scanning as a prerequisite for providing abortion services.* **Remark:** • Legal regulation that limits the availability of abortion by gestational age may require or result in ultrasounds being used to verify gestational age prior to abortion, even though this is not necessary from a clinical perspective. Removing legal gestational age limits on access to abortion (see Recommendation 3) should result in unnecessary pre-abortion ultrasound being avoided, and increase the availability of abortion in settings where ultrasound is difficult to access. * On a case-by-case basis, there may be clinical reasons for using ultrasound scanning prior to abortion.	47`

SECTION **Topic area** Recommendation or best practice statement number and type	**Recommendation or best practice statement**	**Page number**
Pain management for abortion		
11–14 (CS) for surgical abortion and for prior cervical priming *NOTE: NEW recommendations 12, 13 and 14 indicate pain management that is ADDITIONAL to NSAIDS (11a)*	11. For pain management for surgical abortion at any gestational age: **a. Recommend** that pain medication should be offered routinely (e.g. non-steroidal anti-inflammatory drugs [NSAIDS]) and that it should be provided to those who want it; and **b. Recommend against** the routine use of general anaesthesia. 12. (NEW) For pain management for surgical abortion at < 14 weeks: **a. Recommend** the use of a paracervical block; and **b. Suggest** that the option of combination pain management using conscious sedation plus paracervical block should be offered, where conscious sedation is available. 13. (NEW) For pain management for cervical priming with osmotic dilators prior to surgical abortion at ≥ 14 weeks: **Suggest** the use of a paracervical block. **Remark:** • For cervical priming, additional pain medication can be considered, such as the use of intravaginal gel. (See Recommendations 17–20 below on cervical priming) 14. (NEW) For pain management for surgical abortion at ≥ 14 weeks: **a. Recommend** the use of a paracervical block; and **b. Suggest** that the option of combination pain management using conscious sedation plus paracervical block should be offered, where conscious sedation is available.	49
15 and 16 (CS) for medical abortion *NOTE: NEW recommendation 16 indicates pain management that is ADDITIONAL to NSAIDS (15)*	15. For medical abortion at any gestational age: **Recommend** that pain medication should be offered routinely (e.g. non-steroidal anti-inflammatory drugs [NSAIDs]) and that it should be provided for the individual to use if and when wanted. 16. (NEW) For pain management for medical abortion at ≥ 12 weeks: **Suggest** consideration of additional methods to control pain or discomfort due to increased pain with increasing gestational age. Such methods include certain anti-emetics and epidural anaesthesia, where available. **Remark:** • For medical abortion at gestational ages < 14 weeks, if NSAIDS (e.g. ibuprofen) are not available or not an option, then acetaminophen can be considered for pain control.	51
Cervical priming prior to surgical abortion		
17 (CS) at < 12 weeks	Prior to surgical abortion at < 12 weeks: **a.** If cervical priming is used: **Suggest** the following medication regimens: • Mifepristone 200 mg orally 24–48 hours prior to the procedure • Misoprostol 400 µg sublingually 1–2 hours prior to the procedure • Misoprostol 400 µg vaginally or buccally 2–3 hours prior to the procedure **b. Recommend against** the use of osmotic dilators for cervical priming. **Remarks:** • The sublingual route is more effective for misoprostol administration. • Appropriate pain medication should be provided.	54

SECTION **Topic area** Recommendation or best practice statement number and type	**Recommendation or best practice statement**	**Page number**
18 (CS) (NEW) at ≥ 12 weeks	Prior to surgical abortion at later gestational ages: **a.** For surgical abortion at ≥ 12 weeks: **Suggest** cervical priming prior to the procedure. **b.** For surgical abortion between 12 and 19 weeks: **Suggest** cervical priming with medication alone (a combination of mifepristone plus misoprostol is preferred) or with an osmotic dilator plus medication (mifepristone, misoprostol, or a combination of both). **c.** For surgical abortion between 12 and 19 weeks, when using an osmotic dilator for cervical priming: **Suggest** that the period between osmotic dilator placement and the procedure should not extend beyond two days. **d.** For surgical abortion at ≥ 19 weeks: **Recommend** cervical priming with an osmotic dilator plus medication (mifepristone, misoprostol, or a combination of both). **Remark:** • There was limited evidence for cervical priming for gestational ages between 12 and 14 weeks and therefore health workers should use clinical judgement to decide on the most convenient method for cervical priming prior to vacuum aspiration for this gestational age range.	55
19 (SD) with medication, at any gestational age	Prior to surgical abortion at any gestational age: **a. Recommend** cervical priming with medication by traditional and complementary medicine professionals, auxiliary nurses/ANMs, nurses, midwives, associate/advanced associate clinicians, generalist medical practitioners and specialist medical practitioners. **b. Suggest** cervical priming with medication by community health workers, pharmacy workers and pharmacists. • Condition: Provision of medication for the purpose of cervical priming is part of the surgical abortion process so the health worker needs to ensure continuity of care of the woman obtaining the medicines prior to the abortion procedure.	56
20 (SD) with osmotic dilators, at ≥ 12 weeks	Prior to dilatation and evacuation (D&E) at ≥ 12 weeks: **a. Recommend** cervical priming with osmotic dilators by auxiliary nurses/ANMs, nurses, midwives, associate/advanced associate clinicians, generalist medical practitioners and specialist medical practitioners. **b. Suggest** cervical priming with osmotic dilators by traditional and complementary medicine professionals. • Condition: Health worker ensures continuity of care from the time of cervical priming to the D&E.	57
Provider restrictions		
21 (LP)	**Recommend against** regulation on who can provide and manage abortion that is inconsistent with WHO guidance. **Remark:** • Where law or policy regulate who may provide or manage abortion, that regulation should be consistent with WHO guidance, which is presented throughout Chapter 3 of this guideline.	59
Conscientious objection		
22 (LP)	**Recommend** that access to and continuity of comprehensive abortion care be protected against barriers created by conscientious objection. **Remarks:** • In spite of the human rights obligation to ensure conscientious objection does not hinder access to quality abortion care, and previous WHO recommendations aimed at ensuring conscientious objection does not undermine or hinder access to abortion care, conscientious objection continues to operate as a barrier to access to quality abortion care. It is critical that States ensure compliance with regulations and design/organize health systems to ensure access to and continuity of quality abortion care. If it proves impossible to regulate conscientious objection in a way that respects, protects and fulfils abortion seekers' rights, conscientious objection in abortion provision may become indefensible. • The evidence reviewed considered the impact of conscientious objection on access to and availability of abortion care and not the effectiveness of regulating conscientious objection in terms of improvements in those outcomes. However, international human rights law provides some guidance as to how States can ensure that human rights of abortion seekers are respected, protected and fulfilled (see details in main text).	60

SECTION **Topic area** Recommendation or best practice statement number and type	**Recommendation or best practice statement**	**Page number**
ABORTION		
Methods of surgical abortion		
23 (CS) at < 14 weeks	For surgical abortion at < 14 weeks: **a. Recommend** vacuum aspiration. **b. Recommend against** the practice of dilatation and sharp curettage (D&C), including sharp curette checks (i.e. to "complete" the abortion) following vacuum aspiration. **Remarks:** • Observational studies indicate that vacuum aspiration is associated with fewer complications than D&C; however, randomized controlled trials were underpowered to detect a difference in complication rates. • No evidence supports the use of sharp curette checks following vacuum aspiration. • The quality of the evidence based on randomized controlled trials is low to moderate.	63
24 (SD) vacuum aspiration at < 14 weeks	For surgical abortion at < 14 weeks: **a. Recommend** vacuum aspiration by traditional and complementary medicine professionals, nurses, midwives, associate/advanced associate clinicians, generalist medical practitioners and specialist medical practitioners. **b. Suggest** vacuum aspiration by auxiliary nurses/ANMs. • Condition: In contexts where established health system mechanisms involve auxiliary nurses/ANMs in providing basic emergency obstetric care, and where referral and monitoring systems are strong.	64
25 (CS) at ≥ 14 weeks	For surgical abortion at ≥ 14 weeks: **Recommend** dilatation and evacuation (D&E). **Remark:** • Vacuum aspiration can be used during a D&E (i.e. for the purpose of amniotomy or tissue removal at the end of the D&E).	65
26 (SD) D&E at ≥ 14 weeks	For surgical abortion at ≥ 14 weeks: **a. Recommend** D&E by generalist medical practitioners and specialist medical practitioners. **b. Suggest** D&E by traditional and complementary medicine professionals, midwives and associate/advanced associate clinicians. • Condition: In settings where established health system mechanisms exist to include these health workers in other tasks related to maternal and reproductive health.	65
Medical management of induced abortion		
27 (CS) at < 12 weeks	For medical abortion at < 12 weeks: **a. Recommend** the use of 200 mg mifepristone administered orally, followed 1–2 days later by 800 µg misoprostol administered vaginally, sublingually or buccally. The minimum recommended interval between use of mifepristone and misoprostol is 24 hours.* **b.** When using misoprostol alone: **Recommend** the use of 800 µg misoprostol administered vaginally, sublingually or buccally.* **c.** (NEW) **Suggest** the use of a combination regimen of letrozole plus misoprostol (letrozole 10 mg orally each day for 3 days followed by misoprostol 800 µg sublingually on the fourth day) as a safe and effective option.*‡ **Remarks:** • Evidence from clinical studies demonstrates that the combination regimen (Recommendation 27a) is more effective than misoprostol alone. • All routes are included as options for misoprostol administration, in consideration of patient and provider preference. • The suggested combination regimen of letrozole plus misoprostol may be safe and effective up to 14 weeks of gestation. * Repeat doses of misoprostol can be considered when needed to achieve success of the abortion process. In this guideline we do not provide a maximum number of doses of misoprostol. ‡ Further evidence is needed to determine the safety, effectiveness and acceptability of the letrozole plus misoprostol combination regimen at later gestational ages, especially in comparison with that of the mifepristone plus misoprostol combination regimen (the available evidence focused on comparison with the use of misoprostol alone).	68

SECTION **Topic area** Recommendation or best practice statement number and type	**Recommendation or best practice statement**	**Page number**
28 (SD) at < 12 weeks* in whole or in part (i.e. performing all or some of the subtasks)‡	For medical abortion at < 12 weeks: **Recommend** medical management by self (see Recommendation 50), community health workers, pharmacy workers, pharmacists, traditional and complementary medicine professionals, auxiliary nurses/ANMs, nurses, midwives, associate/advanced associate clinicians, generalist medical practitioners and specialist medical practitioners. * Available evidence for the independent provision of medical abortion by non-physicians is for pregnancy durations up to 10 weeks (70 days). ‡ For this recommendation, the medical abortion regimens covered in the available evidence were mifepristone plus misoprostol, or misoprostol alone (the regimen using letrozole was not included).	69
29 (CS) at ≥ 12 weeks	For medical abortion at ≥ 12 weeks: **a. Suggest** the use of 200 mg mifepristone administered orally, followed 1–2 days later by repeat doses of 400 µg misoprostol administered vaginally, sublingually or buccally every 3 hours.*‡ The minimum recommended interval between use of mifepristone and misoprostol is 24 hours. **b.** When using misoprostol alone: **Suggest** the use of repeat doses of 400 µg misoprostol administered vaginally, sublingually or buccally every 3 hours.*‡ **Remarks:** • The combination regimen (Recommendation 29a) is more effective than use of misoprostol alone. • Evidence suggests that the vaginal route is the most effective. Consideration for patient and provider preference suggests the inclusion of all routes. • Pregnancy tissue should be treated in the same way as other biological material unless the individual expresses a desire for it to be managed otherwise. * Misoprostol can be repeated at the noted interval as needed to achieve success of the abortion process. Providers should use caution and clinical judgement to decide the maximum number of doses of misoprostol in pregnant individuals with prior uterine incision. Uterine rupture is a rare complication; clinical judgement and health system preparedness for emergency management of uterine rupture must be considered with later gestational age. ‡ The dose of misoprostol should be reduced for induced abortion beyond 24 weeks due to limited data. Clinical judgement should be used to determine the appropriate dosage, recognizing the greater sensitivity of the uterus to prostaglandins.	71
30 (SD) at ≥ 12 weeks	For medical abortion at ≥ 12 weeks: **a. Recommend** medical management by generalist medical practitioners and specialist medical practitioners. **b. Suggest** medical management by traditional and complementary medicine professionals, auxiliary nurses/ANMs, nurses, midwives and associate/advanced associate clinicians. • Condition: In contexts where established and easy access to appropriate surgical backup and proper infrastructure is available to address incomplete abortion or other complications.	71
Missed abortion		
31 (CS) (NEW) Medical management at < 14 weeks	For missed abortion at < 14 weeks, for individuals preferring medical management: **Recommend** the use of combination mifepristone plus misoprostol over misoprostol alone. • Recommended regimen: 200 mg mifepristone administered orally, followed by 800 µg misoprostol administered by any route (buccal, vaginal or sublingual).* • Alternative regimen: 800 µg misoprostol administered by any route (buccal, vaginal or sublingual).‡ **Remarks:** • The decision about the mode of management (expectant, medical or surgical) of missed abortion should be based on the individual's clinical condition and preference for treatment. • Expectant management can be offered as an option on the condition that the woman, girl or other pregnant person is informed of the longer time for expulsion of the pregnancy tissue and the increased risk of incomplete emptying of the uterus. • Pregnancy tissue should be treated in the same way as other biological material unless the individual expresses a desire for it to be managed otherwise. * The minimum recommended interval between use of mifepristone and misoprostol is 24 hours. ‡ If using the alternative regimen (misoprostol alone), it should be noted that at gestational ages ≥ 9 weeks, evidence shows that repeat dosing of misoprostol is more efficacious to achieve success of the abortion process. In this guideline we do not provide a maximum number of doses of misoprostol.	74

SECTION Topic area Recommendation or best practice statement number and type	Recommendation or best practice statement	Page number
Intrauterine fetal demise		
32 (CS) Medical management at ≥ 14 to ≤ 28 weeks	For medical management of IUFD at ≥ 14 to ≤ 28 weeks: **Suggest** the use of combination mifepristone plus misoprostol over misoprostol alone. • Suggested regimen: 200 mg mifepristone administered orally, followed 1–2 days later by repeat doses of 400 µg misoprostol administered sublingually or vaginally every 4–6 hours.*‡ The minimum recommended interval between use of mifepristone and misoprostol is 24 hours. • Alternative regimen: repeat doses of 400 µg misoprostol administered sublingually or vaginally every 4–6 hours.*‡ **Remarks:** • Evidence from clinical studies indicates that the combination regimen is more effective than the use of misoprostol alone. • Pregnancy tissue should be treated in the same way as other biological material unless the individual expresses a desire for it to be managed otherwise. * Misoprostol can be repeated at the noted interval as needed to achieve success of the abortion process. Providers should use caution and clinical judgement to decide the maximum number of doses of misoprostol in pregnant individuals with prior uterine incision. Uterine rupture is a rare complication; clinical judgement and health system preparedness for emergency management of uterine rupture must be considered with later gestational age. ‡ The dose of misoprostol should be reduced for IUFD beyond 28 weeks due to limited data. Clinical judgement should be used to determine the appropriate dosage, recognizing the greater sensitivity of the uterus to prostaglandins.	76
33 (SD) (NEW) Medical management at ≥ 14 to ≤ 28 weeks	For IUFD at ≥ 14 to ≤ 28 weeks: **a. Recommend** medical management by generalist medical practitioners and specialist medical practitioners. **b. Suggest** medical management by traditional and complementary medicine professionals, auxiliary nurses/ANMs, nurses, midwives and associate/advanced associate clinicians. • Condition: In contexts where established and easy access to appropriate surgical backup and proper infrastructure is available to address incomplete abortion or other complications.	76
POST-ABORTION		
Follow-up care or additional services		
34 (CS)	Following uncomplicated surgical abortion or medical abortion: **Recommend** that there is no medical need for a routine follow-up visit. However, information should be provided about the availability of additional services if they are needed or desired. **Remarks:** • Women, girls and other pregnant persons must be adequately informed about symptoms of ongoing pregnancy (which may or may not indicate failure of the abortion) and other medical reasons to return for follow-up, such as prolonged heavy bleeding, no bleeding at all with medical management of abortion, pain not relieved by medication, or fever. • The quality of the evidence was low (observational studies and indirect evidence).	80
Incomplete abortion		
35 and 36 (CS)	**35.** For incomplete abortion at < 14 weeks: **Recommend** either vacuum aspiration or medical management. **36a.** For the medical management of incomplete abortion at < 14 weeks uterine size: **Suggest** the use of 600 µg misoprostol administered orally or 400 µg misoprostol administered sublingually. **36b.** For the medical management of incomplete abortion at ≥ 14 weeks uterine size: **Suggest** the use of repeat doses of 400 µg misoprostol administered sublingually, vaginally or buccally every 3 hours.* **Remarks:** • The decision about the mode of management of incomplete abortion should be based on the individual's clinical condition and preference for treatment. • Expectant management of incomplete abortion can be as effective as misoprostol; it can be offered as an option on the condition that the woman, girl or other pregnant person is informed of the longer time for expulsion of the pregnancy tissue and the increased risk of incomplete emptying of the uterus. • Recommendation 35 was extrapolated from research conducted in women with reported spontaneous abortion. * Misoprostol can be repeated at the noted interval as needed to achieve success of the abortion process. At gestational ages ≥ 14 weeks, providers should use caution and clinical judgement to decide the maximum number of doses of misoprostol in pregnant individuals with prior uterine incision. Uterine rupture is a rare complication; clinical judgement and health system preparedness for emergency management of uterine rupture must be considered with advanced gestational age.	81

SECTION **Topic area** Recommendation or best practice statement number and type	**Recommendation or best practice statement**	**Page number**
37 (SD) Medical management with misoprostol at < 14 weeks	For uncomplicated incomplete abortion at < 14 weeks: **Recommend** medical management with misoprostol by community health workers, pharmacy workers, pharmacists, traditional and complementary medicine professionals, auxiliary nurses/ANMs, nurses, midwives, associate/advanced associate clinicians, generalist medical practitioners and specialist medical practitioners.	82
38 (SD) Vacuum aspiration at < 14 weeks	For uncomplicated incomplete abortion at < 14 weeks: **a. Recommend** vacuum aspiration by traditional and complementary medicine professionals, nurses, midwives, associate/advanced associate clinicians, generalist medical practitioners and specialist medical practitioners. **b. Suggest** vacuum aspiration by auxiliary nurses/ANMs. • Condition: In contexts where established health system mechanisms involve auxiliary nurses/ANMs in providing basic emergency obstetric care, and where referral and monitoring systems are strong.	83
Management of non-life-threatening complications		
39 (SD) Infection	For non-life-threatening post-abortion infection: **Recommend** initial management by traditional and complementary medicine professionals, auxiliary nurses/ANMs, nurses, midwives, associate/advanced associate clinicians, generalist medical practitioners and specialist medical practitioners.* * For the pharmacists, pharmacy workers and community health workers, it is important that they are equipped with the knowledge to recognize signs and symptoms of this complication.	85
40 (SD) Haemorrhage	For non-life-threatening post-abortion haemorrhage: **Recommend** initial management by traditional and complementary medicine professionals, auxiliary nurses/ANMs, nurses, midwives, associate/advanced associate clinicians, generalist medical practitioners and specialist medical practitioners.* * For the pharmacists, pharmacy workers and community health workers, it is important that they are equipped with the knowledge to recognize signs and symptoms of this complication.	86
Timing of post-abortion contraception		
41 (CS) Medical eligibility criteria (MEC) for contraceptive use	The following contraceptive methods may be started immediately (MEC Category 1 – no restrictions) after a surgical or medical abortion (first and second trimester, and also after a septic abortion): combined hormonal contraceptives (CHCs), progesterone-only contraceptives (POCs) and barrier methods (condoms, spermicide, diaphragm, cap – note: The diaphragm and cap are unsuitable until 6 weeks after second-trimester abortion). Intrauterine devices (IUDs) may be started immediately after a first-trimester surgical or medical abortion (MEC Category 1 – no restrictions) or after second-trimester abortion (MEC Category 2 – the advantages generally outweigh the risks), but should not be started immediately after septic abortion (MEC Category 4 – insertion of an IUD may substantially worsen the condition). Fertility-awareness-based (FAB) methods: Symptom-based methods should only be started after abortion with "caution" (special counselling may be needed to ensure correct use of the method in this circumstance) and the use of calendar-based methods should be delayed (until the condition is evaluated; alternative temporary methods of contraception should be offered).	88
42 (CS) Contraception and surgical abortion	For individuals undergoing surgical abortion and wishing to use contraception: **Recommend** the option of initiating the contraception at the time of surgical abortion. **Remark:** • The quality of evidence based on randomized controlled trials was very low.	89

SECTION **Topic area** Recommendation or best practice statement number and type	**Recommendation or best practice statement**	**Page number**
43 (CS) Contraception and medical abortion	For individuals undergoing medical abortion with the combination mifepristone and misoprostol regimen or with misoprostol alone: **a.** For those who choose to use **hormonal contraception** (pills, patch, ring, implant or injections): **Suggest** that they be given the option of starting hormonal contraception immediately after the first pill of the medical abortion regimen. **b.** For those who choose to have an **IUD** inserted: **Suggest** IUD placement at the time that success of the abortion procedure is determined. **Remark (for Recommendations 43a and b):** • This recommendation applies to the combination mifepristone plus misoprostol regimen and the use of misoprostol alone. The letrozole plus misoprostol combination regimen is not mentioned here because the included studies informing these recommendations did not assess this regimen. **Remarks (for Recommendation 43a only):** • Immediate initiation of intramuscular depot medroxyprogesterone acetate (DMPA) is associated with a slight decrease in the effectiveness of medical abortion regimens. However, immediate initiation of DMPA should still be offered as an available contraceptive method after an abortion. • Indirect evidence was used as a basis for decision-making on initiation of hormonal contraception as an option for individuals undergoing medical abortion with misoprostol alone. • No data were available on the use of combined hormonal contraception (pills or injections) by those undergoing medical abortion. • Individuals who choose to initiate the contraceptive ring should be instructed to check for expulsion of the ring in the event of heavy bleeding during the medical abortion process.	89
44 (SD) Intrauterine devices (IUDs)	For intrauterine devices (IUDs): **a. Recommend** insertion/removal by auxiliary nurse midwives, nurses, midwives, associate/advanced associate clinicians, generalist medical practitioners and specialist medical practitioners. **b. Suggest** insertion/removal by traditional and complementary medicine professionals (TCMPs) and auxiliary nurses (ANs). • Condition (TCMPs): In contexts with established health system mechanisms for the participation of these professionals in other tasks related to maternal and reproductive health. • Condition (ANs): In the context of rigorous research.	90
45 (SD) Contraceptive implants	For contraceptive implants: **a. Recommend** insertion/removal by nurses, midwives, associate/advanced associate clinicians, generalist medical practitioners and specialist medical practitioners. **b. Suggest** insertion/removal by community health workers (CHWs), traditional and complementary medicine professionals (TCMPs), auxiliary nurses (ANs)/ANMs. • Condition (CHWs): In the context of rigorous research. • Condition (TCMPs): In contexts with established health system mechanisms for the participation of these professionals in other tasks related to maternal and reproductive health and where training in implant removal is given along with training in insertion. • Condition (ANs/ANMs): In the context of targeted monitoring and evaluation.	90
46 (SD) Injectable contraceptives	For injectable contraceptives (initiation and continuation): **Recommend** administration by self (see Recommendation 51), community health workers, pharmacy workers, pharmacists, traditional and complementary medicine professionals, auxiliary nurses/ANMs, nurses, midwives, associate/advanced associate clinicians, generalist medical practitioners and specialist medical practitioners.	91
47 (SD) Tubal ligation	For tubal ligation: **a. Recommend** tubal ligation by associate/advanced associate clinicians, generalist medical practitioners and specialist medical practitioners. **b. Suggest** tubal ligation by nurses and midwives. • Condition: In the context of rigorous research.	92

SECTION **Topic area** Recommendation or best practice statement number and type	**Recommendation or best practice statement**	**Page number**
SERVICE-DELIVERY OPTIONS AND SELF-MANAGEMENT APPROACHES		
Telemedicine approaches to delivering medical abortion care		
48 (SD) (NEW)	**Recommend** the option of telemedicine as an alternative to in-person interactions with the health worker to deliver medical abortion services in whole or in part. **Remarks:** • The above recommendation applies to assessment of eligibility for medical abortion, counselling and/or instruction relating to the abortion process, providing instruction for and active facilitation of the administration of medicines, and follow-up post-abortion care, all through telemedicine. • Hotlines, digital apps or one-way modes of communication (e.g. reminder text messages) that simply provide information were not included in the review of evidence for this recommendation.	95
Service-delivery approaches for provision of information, counselling and medical abortion		
49 (SD) (NEW)	**Best Practice Statement on service delivery** **Part 1.** There is no single recommended approach to providing abortion services. The choice of specific health worker(s) (from among the recommended options) or management by the individual themself, and the location of service provision (from among the recommended options) will depend on the values and preferences of the woman, girl or other pregnant person, available resources, and the national and local context. A plurality of service-delivery approaches can co-exist within any given context. **Part 2.** Given that service-delivery approaches can be diverse, it is important to ensure that for the individual seeking care, the range of service-delivery options taken together will provide: • access to scientifically accurate, understandable information at all stages; • access to quality-assured medicines (including those for pain management); • back-up referral support if desired or needed; • linkages to an appropriate choice of contraceptive services for those who want post-abortion contraception.	96
Self-management of medical abortion at < 12 weeks		
50 (SELF-MANAGEMENT)	For medical abortion at < 12 weeks (using the combination of mifepristone plus misoprostol or using misoprostol alone): **Recommend** the option of self-management of the medical abortion process in whole or any of the three component parts of the process: • self-assessment of eligibility (determining pregnancy duration; ruling out contraindications) • self-administration of abortion medicines and management of the abortion process outside of a health-care facility and without the direct supervision of a trained health worker • self-assessment of the success of the abortion. **Remarks:** • There was more evidence for self-management of medical abortion (with either of the regimens) for pregnancies before 10 weeks of gestation. • This recommendation applies to the combination regimen of mifepristone plus misoprostol, and the use of misoprostol alone. The included studies informing these recommendations did not assess the letrozole plus misoprostol regimen. • All individuals engaging in self-management of medical abortion must also have access to accurate information, quality-assured medicines including for pain management, the support of trained health workers and access to a health-care facility and to referral services if they need or desire it. • Restrictions on prescribing and dispensing authority for abortion medicines may need to be modified or other mechanisms put in place for self-management within the regulatory framework of the health system.	98

SECTION **Topic area** Recommendation or best practice statement number and type	**Recommendation or best practice statement**	**Page number**
Self-management approaches for post-abortion contraception (see also Timing of post-abortion contraception, Recommendations 41–47 above)		
51 (SELF-MANAGEMENT) Injectable contraception (initiation and continuation)	**Recommend** the option of self-administration of injectable contraception in the post-abortion period. **Remark:** • The administration of an injectable contraceptive involves using a syringe and may be intramuscular or subcutaneous. Compact pre-filled auto-disable devices have been developed to facilitate the self-administration process.	100
52 (SELF-MANAGEMENT) Over-the-counter oral contraceptive pills	**Recommend** that over-the-counter oral contraceptive pills (OCPs) should be made available without a prescription for individuals using OCPs.	101
53 (SELF-MANAGEMENT) Over-the-counter emergency contraceptive pills	**Recommend** making over-the-counter emergency contraceptive pills available without a prescription to individuals who wish to use emergency contraception.	101
54 (SELF-MANAGEMENT) Condom use	The consistent and correct use of male and female condoms is highly effective in preventing the sexual transmission of HIV; reducing the risk of HIV transmission both from men to women and women to men in serodiscordant couples; reducing the risk of acquiring other STIs and associated conditions, including genital warts and cervical cancer; and preventing unintended pregnancy.	101

Chapter 1.

Introduction

1.1 Background and context

Sexual and reproductive health is fundamental to individuals, couples and families, and to the social and economic development of communities and nations *(1)*. As provided in the Constitution of the World Health Organization (WHO), the organization's objective is "the attainment by all peoples of the highest possible level of health", and to fulfil that objective, WHO's functions include providing technical assistance to countries in the field of health *(2, Articles 1 and 2)*. Universal access to sexual and reproductive health (SRH) information and services is central to both individual and community health, as well as the realization of human rights, including the right to the highest attainable standard of SRH *(3)*. In addition, the increased SRH risks in humanitarian settings, including armed conflict, require specific attention from a human rights perspective *(4 [para. 7], 5, 6 [paras 19-24])*.

In the wake of the COVID-19 pandemic and based on lessons learnt from previous disease outbreaks – when SRH services have been severely disrupted, causing individuals to feel disempowered and be exposed to preventable health risks – WHO has included comprehensive abortion care in the list of essential health services in certain recent technical publications and guidance *(7-12)*.[1] Abortion care encompasses management of various clinical conditions including spontaneous and induced abortion (of both non-viable and viable pregnancies) and intrauterine fetal demise, and also post-abortion care, including management of incomplete abortion. Strengthening access to abortion care within the health system is fundamental to meeting the Sustainable Development Goals (SDGs) relating to good health and well-being (SDG3) and gender equality (SDG5) *(13)*. WHO's Global Reproductive Health Strategy, which seeks to accelerate progress towards achievement of international development goals, identifies elimination of unsafe abortion[2] as a priority mandate *(1)*. The importance of quality abortion care to health is similarly underscored by the United Nations Global Strategy for Women's, Children's and Adolescents' Health, which includes evidence-based interventions for abortion and post-abortion care as one effective way to help individuals thrive and communities transform *(14)*.

Quality abortion care is foundational to this guidance. Quality of care (see Glossary) encompasses multiple components: effectiveness, efficiency, accessibility, acceptability (e.g. patient centred), equity and safety. Effective care includes the delivery of evidence-based care that improves the health of individuals and communities, and is responsive to their needs. Efficient care optimizes resource use and minimizes waste. Quality abortion care must be both accessible (timely, affordable, geographically reachable, and provided in a setting where skills and resources are appropriate to medical need) and acceptable (incorporating the preferences and values of individual service users and the cultures of their communities). It is imperative that abortion care is equitable, and that health care does not vary in quality based on the personal characteristics of the person seeking care, such as their gender, race, ethnicity, socioeconomic status, education, if they are living with a disability, or based on

1 When considering the concept of "essential health services", it is important to note that different areas, even within the same country, may require different approaches to designate essential health services and to reorient health system components to maintain these services *(7)*.

2 "Unsafe abortion" refers to abortion when it is carried out by a person lacking the necessary skills or in an environment that does not conform to minimal medical standards, or both.

their geographic location within a country. And finally, quality abortion care implies that it is safely delivered and minimizes risks and harms to service users *(15)*. Underpinning these components is the principle that provision of quality abortion care would be in compliance with human rights.

Globally, abortion is a common procedure, with 6 out of 10 unintended pregnancies and 3 out of 10 of all pregnancies ending in induced abortion *(16)*. When abortion is safe – defined as being carried out using a method recommended by WHO, appropriate to the gestational age, and by someone with the necessary skills *(17)* – the risks are very low. However global estimates demonstrate that 45% of all abortions are unsafe, including 14.4% considered to be "least safe" *(18)*. This is a critical public health and human rights issue; unsafe abortion is increasingly concentrated in developing countries and among groups in vulnerable and marginalized situations. In countries where induced abortion is highly restricted by law or unavailable due to other barriers, safe abortion has often become the privilege of the rich, while poor women have little choice but to resort to the services of unskilled providers in unsafe settings, or induce abortion themselves often using unsafe methods, leading to deaths and morbidities that become the social and financial responsibility of the public health system, and denial of women's human rights. The legal status of abortion has no effect on a woman's likelihood of seeking induced abortion, but it dramatically affects her access to safe abortion *(19)*.

Between 4.7% and 13.2% of all maternal deaths are attributed to unsafe abortions *(20, 21)*. This equates to between 13 865 and 38 940 lives lost annually, due to the failure to provide safe abortion, with many more experiencing serious morbidities. Developing countries bear the burden of 97% of unsafe abortions *(18)*. The proportion of abortions that are unsafe is also significantly higher in countries with highly restrictive abortion laws than in those with less restrictive laws *(18)*. Over half (53.8%) of all unsafe abortions occur in Asia (the majority of those in south and central Asia), while another quarter (24.8%) occur in Africa (mainly in eastern and western Africa), and a further fifth (19.5%) in Latin America and the Caribbean *(18)*. The subregions where the highest proportions of abortions have been categorized as "least safe" are northern, eastern, western and middle Africa (approximately 45–70% of all abortions are "least safe"), followed by the Caribbean, Oceania and Central America (approximately 25–30% of all abortions are "least safe") *(18)*. A review of facility-based treatment for complications of unsafe abortion in 26 developing countries in 2012 indicated that 7 million women were treated in developing countries for complications of unsafe abortion that year – a rate of 6.9 per 1000 women aged 15–44 years *(22)*.

Abortion, using medication or a simple outpatient surgical procedure, is a safe health-care intervention, when carried out with a method appropriate to the gestational age of pregnancy and – in the case of a facility-based procedure – by a person with the necessary skills. In these circumstances, complications or serious adverse effects are rare. Medical abortion has revolutionized access to quality abortion care globally. Studies have demonstrated that medicines for abortion can be safely and effectively self-administered outside of a facility (e.g. at home). Individuals with a source of accurate information and access to a trained health worker (in case they need or want support at any stage of the process) can safely self-manage their abortion process in the first 12 weeks of gestation. Service delivery with minimal medical supervision can significantly improve access, particularly in restricted settings and crisis situations, as well as improve privacy, convenience and acceptability of the abortion process without compromising safety and effectiveness *(23)*.

However, in both low- and high-resource settings, law, policy and practical barriers can make it difficult to access quality abortion care. Multiple actions are needed at the legal, health system and community levels so that everyone who needs it has access to comprehensive abortion care (CAC), i.e. information, abortion management (including induced abortion, and care related to pregnancy loss/spontaneous abortion) and post-abortion care.

1.2 Guideline objective, rationale, target audience, inclusivity and structure

Guidelines are the fundamental means through which WHO fulfils its technical leadership in health (24). WHO guidelines are subject to a rigorous quality assurance process that generates recommendations for clinical practice or public health policy with the aim of achieving the best possible individual or collective health outcomes. Towards this aim, WHO has made a commitment to integrate human rights into health-care programmes and policies at national and regional levels by looking at underlying determinants of health as part of a comprehensive approach to health and human rights.

1.2.1 Objective and rationale

The objective of this guideline is to present the complete set of all WHO recommendations and best practice statements relating to abortion, with the goal of enabling evidence-based quality abortion care globally.

This guideline updates and replaces the recommendations in the following previous WHO guidance:

- *Safe abortion: technical and policy guidance for health systems, second edition* (2012)
- *Health worker roles in providing safe abortion care and post-abortion contraception* (previously known as the "task sharing" guidance) (2015), and
- *Medical management of abortion* (2018).

This guideline is intended to provide concrete information and guidance, integrating aspects of care across all domains needed to provide quality abortion care: Law and policy, Clinical services and Service delivery. This guidance contains new recommendations consolidated with existing recommendations that remain unchanged and some that have been updated after re-assessment, using the same rigorous methods for both new and updated recommendations (see Annex 4: Methods). Among the recommendations are seven concerning the laws and policies that should or should not be in place, in order to fully implement and sustain quality abortion care: three recommendations relating to abortion regulation are presented in Chapter 2 and four more relating to laws and policies affecting clinical and health worker practices are presented in Chapter 3. All the other recommendations address methods of abortion and related clinical care as well as service delivery by a range of health workers and approaches, including self-management by the abortion seeker, reflecting recent changes in all these aspects of abortion care. Emerging areas of interest and research priorities in abortion care are identified in Chapter 4.

As a key part of the rationale for developing this updated and consolidated guideline, important contextual information – which is integral to this guidance, as context for the recommendations and best practice statements – is presented in the remainder of this first chapter. This information is not in the form of WHO recommendations but rather it describes the underlying determinants of quality abortion care, and thus must be carefully considered. Section 1.3 below describes an enabling environment for comprehensive abortion care (i.e. a law and policy framework supportive of human rights; access to information; and health system factors) and section 1.4 delves further into key health system considerations (universal health coverage and primary health care; health financing; health workforce training; health-care commodities; and monitoring and evaluation). Where relevant, this document incorporates and builds upon considerations captured in other existing WHO guidance, including *Consolidated guideline on the sexual and reproductive health and rights of women living with HIV (25)* and *WHO consolidated guideline on self-care interventions for health: sexual and reproductive health and rights (26)*.

1.2.2 Target audience

This guidance seeks to provide recommendations for national and subnational policy-makers, implementers and managers of sexual and reproductive health (SRH) programmes, members of nongovernmental organizations and other civil society organizations and professional societies, as well as health workers and other stakeholders in the field of sexual and reproductive health and rights (SRHR), to support them in ensuring that evidence-based, quality abortion care is available and accessible globally.

1.2.3 Equity, inclusivity and people-centred care

The needs of all individuals with respect to abortion are recognized and acknowledged in this guidance. A human rights approach that advances gender equality is essential and must be applied in all contexts providing services to people seeking health care. To provide quality abortion care throughout the health system, services should also be integrated where possible with other SRH services, such as evidence-based HIV and sexually transmitted infection (STI) testing and treatment, and family planning/contraception, and should be friendly and welcoming to youth and people from sexual and gender minorities, people living with disabilities, and all groups in vulnerable and marginalized situations.

WHO guidelines systematically incorporate consideration of the values and preferences of end-users of the recommended or suggested interventions into the process of developing the guidance. To gain more in-depth understanding of the values and preferences of individuals seeking abortion care, WHO conducted a global

survey and convened a technical meeting on this subject with stakeholders in September 2019 attended by 19 participants from 15 different countries/organizations. The key themes that emerged were the importance of equity, inclusivity and meeting the needs of those living in the most vulnerable and marginalized situations. In addition, a youth-led technical meeting was convened in April 2021 with 16 youths (representing 13 countries across all WHO regions) from the Youth for Abortion Task Force, to learn about the concerns of youth. The Task Force was formed by the International Youth Alliance for Family Planning (IYAFP) – a collective of young individuals, youth associations, organizations and communities with a common mission to support provision of and access to comprehensive reproductive health services (see Web annex B: Technical meetings during guideline development). Women living with HIV are one example among many of a marginalized population with unique vulnerabilities in the context of abortion care. Women living with HIV face unique challenges and are vulnerable to SRH-related human rights violations within their families and communities, as well as at health-care facilities where they seek care. An enabling environment is essential to promote more effective interventions and better health outcomes for all abortion seekers (see section 1.3).

All individuals have the right to non-discrimination and equality in SRH care and services. The right to be free from discrimination is stated in the Universal Declaration of Human Rights and in other universal human rights treaties and regional human rights instruments. It has been affirmed that the right to non-discrimination guaranteed by the International Covenant on Economic, Social and Cultural Rights (ICESCR) includes sexual orientation, gender identity and sex characteristics. The international human rights system has been strengthening the promotion and protection of human rights without distinction. The protection of persons based on their sexual orientation and gender identity are based on international law, complemented and supplemented by State practice *(27)*. As stated in the 2018 report of the Independent Expert on protection against violence and discrimination based on sexual orientation and gender identity to the United Nations General Assembly, "The right to effective recognition of one's gender identity is linked to the right to equal recognition before the law" *(28, para. 20)*.

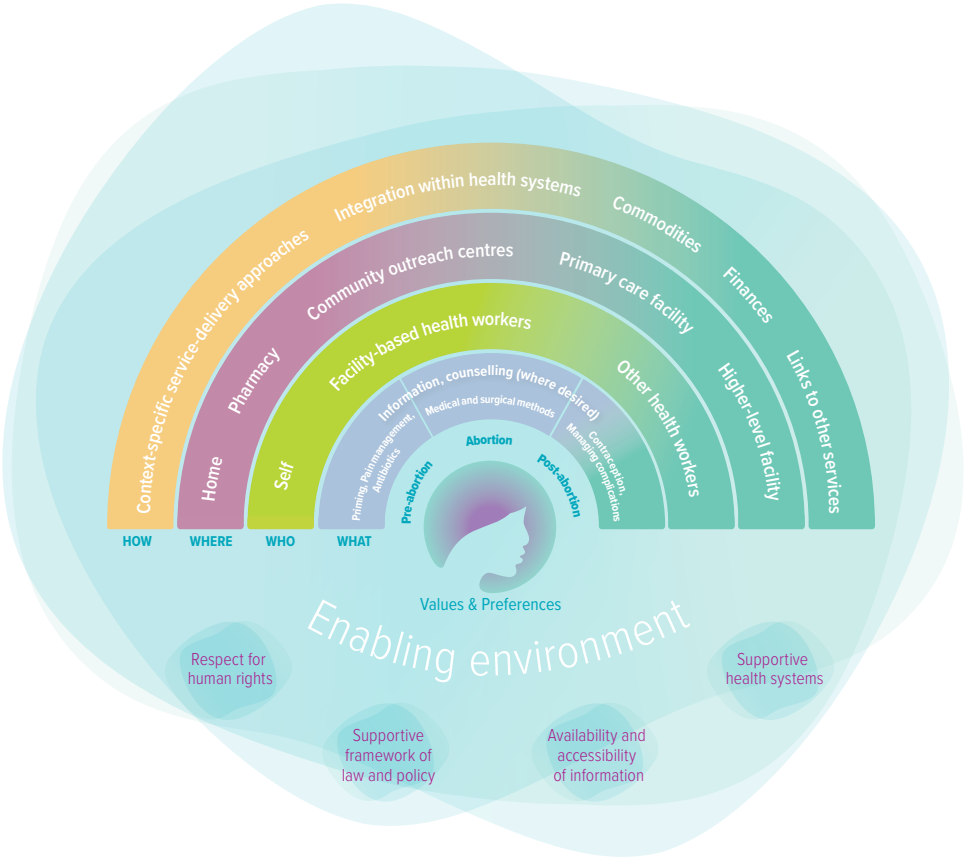
In this guideline, we recognize that most of the available evidence on abortion can be assumed to be derived from research among study populations of cisgender women, and we also recognize that cisgender women, transgender men, nonbinary, gender-fluid and intersex individuals with a female reproductive system and capable of becoming pregnant may require abortion care. To be concise and facilitate readability of this guideline, when referring to all gender diverse people who may require abortion care, we use the word "women" most often, although we also variously use the terms "individual", "person" and "abortion seeker". Providers of SRH services, including abortion care, must consider the needs of – and provide equal care to – all individuals; gender identity or its expression must not lead to discrimination.

This guideline takes an integrated, people-centred approach to health services *(29)*. People-centred care requires that individuals have the education and support they need to make decisions and participate in their own health care *(30)*. Individual health preferences may vary; no one model of abortion care will meet the needs of everyone seeking abortion care. The core values of dignity, autonomy, equality, confidentiality, communication, social support, supportive care, and trust are foundational to abortion care and are reflected throughout this guidance *(31)*.

1.2.4 Conceptual structure of the guideline

As illustrated in Figure 1.1, this guideline is centred on the values and preferences of abortion seekers, and considers them as active participants in as well as beneficiaries of health services. This guidance emphasizes that – as a woman, girl or other pregnant person moves through the abortion care pathway (pre-abortion, abortion, post-abortion) – health services must be integrated within the health sector to ensure that service delivery meets their needs equitably and without discrimination. As each individual moves through this pathway, the guideline provides specific recommendations on the interventions needed (i.e. the "what"), and guidance on the individuals who may safely carry them out (i.e. the "who"). The guideline also provides information on the locations where services can be provided (i.e. the "where") and outlines service-delivery models that can be used (i.e. the "how"). The enabling environment, described in the remainder of this chapter, provides the context for the effective implementation of these interventions.

Figure 1.1: Conceptual framework for abortion care



1.3 An enabling environment for comprehensive abortion care

A person's environment plays a crucial role in shaping their access to care and influencing their health outcomes. An enabling environment is the foundation of quality, comprehensive abortion care. The three cornerstones of an enabling environment for abortion care are outlined in Box 1.1 and elaborated in the text of this section:

1. respect for human rights including a supportive framework of law and policy
2. the availability and accessibility of information, and
3. a supportive, universally accessible, affordable and well functioning health system.

For clarification, this section of the guideline document does not provide recommendations – rather it details the components and aspects that would comprise an overall enabling environment for quality abortion care, based on WHO best practices, which would provide the ideal context to best facilitate the recommendations in the later sections of this chapter and in Chapter 3. While this enabling environment represents an ideal context, complete implementation of the components of this enabling environment is not necessarily a precondition to implementation and application of the recommendations contained in this guideline.

BOX 1.1: Core components of an enabling environment for abortion care

Respect for human rights including a supportive framework of law and policy

- Countries ratify international and regional human rights treaties and conventions addressing health, including sexual and reproductive health (SRH).
- Laws and policies promote SRH for all, and are consistent with sexual and reproductive health and rights.
- There are appropriate administrative, political and judicial arrangements to facilitate quality abortion care, including accessible, transparent and effective mechanisms providing remedies. These include:
  - accessible mechanisms for women to challenge denial of abortion in a timely manner, and
  - appropriate monitoring mechanisms for failure to facilitate quality care, including regular review and reform of law and policy to recognize and remove barriers to quality abortion care.
- Policies minimize the rate of unintended pregnancy by providing quality contraceptive information and services, including a full range of contraceptive methods (emergency, short-acting and long-acting methods).
- All people and communities receive the health services they need, without suffering financial hardship and without any discrimination.

Availability and accessibility of information

- Evidence-based comprehensive sexuality education (CSE) is provided for all individuals and made available in multiple and accessible forms and languages.
- Accurate, non-biased and evidence-based SRH information, including on abortion and contraceptive methods, is widely available in multiple and accessible forms and languages.

Supportive, universally accessible, affordable and well functioning health system

- Universal health coverage (UHC) ensures that all individuals can receive the care they need without financial hardship (see section 1.4.1).
- The health system is adequately resourced, meaning that resources including essential medicines, supplies, equipment, workforce and financial allocations are available, accessible, acceptable, affordable and of good quality.
- Equitable access to quality-assured essential medicines and health products is ensured.
- Leadership and clinical standards promote evidence-based SRH services.
- The organization of the health system ensures respect for SRH and human rights, including non-discrimination and equality, and for autonomy in decision-making.
- The workforce is robust and receives competency-based training and is skilled in the provision of evidence-based SRH counselling and service delivery.
- In addition to technical training, SRH services are provided by persons who are trained in the content and meaning of the law and trained and empowered to interpret and apply law and policy in rights-compliant ways.
- Confidentiality and privacy of care are ensured, and there are efforts to counteract abortion stigma.
- There is access to safe and timely comprehensive abortion care and women do not have to resort to unsafe abortion.
- Health financing policies should avoid making access to SRH services conditional on direct payment from patients at the point of service.
- Care is always provided respectfully and with compassion.
- Communities are engaged and supportive.

1.3.1 Human rights including a supportive framework of law and policy

An enabling environment is one in which the human rights of individuals are respected, protected and fulfilled. This entails regular review and, where necessary, revision of regulatory, law and policy frameworks, and the adoption of measures to ensure compliance with evolving international human rights standards (see Annex 2).

Throughout this guideline we refer to human rights standards in international law, the applicability of which in a specific setting will depend on factors such as the State's ratification of relevant human rights instruments. The sources of these human rights standards are detailed in Web annex A: Key international human rights standards on abortion.

(i) Sexual and reproductive health and rights

Sexual and reproductive health and rights are grounded in a range of human rights recognized and guaranteed in national and international law, and are inextricably linked to the achievement of public health policy goals, including the SDGs *(32, 33)*. People have a range of sexual and reproductive rights, which are relevant to information and services across the continuum of care for abortion (see Box 1.2). Overarching all of them are principles of non-discrimination and equality, and the right to the highest attainable standard of physical and mental health, including in the provision of SRH services *(3, para. 7)*. These are all underpinned by States' obligations to ensure that laws and policies, institutional arrangements and social practices do not prevent people from the effective enjoyment of their right to SRH *(3, para. 8)*.

Box 1.2 provides a general description of certain human rights as established by international law instruments and their associated obligations and principles relevant to SRH.

(ii) Prevention of unsafe abortion and reduction of maternal mortality and morbidity

Taking measures to prevent unsafe abortion is a core obligation of the right to SRH *(3, para. 49)*. International human rights law requires States to take steps to reduce maternal mortality and also to effectively protect women from the physical and mental risks (morbidity) associated with unsafe abortion *(43, paras 6, 9, 24, 30-33)*. Treaty monitoring bodies (see Annex 2) have confirmed that States must revise their laws to ensure this protection *(36, para. 8)*. Thus, the United Nations Committee on Economic, Social and Cultural Rights (CESCR) has confirmed that States must liberalize restrictive abortion laws, guarantee access to quality abortion and post-abortion care, and respect the right of women to make autonomous decisions about their SRH *(3, para. 28)*. In all situations, States have a duty under international human rights law to ensure that the regulation of abortion (see Chapter 2) does not cause women and girls to resort to unsafe abortions *(36, para. 8)*. As a matter of international human rights law, States must provide essential medicines listed under WHO's Action Programme on Essential Drugs *(46, para. 12a)*. States must also take steps to prevent the stigmatization of people seeking abortion *(36, para. 8)*. In addition, policies must seek to minimize the rate of unintended pregnancy by ensuring provision of quality contraceptive information and services, including a full range of contraceptive methods (emergency, short-acting and long-acting methods).

(iii) Rights-based regulation of abortion

The right to SRH requires States to ensure that health-care facilities, goods and services are available, accessible, acceptable and of good quality *(46, paras 8, 12)*. This should inform all parts of the regulation of abortion.

Treaty monitoring bodies have called for the decriminalization of abortion in all circumstances. They have further clarified States' human rights obligations in relation to abortion. These include that:

- States may not regulate pregnancy or abortion in a manner that runs contrary to their core obligation to ensure that women and girls do not have to resort to unsafe abortions. If they do, their restrictions on access to abortion must be revised *(36, para. 8)*.
- The regulation of abortion must not jeopardize the lives of pregnant women, subject them to physical or mental pain or suffering (including where this constitutes torture or cruel, inhuman or degrading treatment or punishment), discriminate against them, or interfere arbitrarily with their privacy *(36, para. 8)*.
- The regulation of abortion must be evidence based and proportionate to ensure respect for human rights *(37, para. 18)*.

BOX 1.2: Selected human rights, as specified in relevant international law instruments, and their associated obligations and principles relevant to sexual and reproductive health and rights and abortion in particular

Human right	Selected human rights principles and obligations relevant to abortion
The right to the highest attainable standard of physical and mental health, including sexual and reproductive health and rights	• States have an obligation to respect, protect and fulfil the right of everyone to sexual and reproductive health and rights *(34, Article 12)*. This includes: ▫ the removal of legal provisions, including criminal laws, which penalize women who have undergone abortion or medical practitioners who offer these services *(3, 35-38)*; ▫ ensuring that women are not prevented from accessing health services by health professionals' exercise of conscientious objection (e.g. where abortion is legal, if a doctor refuses to perform it, the health system must provide a referral to an alternative health-care provider) *(3, 39)*; ▫ eliminating barriers to the provision of abortion services including barriers that lead women to resort to unsafe abortions – this should include eliminating unacceptable delays in providing medical attention *(3, 36, 38, 40-42)*; ▫ undertaking measures to prevent unsafe abortions and ensure access to post-abortion care in all circumstances, on a confidential basis and without the threat of criminal prosecution or punitive measures *(3, 36-38, 40, 41, 42 [para. 33], 43-47);* ▫ undertaking measures to prevent and eliminate discrimination, stigmatization and negative stereotyping that hinder access to sexual and reproductive health (SRH), including against people seeking abortion and health-care providers offering abortion care services *(36, 38)*. • States must ensure that sexual and reproductive health-care facilities, goods and services are available, acceptable and of good quality. This includes: ▫ ensuring an adequate number of sexual and reproductive health-care facilities, goods and services (e.g. trained and skilled medical and health-care personnel *[42, 46, 48]* and scientifically approved and unexpired medicines for abortion and post-abortion care *[49]*, as well as the availability of safe abortion in cases of rape and incest *[3, 36, 42, 50, 51]*); ▫ ensuring that health care and services, including SRH and essential medicines are physically and geographically accessible and affordable to all individuals, either provided at no cost or based on ensuring that health expenses do not expose individuals to suffering financial hardship *(46)*; ▫ ensuring that information about SRH is accessible *(3, 52)* (e.g. institutions and individuals should be able to provide accurate health-care information, including information on abortion, without fear of criminal sanction *[41, 50, 51]*); ▫ ensuring that delivery of services is respectful of the culture of individuals, minorities, peoples and communities, and sensitive to gender, age, disability, sexual diversity and life-cycle requirements *(53, para. 20)*.
The right to non-discrimination and equality	• States must ensure that individuals enjoy equal access to the same range, quality and standard of SRH information, goods and services *(36, 45, 52)*. • States must acknowledge and take measures to address access to safe abortion and post-abortion care for particular groups of individuals, especially those who are marginalized, have limited resources, live in rural areas, and/or are from minorities, as they are more likely to experience intersecting forms of discrimination *(3, 36-38, 40, 41, 42 [para. 33], 43-47, 49, 54 [para. 45])*. • States must repeal or reform discriminatory laws, policies and practices that nullify or impair the ability of individuals to access SRH, such as criminalization of abortion and restrictive abortion laws *(3, 35-38, 41, 42 [para. 22], 55)*. • States must remove all legal, procedural, practical and social barriers impeding individuals' equal and non-discriminatory access to SRH, including abortion, and should repeal measures such as third-party authorization requirements (i.e. from husbands, partners, parents or guardians, or health authorities), biased counselling, mandatory waiting periods, and restrictions based on being an unmarried woman *(3, 35-38)*. • States must take steps to prevent the imposition of forced abortion, in particular on women and girls from marginalized groups *(37, 40, 47, 52, 56)*.
The right to life	• States must ensure that measures designed to regulate access to abortion do not jeopardize the life of the woman, girl or other pregnant person, subject them to physical or mental pain or suffering or discriminate against them, or arbitrarily interfere with their privacy *(36)*. • States must provide effective and confidential access to safe, legal abortion where the life or health of the woman, girl or other pregnant person is at risk, or where carrying a pregnancy to term would cause the pregnant individual substantial pain or suffering, and in cases where the pregnancy is the result of rape or incest or where the pregnancy is not viable *(36)*. • States must take steps to reduce maternal morbidity and mortality, including addressing unsafe abortion, taking into account exacerbated challenges in certain settings *(3, 36-38, 40, 43)*.

Human right	Selected human rights principles and obligations relevant to abortion
The right to privacy	• States must respect the right of individuals to make autonomous decisions about their sexual and reproductive health, including whether or not to undergo an abortion *(35, 36, 57)*. • SRH services including abortion and post-abortion care must be provided in a way that respects fully the woman's, girl's or other pregnant person's privacy and guarantees confidentiality *(35, 36)*. • Medical and health-care professionals must not be required or mandated to report cases of women who have undergone abortions *(36, 37, 40, 48)*. • Denial of therapeutic abortion may interfere arbitrarily with the right to privacy *(57)*. • Third-party authorization requirements may violate the right to privacy *(3, 36, 38)*.
The right to be free from torture, cruel, inhuman and degrading treatment and punishment, including the right to physical and mental integrity	• Forced abortion, criminalization of abortion, denial or delay of safe abortion care and/or post-abortion care, and abuse and mistreatment of women and girls seeking SRH information, goods and services are forms of gender-based violence *(44, 55)*, which – depending on the circumstances – may amount to torture, cruel, inhuman or degrading treatment *(55)*. • States must ensure that measures regulating abortion do not subject individuals to substantial physical or mental pain or suffering, such as where a pregnancy is the result of rape *(36)*. • State laws and policies must not permit abortions without the free and informed consent of the concerned individual *(40, 41, 48, 52, 56, 58)*. • States must prevent and prosecute forced abortions conducted by public officials and private actors, including when conducted on women with disabilities or according with coercive family planning laws and policies as well as in the context of a conflict *(40, 41, 48, 52, 56, 58)*. • States should ensure that individuals seeking a safe legal abortion are not subjected to humiliating and judgemental attitudes leading to the denial or delay of such services in a context of extreme vulnerability for these individuals and where timely health care is essential *(35)*. • Criminalization of abortion may amount to torture, cruel, inhuman or degrading treatment, including the practice of extracting confessions for prosecution purposes from individuals seeking emergency medical care because of illegal abortion in a particular context *(55)*.
The right to decide freely and responsibly on the number, spacing and timing of children and to have the information and means to do so	• States must ensure access to family planning and SRH information and services, including affordable contraceptive methods to enable women and adolescents to make autonomous and informed decisions on their reproductive health *(42 [para. 33], 49 [para. 33])*. • States must ensure that women with disabilities can exercise their right to decide on the number and spacing of children *(52, 59 [Article 3(3)])*.
The right to information and education including on sexual and reproductive health	• States must take measures to ensure up-to-date, accurate information on SRH is publicly available and accessible to all individuals, in appropriate languages and formats *(3, 50-52)*. • States must ensure that educational institutions incorporate unbiased, scientifically accurate, evidence-based, age-appropriate and comprehensive sexuality education into their required curricula *(3, para. 63)*. • States must make accurate, evidence-based abortion information available to individuals on a confidential basis *(3 [para. 63], 50-52)*. • This information must be presented in a way that can be understood by the person receiving it *(3, 52)*. • The choice by an individual to refuse information when offered must be respected. • States must ensure that informed consent is provided freely, safeguarded effectively, and based on complete provision of high-quality, accurate and accessible information.
The right to benefit from scientific progress and its realization	• States must ensure adequate access to essential medicines in an affordable manner *(46, 49, 54)*. • States must ensure access to necessary, up-to-date scientific technologies, in particular contraception and medicines for abortion, without discrimination *(42, 49)*.

Note: For further information, see Web annex A: Key international human rights standards on abortion. Wording used in this box reflects original language used in the source documents (human rights treaties).

- Access to abortion must be available when carrying a pregnancy to term would cause the woman substantial pain or suffering. This includes but is not limited to situations where her life and health are at risk, where the pregnancy is the result of rape or incest, or where the pregnancy is not viable *(36, para. 8)*. Treaty monitoring bodies have also recommended making abortion available in cases of fetal impairment, while putting in place measures to protect against discrimination on the basis of disability in society *(60)*.
- States should not criminalize having an abortion, those who have an abortion, or those who support someone having an abortion *(3 [paras 20, 34], 36 [para. 8], 55 [para. 18], 61 [para. 51(l)], 62 [para. 60], 63 [paras 82, 107])*.
- States should not require health workers to report women who have had or who are suspected to have had an abortion *(40, para. 20)*.
- States must provide essential primary health care *(64, para. 10)* (see also section 1.4.1: Universal health coverage and primary health care; section 1.4.4: Commodities; Annex 2: Selected human rights treaties and their treaty monitoring bodies; and also Web annex A: Key international human rights standards on abortion).

(iv) Accessibility of abortion care

Where it is lawful, abortion must be accessible in practice. This requires both ensuring that health-care facilities, commodities and services are accessible (including sufficient providers; see section 3.3.8 on provider restrictions), and that law and policy on abortion is formulated, interpreted and applied in a way that is compatible with human rights. Thus, where abortion is currently available on the basis of grounds, meaning under specified circumstances, and in anticipation of moving to a system of abortion on request as recommended (see Recommendation 2: Grounds-based approaches, section 2.2.2), those grounds must be defined and interpreted in a way that gives full effect to women's human rights and that aligns with the following WHO definitions:

> **Health**: a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity *(2)*.
>
> **Mental health**: a state of well-being in which every individual realizes their own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to their community *(65)*.

States must take effective steps to prevent third parties (e.g. parent, spouse, health authority) undermining a person's enjoyment of their right to SRH (see section 3.3.2: Third-party authorization) *(3, para. 59)*, and must also ensure that provider refusal is not a barrier to accessing abortion care (see section 3.3.9: Conscientious objection) *(3 [paras 14, 43], 39 [Ch.1, paras 11, 13])*.

(v) Free and informed consent

International human rights law requires that the provision of abortion be based on the free and informed consent of the person having the abortion with no further authorization required.

International human rights law obliges States to ensure that accurate, evidence-based abortion information *(3 [para. 9], 36 [para. 8])* is available to individuals on a confidential basis *(36 [para. 8], 43)*, and also that their choice to refuse such information when offered is respected *(58, para. 15)*. Receipt of such information is vital as this underpins the right and the ability to make informed decisions and choices about matters regarding one's body and SRH, and to give informed consent (see also section 1.3.2 below).

As a matter of international human rights law, States are obligated to ensure that "informed consent" is:

- documented in advance of a health-care intervention, and provided without coercion, undue influence or misrepresentation *(58, para. 13)*;
- safeguarded through legislative, political and administrative means *(58, para. 7)*, as a fundamental aspect of a range of human rights (i.e. the rights to health, information, freedom from discrimination, and security and dignity of the person);
- based on provision of complete information about the associated benefits, risks and alternatives;
- based on information that is of high quality, accurate and accessible (including ensuring it is available in a range of formats and languages, and in forms that make it accessible to people with reduced capacity), and presented in a manner acceptable to the person consenting.

Further relevant information is provided in section 3.2 on information provision and counselling related to abortion for individual abortion seekers, and in section 3.5.1 on follow-up care and section 3.5.4 on post-abortion contraception. States are obliged to protect women from arbitrary interference when they seek SRH services, and to ensure respect for autonomous decision-making by women, including women with disabilities, regarding their SRH and well-being *(60)*.

Even though women have a right to accurate information, some health workers who object to abortion on the basis of conscience either provide deliberately misleading information or refuse to provide any information about abortion *(66-68)*. States where health workers are allowed to invoke conscientious objection *(3, para. 43)* must regulate and monitor such refusals of abortion care to ensure that women can access accurate information and appropriate services (refer to section 3.3.9: Conscientious objection).

As a matter of international human rights law, States may not restrict women's access to health services on the ground that they do not have the authorization of husbands, partners, parents/guardians or health authorities, because they are unmarried, or because they are women *(39 [Ch.1, paras 14, 21], 3 [paras 41, 43])*. For adolescents, the authorization or consent of parents should not be required before the provision of abortion care (see also section 3.3.2: Third-party authorization). As a general matter, States must recognize children's and adolescents' evolving capacity and their associated ability to take decisions that affect their lives *(69, Article 5)*. In order to ensure protection of adolescents' sexual and reproductive health and rights, the United Nations Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health has suggested that States should consider introducing "a legal presumption of competence that an adolescent seeking preventive or time-sensitive health goods or services, including for sexual and reproductive health, has the requisite capacity to access such goods and services" *(35, para. 60)*. The United Nations Committee on the Rights of the Child (CRC) has also urged States to "review and consider allowing children to consent to certain medical treatments and interventions without the permission of a parent, caregiver or guardian, such as … sexual and reproductive health services, including … safe abortion" *(45, para. 31)*.

People with disabilities have a right to autonomy *(59, Article 3a)*, but face continuing and systemic discrimination in access to SRH services. States are obliged to prohibit and prevent discriminatory denial of SRH services to people with disabilities *(70, para. 66)*. States may not undertake, and must take steps to prevent forced or coerced abortion *(40, para. 11)*, which constitutes torture, cruel, inhuman or degrading treatment *(40 [para. 11], 52 [para. 62])*.

(vi) Post-abortion care

Provision of post-abortion care is a core obligation of States under the right to SRH *(3, para. 49e)*. Regardless of whether abortion is legal or restricted, States are required to ensure access to post-abortion care *(45, para. 70)*. Such care must be available on a confidential basis, without discrimination, and without the threat of criminal prosecution or other punitive measures *(36, para. 8)*. States must also ensure access to a wide range of modern, safe and affordable contraceptive methods *(36 [para. 8], 49 [para. 33])*.

(vii) Accountability for human rights violations

Accountability mechanisms are essential to the protection, respect and fulfilment of sexual and reproductive health and rights. Monitoring and accountability for human rights compliance takes place at national, regional and international levels, as appropriate to the law in question. Monitoring and accountability involve a variety of actors, such as the State itself, civil society organizations, national human rights institutions or international or regional human rights mechanisms. Some such accountability mechanisms include administrative mechanisms for recording and monitoring relevant health outcomes relating to abortion law and policy, and including them in reports to human rights institutions *(39, Ch.1, paras 9, 10, 12, 17)* (see also section 1.4.5 on monitoring and evaluation of abortion care). States must ensure that all persons have access to justice and to a meaningful and effective remedy where their human rights are violated *(39, Ch.1, para. 13)*. These remedies can include adequate, effective and prompt reparation in the form of restitution, compensation, rehabilitation, satisfaction and guarantees of non-repetition *(3, para. 64),* including by reform of law and policy. Mindful of the above, an enabling environment for abortion care would ensure that there are appropriate accountability mechanisms for failures to facilitate quality abortion care, including accessible, transparent and effective accountability mechanisms for women to challenge denial of abortion in a timely manner. In addition, an enabling environment would include appropriate remedies for failure to facilitate quality abortion care, including regular review and reform of law and policy to recognize and remove barriers to quality abortion care. As confirmed by the Committee on the Elimination

of Discrimination against Women (CEDAW), such reform should include "[a]bolish[ing] discriminatory criminalization and review[ing] and monitor[ing] all criminal procedures... [and] decriminaliz[ing] forms of behaviour that can be performed only by women, such as abortion" *(61, para. 51[l])*.

1.3.2 Availability and accessibility of information

An essential first step in improving access to and quality of abortion care is ensuring that all individuals can access relevant, accurate and evidence-based health information and counselling if and when desired. This is required by international human rights law – grounded in the right to information and the right to privacy (see Box 1.2) – and facilitates individual decision-making relating to SRH services, including abortion. Two different types of information about abortion must be available: (i) information of a general nature for the public (described below), and (ii) specific information tailored to be relevant to each person seeking abortion (see section 3.2.1) and underpinning free and informed consent, which was described in section 1.3.1(v).

States parties are to ensure that everyone has a right to receive accurate, non-biased and evidence-based information on SRH. Relatedly, as part of their obligation to reduce maternal mortality and morbidity, States must ensure the provision of comprehensive, non-discriminatory, scientifically accurate and age-appropriate education on sexuality and reproduction, including information on abortion, both in and out of schools *(46, 71 [Articles 10, 16], 72)* and must ensure that comprehensive sexuality education (CSE) is available to minors without the consent of their parents or guardians *(45, para. 31)*. In an enabling environment all persons would be provided with all the necessary information to make an informed decision regarding the use of contraception, including information on where and how to obtain an abortion or contraception, the costs of services, and the specifics of any local laws. The growing use of self-management of abortion (see section 3.6.2) underlines the need to ensure that accurate information about abortion is available to all who may seek it.

As a matter of international human rights law, the provision of information on abortion should not be criminalized, even in contexts where the procedure itself may be illegal (see section 2.2.1: Criminalization of abortion). To ensure that accurate information is broadly accessible, including for those with low literacy, an enabling environment would provide that such information is shared using a variety of formats/media as appropriate for the intended audience (e.g. videos, social media). The United Nations CESCR has confirmed that "[t]he dissemination of misinformation and the imposition of restrictions on the right of individuals to access information about SRH also violates the duty to respect human rights. ... Such restrictions impede access to information and services, and can fuel stigma and discrimination" *(3, para. 41)*.

1.3.3 Health system factors

Within the health system, multiple actions are needed to realize human rights obligations. Actions to facilitate and strengthen abortion-related service delivery should be based on human rights, local health needs and a thorough understanding of the service-delivery system and the broader social, cultural, political and economic context. National standards and guidelines for abortion care should be evidence based and periodically updated, and should provide the necessary guidance to achieve equal access to comprehensive abortion care. Leadership should also promote evidence-based SRH services according to these standards and guidelines.

The right to the highest attainable standard of physical and mental health includes the right to respectful health care as well as the right to be free from violence and discrimination *(73)*. The right to benefit from scientific progress and its realization entitles women to access to up-to-date scientific technologies necessary for women. This means States must ensure access to modern and safe forms of contraception (including emergency contraception), abortion medicines, assisted reproductive technologies, and other SRH goods and services, on the basis of non-discrimination and equality *(49, para. 33)*. To achieve a high standard of respectful care, health systems should be organized and managed in a manner that ensures respect for people's SRH and human rights *(73)*. Respectful health care recognizes individuals' rights, respects their agency and autonomy in decision-making, and incorporates their values and preferences into care.

In addition to policy and regulatory barriers, other barriers may further limit the availability of abortion services, including: stigma; formal and informal costs; lack of commodities, services, trained providers and information; and/or the unwillingness of some health workers to provide care. This leaves particular groups of people – such as those living in rural settings, those facing financial hardship, adolescents, unmarried, transgender or nonbinary individuals, those with less access to education and those living with HIV – disproportionately vulnerable to

barriers to obtaining abortion care. As part of an enabling environment, a health system should be adequately resourced, meaning that resources (e.g. essential medicines, supplies, equipment, workforce, financial allocations) are available, fairly distributed and efficiently used. In this way, adequate and equitable access to quality-assured essential medicines and equipment should be assured. Relatedly, health financing policies should avoid making access to SRH services conditional on direct payment from patients at the point of service, and the health workforce should be skilled in providing evidence-based SRH services, including counselling.

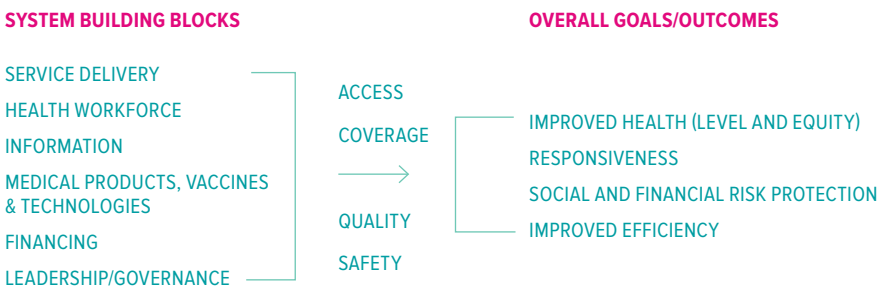
Abortion stigma is common, and has negative psychological consequences for individuals seeking abortion and health workers providing abortion care *(31, 74, 75),* and can also be detrimental to health outcomes. Abortion stigma is a social process, and is dependent upon the context, but may be considered as an exercise of power and control of one group over members of a less powerful group, who are considered different, negatively stereotyped, discriminated against and marginalized within society *(75, 76).* Work is needed across sectors to counteract stigma; health systems should recognize the risks and effects of stigma, and implement solutions to not only ensure privacy and confidentiality, but also to support health workers. Care should always be provided respectfully and with compassion. In an enabling environment, communities are also engaged and supportive. Those who assist and support abortion seekers – their partners, friends, family members – also require support within the health system and broader environment.

More in-depth consideration of key health system factors is provided in section 1.4 below.

1.4 Health system considerations

The health system refers to all organizations, people and actions whose *primary intent* is to promote, restore or maintain health *(77).* The health system consists of the six core building blocks, as listed in Figure 1.2, which support four overall goals and outcomes, as shown below. This section addresses in detail health system considerations relevant to an enabling environment for abortion care.

Figure 1.2: The WHO health system framework



Source: WHO, 2007 *(77).*

A well functioning health system, with all the "blocks" working in harmony, depends upon having trained and motivated health workers, a well maintained infrastructure and a reliable supply of medicines and technologies, backed by adequate financing, strong health plans and evidence-based policies. Health-care services provided via the health system are not restricted to those provided at a health-care facility; health care and services can also be received through community-based providers (e.g. health visitors, pharmacists), digital interventions or self-care approaches (e.g. telemedicine).

1.4.1 Universal health coverage and primary health care

Universal health coverage (UHC) means ensuring that all people have access to the promotive, preventive, curative, rehabilitative and palliative health services they need, which must be of sufficient quality to be effective, while also ensuring that the use of these services does not expose any users to financial hardship *(30).* UHC is integral to the achievement of SDG target 3.8: Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable

essential medicines and vaccines for all. The aim of this target is to accelerate efforts to ensure that all people and communities receive the full spectrum of essential, quality health services they need across the life course, without suffering financial hardship.

To establish an enabling environment, there is a need for abortion care to be integrated into the health system across all levels (including primary, secondary and tertiary) – and supported in the community – to allow for expansion of health worker roles, including self-management approaches. Such integration is a complex process that can occur through service delivery, financing mechanisms and/or inclusion in health benefits packages. While inclusion in health benefits packages may enhance access to and delivery of abortion care, in many countries abortion care is not explicitly recognized in the standard package, contributing to inequitable access to services *(78)*.

From a health financing perspective, improving access to comprehensive abortion care, as part of UHC, requires shifting the burden of financing away from individuals towards domestic public funding, which combines tax revenue and prepayment schemes to cover the costs of care *(78)*. Further information is provided in section 1.4.2 below. Meanwhile, from a service-delivery perspective, integrating abortion care within national maternal care and family planning programmes is technically the most straightforward option as abortion services require few, if any, additional provider skills, medicines, equipment or supplies. Furthermore, it is the most efficient option, as it minimizes any additional/marginal costs of implementing abortion services.

Health systems strengthening, by improving performance across all six health system building blocks (see above), is essential to progress towards UHC *(77)*. The use of new and innovative technologies and approaches for providing, facilitating or supporting abortion services must be incorporated into country programmes and health benefits packages. WHO's UHC Compendium provides a list of all interventions related to abortion care to be considered for inclusion within a country's UHC package *(79)*.[3]

To ensure both access to abortion and achievement of UHC, abortion must be centred within primary health care (PHC), which itself is fully integrated within the health system, facilitating referral pathways for higher-level care when needed. PHC is a multisectoral, societal approach to health that aims to ensure the highest possible level of health and well-being for all individuals, by focusing on people's needs and preferences (as individuals, families and communities) along the continuum of care from health promotion and disease prevention to treatment, rehabilitation and palliative care *(30)*. Quality PHC is evidence-informed, community-delivered and person-centred. Making abortion available and accessible within PHC is a safe and effective strategy to advance equitable access to, and provide an enabling environment for, abortion.

1.4.2 Health financing

Health financing is a core function of health systems that can enable progress towards UHC by improving effective service coverage and financial protection. To improve effective service coverage, health financing arrangements for abortion services should ensure the production costs are met so that health-care providers have the means to carry out these activities without financial constraints. To improve financial protection, the health system must guarantee that the share of the costs – production costs and the costs of access to services – borne by patients is not a barrier to full use of services. WHO's approach to health financing focuses on the following core functions:

- raising revenue – establishing sources of funds, including government budgets, compulsory or voluntary prepaid insurance schemes, direct out-of-pocket payments by users, and external aid;
- pooling funds – the accumulation of prepaid funds on behalf of some or all of the population; and
- purchasing services – the payment or allocation of resources to health-care providers.

In addition, all countries have policies indicating which services the population is entitled to, even if not explicitly stated by the government, and by extension any services not covered are usually paid for out of pocket by patients as user fees or co-payments.

To provide an enabling environment, financing of abortion services should take into account costs to the health system while ensuring that services are free or affordable and readily available to all who need them, in support of the goal of achieving UHC. A recent scoping review captured the costs to the health system and to the woman

3 Available by selecting "Sexual and reproductive health" at this link: https://www.who.int/universal-health-coverage/compendium/interventions-by-programme-area or by searching the database at this link: https://www.who.int/universal-health-coverage/compendium/database

by categorizing the economic consequences of abortion and abortion policies through three levels: micro-, meso- and macroeconomic. Assessment of the micro-, meso- and macroeconomic levels provided insight into the documented economic consequences of abortions at the individual, community and health system levels *(80-82)*.

Cost to the facility or health system

In regard to costs to the health-care facility and health system, the findings of the review on the mesoeconomic outcomes confirmed that limited resources negatively affect facilities' ability to meet demand and provide quality services *(81)*. Furthermore, the costs of post-abortion care, including treatment of post-abortion complications, consume a disproportionate amount of facilities' resources in many settings, posing a burden to health systems by further depleting their overstretched resources. Therefore, financial savings can be made by maintaining or even improving the quality of abortion care services, and also by decentralizing services and legalizing abortion, as indicated in the macroeconomic assessment *(82)*.

Providing access to quality abortion care is considerably less costly than treating the complications of unsafe abortion *(83-87)*. Costs for providing abortion care with vacuum aspiration include infrequent, modest capital investments, such as purchase of a suction machine for electric vacuum aspiration (EVA) or manual vacuum aspiration (MVA) equipment, an examination table, a steam sterilizer or autoclave, and possibly also renovation of waiting, consultation and recovery rooms, and toilets. Recurrent costs for surgical or medical abortion include those associated with purchasing instruments and supplies that will need to be restocked regularly, such as cannulae and MVA aspirators, antiseptic solutions and high-level disinfectants used for instrument processing, and medicines for pain management, infection prevention and medical abortion.

Decisions about which abortion methods to offer and how to organize services directly influence the cost of providing services and their affordability. Two organizational issues are of particular importance for both increasing safety and reducing costs: (i) preferential use of either vacuum aspiration or medical abortion, and (ii) facilitating the provision of abortion (e.g. improved access to abortion services, integration into primary health care). Expanding the role of health workers in abortion provision and exploring innovative modes of service-delivery, such as telemedicine and hotlines, have also been identified as cost-saving strategies for national health systems *(82)*.

Making services affordable for women

In countries where legal access to abortion is available, it remains a challenge to provide abortion services that are publicly funded and free at the point of care *(88)*. Furthermore, in some settings, financial protection is restricted to specific demographic groups of individuals seeking abortion or certain legal categories of abortion. Abortion seekers may be charged substantial additional fees (on top of the official charges), creating a barrier for many, especially when combined with travel expenses and opportunity costs, such as time lost from paid and unpaid work. In some settings, reimbursement rates for private or public providers working with nongovernmental organizations are well below the cost of providing care. The barrier of high costs of abortion medicines and/or services is likely to generate higher costs for the health system, since these costs force many – especially among the adolescent population *(89)* – to present at a later gestational age or to use unsafe providers or methods, thus increasing the rates of hospitalization for serious complications *(80, 90-92)*. Higher rates of complications, additional fees and high costs all also contribute to the stigmatization of abortion.

Respect, protection and fulfilment of the right to health requires States to guarantee, at a minimum, universal and equitable access to affordable, acceptable and quality SRH services, goods and facilities, in particular for women and disadvantaged and marginalized groups *(3, para. 49)*. Thus, in order to provide an enabling environment for abortion care, ability to pay should not have any bearing on women's ability to access legal abortion services *(3 [para. 17], 35 [para. 31], 39 [Ch.1, para. 21])*.

As part of an enabling environment, considerations of gender equality, human rights and equity should guide the design of health financing policy to reduce if not eliminate the financial barriers for the most vulnerable, and to ensure equitable access to good-quality services *(93)*. The CEDAW Committee has described fees for abortion as being burdensome to women's informed choice and autonomy *(94, para. 37)*. Where user fees are charged for abortion, this should be based on careful consideration of ability to pay, and fee waivers should be available for those who are facing financial hardship and adolescent abortion seekers. It should be noted, however, that evidence on the success of fee waivers in addressing financial barriers and improving access to quality

abortion care is mixed and inconclusive *(95)*. Numerous treaty monitoring bodies (see Annex 2) have recognized that abortion services must be economically accessible, recommending that States lower the cost of abortion or otherwise provide financial support when needed *(96 [paras 37(b), 38(b)], 97 [para. 24], 98 [paras 38, 39])*. Relatedly, the Committee against Torture (CAT) has called on States to ensure free access to abortion in cases of rape *(99, para. 15a)*. With the above in mind, as far as possible, abortion services and supplies should be mandated for coverage under insurance plans as inability to pay is not an acceptable reason to deny or delay abortion care. Furthermore, having transparent procedures in all health-care facilities can ensure that informal charges are not imposed by staff.

1.4.3 Health workforce competencies and training

Health workers are all people engaged in actions whose primary intent is to enhance health *(100)*. The delivery of high-quality care requires an adequate supply of competent health workers, who are equitably distributed, and with an optimal skills mix at the facility, outreach and community levels *(101)*. All health workers need to be adequately supported to provide competent care. The competencies required to provide or support abortion care align with competencies required in many different areas of health *(102, 103)*. WHO is currently developing a global competency framework for universal health coverage (UHC), which identifies the required competencies for primary health care workers to provide the full spectrum of promotive, preventive, diagnostic, curative and palliative care *(104, 105)*.

Delivery of care and treatment services should be accomplished in a people-centred, non-judgemental and non-directive way, allowing individuals to lead the decision-making about their own care in an informed and supported fashion *(106)*. As part of ensuring an enabling environment, it is particularly important that training for health workers involved with SRH services incorporates:

- the unique competencies required for SRH services, in particular for abortion care;
- provision of people-centred care;
- human rights, and the content and meaning of the law, and how to interpret and apply law and policy in rights-compliant ways;
- communication to enable informed decision-making;
- values clarification;
- interprofessional teamworking; and
- empathetic and compassionate approaches to care *(105)*.

These skills should be included in training programmes and promoted by professional societies. It is especially critical that the attitudes and behaviours of health workers be inclusive, non-judgemental and non-stigmatizing, and that they promote safety and equality. Managers of health care – whether in the public or private sector – are responsible for delivering services appropriately and meeting standards based on professional ethics and internationally agreed human rights principles.

1.4.4 Commodities

Provision of primary health care includes access to safe, effective, quality-assured and affordable medicines, including medicines for abortion and post-abortion care (i.e. antibiotics and pain control medicines as well as abortion medicines and post-abortion contraceptives).

The WHO Model List of Essential Medicines (also known as the Essential Medicines List, or EML) includes the minimum medicines needed for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected based on current and estimated future public health relevance, and potential for safe and cost-effective treatment. Both mifepristone and misoprostol have been included in the WHO Model Lists of Essential Medicines since 2005. In 2019, these medicines were moved from the complementary to the core list of essential medicines in the 21st EML and the requirement for “close medical supervision” for their use was removed *(107)*. The relevant abortion medicines included in the 21st EML and also the more recent 22nd EML are indicated in Table 1.1.

Table 1.1 Medicines included in the WHO Model List of Essential Medicines (EML) and their indications

Indication included in EML	Medicines included in the EML
Induced abortion	• Mifepristone (200 mg) and misoprostol (200 µg) • The medicines are available individually or co-packaged. • The EML specifically mentions the following co-packaged formulation: 1 tablet mifepristone (200 mg) + 4 tablets misoprostol (200 µg).
Management of incomplete abortion and miscarriage	• Misoprostol (200 µg)

Source: WHO EML – 21st list, 2019 *(107)*, 22nd list, 2021 *(108)*.

Within a country, the key elements of a commodity strategy include policy, regulation, procurement and supply chain, as well as links to financing and reimbursement systems *(109)*.

Mifepristone and misoprostol should be listed in relevant national EMLs (NEMLs) or their equivalent, and should be included in the relevant clinical care/service delivery guidelines. In the case of pregnancy tests and MVA equipment, countries may have an Essential Medical Devices List or a similar list for medical devices. Pregnancy tests and quality MVA devices should be included on these lists as part of a commodity strategy.

Inclusion in the NEML is one important component of ensuring that quality medicines are available. Misoprostol, mifepristone, surgical abortion equipment and other relevant health products should be included in national procurement tenders as well as in supply chain monitoring activities. Procurement activities should include forecasting methods that are appropriate to the products and to the country context with a goal of ensuring continuous supply *(110)*. Central Medical Stores (CMS) entities should ensure that specifications for the procurement of safe abortion medicines are coordinated with national medicines regulatory authorities (NMRAs) and that they clearly specify quality assurance standards and all other requirements, such as strength, packaging and shelf life.

WHO recommends that the highest level of quality assurance be pursued but recognizes that risk-based approaches may be needed in countries where access to international markets is limited. Risk-based approaches will depend on the context of a given country but may include exceptions based on prior information about a manufacturer, or reliance on information from other regulators *(111)*. Quality-assured medicines include those approved by stringent regulatory authorities (SRAs) *(112)*[4] or listed through WHO Prequalification (PQ).[5] Where such medicines are not available, approval by an NMRA that includes inspection and testing according to accepted standards should be undertaken for mifepristone and misoprostol.[6]

NMRAs are the bodies that provide registration and market authorization for specific products. The NMRA reviews the safety, efficacy and quality of medicines as part of granting market authorization. Such authorization is specific to each medicine made in a particular location by a particular manufacturer. Market authorizations are granted based on an evaluation of a technical dossier presented by the manufacturer, or their agent, confirming the efficacy, quality and safety of the product. Through prequalification, WHO supports a regulatory reliance mechanism where it provides detailed assessment information to NMRAs on products that have been prequalified by WHO, so that the regulatory decision can be made based on WHO's assessment rather than having to duplicate it. Based on the same principle, WHO also supports the sharing of assessment information for SRA-approved products. These processes are both known as WHO Collaborative Registration Procedures (CRPs).[7]

Regulators make determinations regarding the authority to prescribe and dispense medicines. There are examples, including emergency contraception, where regulators have made decisions to change the prescribing authority to improve access and appropriate use, including "over the counter" sales or prescription by a pharmacist without physician consultation. The information that is typically considered includes whether a condition can be reasonably self-diagnosed, the overall safety of the medicine, and the likelihood of misuse

4 SRAs are listed at this web page: https://www.who.int/initiatives/who-listed-authority-reg-authorities/SRAs. In the cited reference (pp. 34–35), SRAs are defined as "a regulatory authority which is a member or an observer of ICH [International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use], or is associated with an ICH member through a legally-binding mutual recognition agreement" (as before 23 October 2015).

5 WHO Prequalification is one standard for all types of products, including medicines (pharmaceuticals and biotherapeutics), vaccines and immunization devices, in vitro diagnostics and vector control products. This listing implies a recommendation but not market authorization.

6 For further information, refer to The International Pharmacopoeia, available at: https://digicollections.net/phint/2020/index.html#p/home

7 For further information, see: https://extranet.who.int/pqweb/medicines/collaborative-procedure-accelerated-registration

or complications with less supervised or unsupervised use of the medicine, among others *(113, 114)*. National programmes should work with regulators to determine the most appropriate evidence-based prescribing and dispensing authorities for the medicines. Restrictions on prescribing authority for some categories of health workers may need to be modified or other mechanisms put in place to make the medicines available for these health workers within the regulatory framework of the health system.

A comprehensive commodity strategy and effective approach to access will require: inclusion of the necessary commodities in the NEML; approval from the NMRA (i.e. market authorization or registration); development of mechanisms for forecasting, procurement, distribution and guidance on prescribing and dispensing; and a plan for post-marketing surveillance.

1.4.5 Monitoring and evaluation of quality abortion care

Effective monitoring and evaluation (M&E) are essential for measuring abortion quality and trends, as a basis for policy dialogue and evidence-based decision-making to further improve service delivery and quality. To support national scale M&E of the quality of abortion care, WHO is developing a quality abortion care M&E framework based on WHO's *Monitoring and evaluation of health systems strengthening: an operational framework (115).* The structure, domains and indicator areas of the framework, categories for inequality disaggregation and standard data sources are presented in Table 1.2. A set of abortion care indicators is under development and will be published in the near future (see Annex 6 for a summary about the progress of this M&E work).

The quality abortion care M&E framework will support M&E at the levels of health system input, service delivery, population outcome and impact. M&E of abortion-related services remains weak in most national health systems. Specific gaps in data collection and use must be identified and addressed.

Health system input monitoring covers governance, health financing, health workforce, health commodities and health information. Within these five categories, quality abortion care health system inputs to track over time include among others:

- Governance: clarification of the legal status of abortion, adherence of induced abortion protocols in national guidelines to global normative guidance (see also section 1.3.1[vii]);
- Financing: inclusion of health financing arrangements for abortion-related care in leading health benefits packages (see section 1.4.2);
- Health workforce: inclusion of competency-based induced abortion care (in line with global normative guidance) in national curricula for relevant categories of health workers (see section 1.4.3);
- Health commodities: inclusion in national essential medicines lists (NEMLs) of mifepristone and misoprostol, monitoring of stock-outs of abortion service commodities at service-delivery points (see section 1.4.4);
- Health management information systems (HMIS): integration of indicators for quality abortion care into the national HMIS.

For this level of input monitoring, data are typically available from administrative sources, including national policy documents, health finance tracking systems, national curricula, logistics management information systems (LMIS) and HMIS.

Service-delivery monitoring tracks the availability of providers trained in and providing induced abortion care, availability of necessary medicines and products at service-delivery points, readiness of the system to provide abortion care to a defined minimum standard, and quality of service delivery, including person-centred care, assessed in part through user and community perspectives. National-level abortion service-delivery monitoring data should be included in health-care facility-level assessments, HMIS and population-based surveys.

Population outcome monitoring for abortion care assesses coverage including (i) access to quality, affordable abortion care, and (ii) population knowledge of access to quality, affordable abortion care. Efforts should be made to disaggregate data by dimensions of inequality, such as ability, age, caste, education, ethnicity, gender, geography and wealth. Population outcome data sources typically include health-care facility-level assessments and population-based surveys and can include HMIS and education management information systems. In many settings, abortion-related population outcome data is a neglected area of data collection and reporting.

Impact measurement for quality abortion care includes abortion-related mortality and morbidity. Estimates in these areas should be disaggregated by dimensions of inequality as much as possible. Data sources include population-based surveys, HMIS and civil registration and vital statistics (CRVS) registries.

Where gaps in data availability are identified, investment should be made to address these. In the short term, statistical modelling may be required to estimate indicator values, particularly at the impact level.

Table 1.2 Monitoring and evaluation of the quality of abortion care

Categories	Indicator areas	Inequality disaggregation	Data sources
Health system input	Governance	Geography: intranational, international	Administrative sources (including national policy documents, health finance tracking systems, national curricula, LMIS and HMIS)
	Health financing		
	Health workforce		
	Health commodities		
	Health information		
Service delivery	Availability of services	Geography: intranational, international	Health-care facility assessment (including patient interviews), population-based survey, HMIS
	Readiness for service delivery		
	Quality of services		
Population outcome	Access to quality, affordable abortion care	Ability, age, caste, education, ethnicity, gender, geography, wealth	Health-care facility assessment, population-based survey, HMIS, education management information systems
	Population knowledge of access to quality, affordable abortion care		
Impact	Abortion-related mortality	Ability, age, caste, education, ethnicity, gender, geography, wealth	CRVS, HMIS, population-based survey
	Abortion-related morbidity		

CRVS: civil registration and vital statistics; HMIS: health management information system; LMIS: logistics management information system

Chapter 2.

Abortion regulation including relevant recommendations

As outlined in Chapter 1, section 1.3, one element of an enabling environment is that law and policy promote and protect sexual and reproductive health and rights (SRHR). A number of common approaches to law and policy on abortion mentioned in Chapter 1 (section 1.3.1) pose barriers to access to abortion, are inconsistent with international human rights legal instruments, and can have negative effects on the exercise of human rights. This chapter reflects evidence on the impacts of these law and policy approaches, considers their human rights implications, and presents evidence-based recommendations to improve law and policy relating to abortion as part of an enabling environment for universal access to quality abortion care. Box 2.1 summarizes the principles of abortion law and policy that would be consistent with key principles of human rights law.

BOX 2.1: Abortion law and policy that are consistent with key principles of human rights law

States must respect, protect and fulfil abortion seekers' rights, including their sexual and reproductive health and rights (SRHR).

States should take positive steps to secure an enabling regulatory and policy environment that will ensure the universal availability, accessibility, acceptability and quality (AAAQ) of abortion and post-abortion care.

Abortion should be fully decriminalized. Regulatory, policy and programmatic barriers – as well as barriers in practice – that hinder access to and timely provision of quality abortion care should be removed. These include grounds-based approaches, gestational age limits, mandatory waiting periods, third-party authorization requirements and provider restrictions. States should also protect access to and continuity of abortion care against barriers created by conscientious objection (refer to Recommendations 1,2,3,6,7,21 and 22 in this guidance).

The regulation of abortion should have the objective of respecting, protecting and fulfilling the SRHR of women; achieving positive health outcomes for women; providing good-quality contraceptive information and services; and meeting the particular needs of marginalized persons, including women facing financial hardship, adolescents, women with disabilities, survivors of sexual and gender-based violence, transgender and non-binary persons, women from ethnic, religious and racial minorities, migrant and displaced women, and women living with HIV, among others. The regulation of abortion should be grounded on and should promote equality and non-discrimination.

Source: Refer to Box 1.2 for references.

2.1 Common approaches to abortion regulation

Almost all countries where abortion is lawfully available regulate abortion differently to other forms of health care *(116)*. Unlike other essential health services, abortion is commonly regulated to varying degrees through the criminal law in addition to regulation under health-care law. Even where abortion is available on certain grounds or until specified gestational ages (often linked to particular grounds), it is usually designated in those cases as a criminal offence if it occurs outside of those specific permitted situations. As a result, people can experience significant barriers in accessing abortion and post-abortion care in such contexts. These barriers persist even though abortion is a safe, effective and non-complex part of sexual and reproductive health (SRH) care, in spite of significant advancements in international human rights law, and notwithstanding the growing frequency with which self-management of abortion occurs safely with little or no contact with the formal health system.

Typical barriers to access to quality abortion care, which may or may not be codified in law, include lack of access to accurate information, the provision of biased information or counselling, the imposition of mandatory waiting periods, third-party authorization requirements, restrictions on the type of facilities or settings where abortion services can lawfully be provided, restrictions on the type of health workers that can lawfully provide services, lack of affordable services, breaches of confidentiality and privacy, failure to safeguard access to and continuity of care where health workers refuse care on the basis of conscientious objection, failure to license or make available essential medicines, and failure to recognize women as individuals who can manage their own abortions.

Restrictive laws, policies and practices often have the effect of making health workers, health-care facilities, committees, ethics boards, police, courts or others the "gatekeepers" for access to quality abortion care by requiring them to determine whether someone "qualifies" for legal abortion. In many cases, this introduces delay in accessing abortion. Such gatekeepers are not always sufficiently informed about the law or willing to interpret and apply law and policy in a way that respects, protects and fulfils abortion seekers' rights. Criminalization of abortion can also have a "chilling effect" more broadly, as it can result in narrow interpretation of applicable law by health workers, including to avoid possible criminal liability (i.e. suppression of actions due to fear of reprisals or penalties). As a consequence, in many settings women's experiences of seeking, accessing and managing abortion are highly variable, with much depending not only on the law but also on the approach of the gatekeeper with whom they interact. Thus, including information on relevant rights, laws and policies in the training and education of health workers is a crucial part of ensuring an enabling environment for quality abortion care (see also Chapter 1, section 1.4.3).

As described above, clear, accessible and rights-based laws and policies are part of an enabling environment for abortion care (see section 1.3). However, in some countries the law on abortion is incoherent, with seemingly conflicting provisions articulated in constitutions, penal codes, health legislation or policy guidance *(117)*. Furthermore, in some cases domestic laws are inconsistent with international human rights standards and incompatible with current public health evidence. Additionally, in certain cases there is a lack of guidance from government to assist providers in identifying when abortion is lawful. Such incoherence can create uncertainty about the law for both those seeking and providing abortion care. The recommendations in this guideline build on human rights law and public health evidence to outline an approach under which abortion is regulated similarly to other health-care interventions, that is, by general health-care law and policy, best practice, training and evidence-based guidelines.

2.2 Recommendations relating to regulation of abortion

Three recommendations relating specifically to the regulation of abortion are presented in this section (Recommendations 1–3) and four additional recommendations, also relating to law and policy and abortion, are presented in Chapter 3, section 3.3: Pre-abortion (Recommendations 6,7,21 and 22). These seven recommendations were formulated by the expert panels formed for the development of this guideline, including expert human rights advisers (all contributors are listed in Annex 1 and the roles of the contributing groups are described in Annex 4).[8] The evidence was first systematically reviewed for each prioritized topic and question, and

8 The expert panels included the Evidence and Recommendations Review Groups (ERRGs) for each of the three domains (Law and policy, Clinical services and Service delivery) and later the Guideline Development Group (GDG), and each phase and each meeting of these groups also involved at least one human rights adviser. For further details on the roles of these groups and the full methodology for the guideline development process, see Annex 4: Methods.

the level of certainty of that evidence was assessed (i.e. based on the quality of the evidence, including the types and sizes of studies conducted and their various limitations).

The direction (in favour or against) and strength of each recommendation was determined by the panel of experts based on the six substantive criteria of the WHO-INTEGRATE framework as applied to each intervention for the specified population – balance of health benefits and harms; human rights and sociocultural acceptability; health equity, non-discrimination and equality; societal implications; financial and economic considerations; feasibility and health system considerations – while also taking into account the meta-criterion: quality of evidence *(118)*.

Recommendations in favour of an intervention are qualified as either strong or weak (with the conditions of use specified for the latter), with the third alternative being a recommendation against the intervention. To clearly indicate the strength and direction of each recommendation, the following wording is used:

- **Recommend** – a strong recommendation in favour of the intervention
- **Suggest** – a weak recommendation in favour of the intervention (requiring additional wording to qualify the recommendation, specifying the conditions of use)
- **Recommend against** – a strong recommendation against the intervention/in favour of the comparison.

For each topic covered, both in this chapter and also in Chapter 3, first brief background information is presented, then the recommendation itself, followed next by a list of remarks (if any) from the expert panel that reviewed the evidence in detail, explaining the conditions and context relevant to the recommendation, and then the rationale, or summary of the evidence base and decision-making process for the recommendation, and finally a box listing any key human rights considerations relevant to the recommendation or broader topic. It should be noted that the 2012 *Safe abortion* guidance provided a composite recommendation related to law and policy; in this guideline, this has been developed into seven separate recommendations using GRADE methodology, but they are not considered to be "new" (i.e. Recommendations 1,2,3,6,7,21,22). The methods are described in full in Annex 4, including the differences in the methods applied for the seven recommendations relating to law and policy issues compared with the other types of recommendations. A summary table linking the topics covered, the research questions, the systematic reviews conducted and the recommendation numbers is provided in Annex 7. The full Evidence-to-Decision (EtD) frameworks are provided online as supplementary material and hyperlinked cross-references to these are supplied with the rationale for new and updated recommendation presented.[9]

9 Supplementary material 1: EtD frameworks for law and policy topics, available at: https://www.who.int/publications/i/item/9789240039483.

2.2.1 Criminalization of abortion

Unlike other health services, abortion is commonly regulated to varying degrees through the criminal law (i.e. criminalized), in addition to regulation under health-care law.

Abortion remains a criminal offence in most countries, with penalties against those who have abortions and/or those who provide abortion services or assist with accessing or managing abortion, sometimes including those who provide information about abortion. In some countries, all of these actions are criminal offences.

Decriminalization is a necessary step for the legalization of abortion, but ensuring that abortion is available, accessible and of high quality may require further legal or regulatory changes beyond decriminalization, including, as applicable, implementing the other recommendations contained in this guideline.

LAW & POLICY Recommendation 1: Criminalization

Recommend the full decriminalization of abortion.

Remarks:

- Decriminalization means removing abortion from all penal/criminal laws, not applying other criminal offences (e.g. murder, manslaughter) to abortion, and ensuring there are no criminal penalties for having, assisting with, providing information about, or providing abortion, for all relevant actors.
- Decriminalization would ensure that anyone who has experienced pregnancy loss does not come under suspicion of illegal abortion when they seek care.
- Decriminalization of abortion does not make women, girls or other pregnant persons vulnerable to forced or coerced abortion. Forced or coerced abortion would constitute serious assault as these are non-consensual interventions.

Note on updating of the recommendation: This and other law and policy recommendations are not new recommendations. WHO's 2012 *Safe abortion* guidance provided a composite recommendation related to law and policy *(19)*; in this guideline, this has been developed into seven separate recommendations using GRADE methodology.

Rationale

Numerous human rights bodies and mandate holders, including the CEDAW Committee *(38)*, the CESCR *(3)*, the United Nations Human Rights Committee *(36)*, and the Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health *(37)*, support the full decriminalization of abortion. They have clarified that States should not criminalize medical procedures needed only by women, including abortion nor criminalize those who have undergone an abortion, or punish or apply criminal sanctions against those who assist women in having abortions. Under international human rights law, States must not require health workers to report cases of women or girls who have had abortions, or whom they suspect of having had abortions, and States must provide post-abortion care in all circumstances and without the risk of criminal sanction. In addition, States must take steps, including revising laws, to reduce maternal morbidity and mortality (including abortion-related morbidity and mortality), and to effectively protect women and girls from the physical and mental risks associated with resorting to unsafe abortion due to the criminalization of abortion (see also Chapter 1, section 1.3.1 on human rights, and Web annex A: Key international human rights standards on abortion, which provides further information as well as references for the above assertions).

In order to identify the impacts of criminalization of abortion on abortion seekers and health workers, a systematic review of studies published between 2010 and 2019 was undertaken, identifying 22 studies conducted in Australia, Brazil, Chile, El Salvador, Ethiopia, Ireland, Mexico, Northern Ireland (United Kingdom), the Philippines, Rwanda, Senegal, the United Republic of Tanzania, Uruguay and Zambia. A summary of the evidence from these studies is presented in Supplementary material 1, EtD framework for Criminalization. The evidence from these studies demonstrated that criminalization delayed access to abortion, including in some cases causing providers to wait until a woman's life was in danger so that abortion could be provided within the legal exceptions to criminal prohibitions. Furthermore, criminalization imposes a range of burdens on women including unnecessary travel and cost, delayed or no access to post-abortion care, distress and stigma. The evidence indicated that criminalization did not impact the decision to have an abortion, prevent women having abortions, or prevent women from seeking information on and referral to services abroad where they can access abortion. Instead, criminalization limits

access to safe and legal abortion, and increases recourse to unlawful and unsafe abortion. When prosecutions take place they may be disproportionately pursued against young, unmarried women and those facing financial hardship and with less access to education. Some countries require health workers to report women and girls when they seek abortion or post-abortion care.

Criminalization can cause health workers to act cautiously, fearing criminal prosecution. As a result, they may be hesitant to provide abortion care even in cases of rape, incest and fatal fetal impairment, when denial of abortion could constitute torture, cruel and inhuman treatment or punishment.

Criminalization contributes to the lower availability of trained abortion providers and a loss of relevant skills in the health workforce. This can have negative effects on health workers who do provide abortion, and can increase bureaucracy within health systems.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO CRIMINALIZATION OF ABORTION

- Availability, accessibility, acceptability and quality must be central to the regulation of sexual and reproductive health (SRH) services.
- Seeking, having, assisting with, or providing abortion to which the pregnant person has provided free and informed consent should never be criminalized.
- States must not require health workers to report cases of women or girls who have had abortions, or whom they suspect of having had abortions.
- Post-abortion care must always be available without the risk of criminal sanction.
- Seeking or providing accurate, evidence-based and non-biased information on abortion must never be criminalized.
- States must take steps, including revising laws, to reduce maternal morbidity and mortality, and to effectively protect women and girls from the physical and mental risks associated with resorting to unsafe abortion.
- Everyone has a right to non-discrimination and equality in accessing SRH services.
- SRH services must be provided in a way that ensures privacy and confidentiality.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

2.2.2 Grounds-based approaches to controlling access to abortion

National laws in most countries permit some abortions, even in settings where abortion is criminalized. Usually abortions will still be permitted under prescribed "grounds", or specific circumstances. The circumstances under which abortion is permitted vary widely across different countries. Some of these circumstances reflect clinical indications (e.g. risk to the health of the pregnant woman or fetal impairment), some relate to the circumstances of conception (e.g. rape), and some relate to socioeconomic circumstances (e.g. economic hardship). Grounds-based approaches are commonly accompanied by gestational age limits, often varying depending on the specific condition under which abortion is permitted. In some countries, abortion is available on request up to a specified gestational age and then limited to specific grounds thereafter.

LAW & POLICY Recommendation 2: Grounds-based approaches

a. Recommend against laws and other regulations that restrict abortion by grounds.

b. Recommend that abortion be available on the request of the woman, girl or other pregnant person.

Remarks:

- Grounds-based approaches to restricting access to abortion should be revised in favour of making abortion available on the request of the woman, girl or other pregnant person.
- Until they are replaced with abortion on request, any existing grounds should be formulated and applied in a manner consistent with international human rights law. This means that the content, interpretation and application of grounds-based law and policy should be revised to ensure human rights compliance. This requires that:
  i. existing grounds are defined, interpreted and applied in a human rights-compliant way;
  ii. abortion is available when carrying a pregnancy to term would cause the woman, girl or other pregnant person substantial pain or suffering, including but not limited to situations where the pregnancy is the result of rape or incest or the pregnancy is not viable;
  iii. abortion is available where the life and health of the woman, girl or other pregnant person is at risk;
  iv. health grounds reflect WHO's definitions of health and mental health (see Glossary); and
  v. there are no procedural requirements to "prove" or "establish" satisfaction of grounds, such as requiring judicial orders or police reports in cases of rape or sexual assault (for sources to support this information, refer to Web annex A: Key international human rights standards on abortion).

Note on updating of the recommendation: This and other law and policy recommendations are not new recommendations. WHO's 2012 *Safe abortion* guidance provided a composite recommendation related to law and policy *(19)*; in this guideline, this has been developed into seven separate recommendations using GRADE methodology.

Rationale

International human rights law requires that abortion be available where carrying a pregnancy to term would cause a woman substantial pain or suffering, or where her life or health is at risk. States may not regulate abortion in a manner that forces women to resort to unsafe abortion and must take steps, including revising laws, to reduce maternal morbidity and mortality, and to effectively protect women and girls from the physical and mental risks associated with unsafe abortion (for further information, please refer to Chapter 1, section 1.3.1[i] and Web annex A: Key international human rights standards on abortion). Grounds-based approaches are often (i) too narrowly defined or (ii) too conservatively applied to ensure abortion is available in these circumstances. The aim to reduce maternal morbidity and mortality, and protect women and girls from the risks associated with unsafe abortion, can be effectively achieved by making abortion available on the request of the pregnant woman or girl.

In order to identify the impacts of grounds-based approaches on abortion seekers and health workers, a systematic review of studies published between 2010 and 2021 was undertaken, identifying 21 studies conducted in Argentina, Australia, Brazil, Chile, Colombia, Ethiopia, Ghana, the Islamic Republic of Iran, Ireland, Israel, Mexico, Rwanda, Thailand, the United Republic of Tanzania, the United Kingdom of Great Britain and Northern Ireland, Uruguay and Zambia. A summary of the evidence from these studies is presented in Supplementary material 1, EtD framework for Grounds-based approaches. The reviewed evidence showed that grounds-based laws contributed to delayed abortion, with delays occurring because of inconsistencies in interpretation or application of health grounds, women waiting for determination of their eligibility for abortion or having their claim that pregnancy resulted from rape

questioned or disbelieved, overly restrictive interpretation of grounds, or disagreement within a medical team about whether a woman satisfies a legal ground. Misinterpretation of the law can also result in denial of abortion. In some cases, health workers waited for a health condition to deteriorate sufficiently to ensure that a woman satisfied a "risk to life" ground, clearly endangering the right to life and potentially violating the right to be free from torture, cruel, inhuman and degrading treatment.

Interpretation of grounds, and thus eligibility for lawful abortion, varies between providers, and providers are not always certain about the law or how it should be applied; interpretation is often narrow and incompatible with human rights law and/or with WHO's definitions of health and mental health, leading to denial of abortion. Women reported significant challenges in accessing care in circumstances where they could not obtain legal support and advice on the permitted grounds. Grounds-based approaches were found to have a particularly negative impact on women facing financial hardship and women with lower educational attainment.

The evidence reviewed for this guidance showed that grounds-based approaches have a disproportionate negative impact on women who seek abortion following rape. These women were often subjected to questioning, protracted delay and bureaucratic processes due to requirements such as reporting the crime to the police or need for a court order, even though it is not human rights compliant to make such reporting or processes a prerequisite for accessing abortion. Even where the law provides that a woman's claim of rape is sufficient to satisfy the legal requirement, providers may require a document or authorization (e.g. court order or police report). In reality this means that obtaining an abortion following rape is laborious and time-consuming. In some cases, delays are so long that women give birth before legal eligibility is determined; in others, women choose instead to resort to unsafe abortion. Thus, "rape grounds" do not satisfy the requirement from international human rights law that abortion be available and accessible in situations of rape. These restrictions also subject the individual to unnecessary trauma, may put them at increased risk from the perpetrator, and may cause women to resort to unsafe abortion.

The evidence also showed that grounds-based approaches that require fetal impairments to be fatal for abortion to be lawful frustrate providers who wish to support patients and leave women no choice but to continue with pregnancy. Being required to continue with a pregnancy that causes significant distress violates numerous human rights. States are obligated to revise these laws to make them compatible with international human rights law.

Under international human rights law, States are required to ensure that women do not have to resort to unsafe abortion. The evidence from the studies described above suggests that grounds-based laws may contribute to an increase in the incidence of unsafe abortion, with people who do not satisfy a ground resorting to unlawful abortion, including unlawful self-management of abortion, some of which may be unsafe. The evidence from the studies also indirectly suggests that grounds-based laws contribute to maternal mortality, because when States shift from a grounds-based approach to permitting abortion on request in the first trimester there is a reduction in maternal mortality (especially for adolescents) as well as a reduction in fertility (birth rates). This suggests a connection between the international obligation to take steps to reduce maternal mortality and morbidity and a shift away from grounds-based approaches.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO GROUNDS-BASED APPROACHES

- Availability, accessibility, acceptability and quality must be central to the regulation of sexual and reproductive health (SRH) services.
- Abortion must be available where carrying a pregnancy to full term would cause a woman substantial pain or suffering, where pregnancy is a result of rape or incest, or where her life or health is at risk.
- States may not regulate abortion in a manner that forces women to resort to unsafe abortion.
- States must take steps, including revising laws, to reduce maternal morbidity and mortality, and to effectively protect women and girls from the physical and mental risks associated with resorting to unsafe abortion.
- Everyone has a right to non-discrimination and equality in accessing SRH services.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

2.2.3 Gestational age limits

Gestational age limits are commonly specified in both liberal and restrictive abortion laws and policies. Imposed through formal law, institutional policy or personal practice by individual health workers, these limits restrict when lawful abortion may be accessed by reference to the gestational age of a pregnancy. In many countries gestational age limits are linked to grounds-based approaches, with gestational age limits varying according to the grounds or circumstances under which abortion is permitted. While methods of abortion may vary by gestational age (see Chapter 3, section 3.4), pregnancy can safely be ended regardless of gestational age. Gestational age limits are not evidence-based; they restrict when lawful abortion may be provided by any method.

International human rights law requires that quality of care be central to the provision and regulation of SRH, and thus that regulation of abortion is evidence-based, scientifically and medically appropriate, and up to date *(3, para. 21)*. Under international human rights law, States may not regulate pregnancy or abortion in a manner that is contrary to their duty to ensure that women and girls do not have to resort to unsafe abortion, and are required to revise their laws accordingly (see Web annex A: Key international human rights standards on abortion).

LAW & POLICY Recommendation 3: Gestational age limits

Recommend against laws and other regulations that prohibit abortion based on gestational age limits.

Note on updating of the recommendation: This and other law and policy recommendations are not new recommendations. WHO's 2012 *Safe abortion* guidance provided a composite recommendation related to law and policy *(19)*; in this guideline, this has been developed into seven separate recommendations using GRADE methodology.

Rationale

In order to identify the impacts of gestational age limits on abortion seekers and health workers, a systematic review of studies published between 2010 and 2020 was undertaken, identifying 21 studies conducted in Australia, Belgium, Mexico, Nepal, South Africa, the United Kingdom and the United States of America (USA). A summary of the evidence from these studies is presented in Supplementary material 1, EtD framework for Gestational age limits. The reviewed evidence demonstrated that – alone or in combination with other regulatory requirements, including grounds-based approaches – gestational age limits delayed access to abortion, especially among women seeking abortions at later gestational ages, women close to the gestational age limit and those living in areas with limited access to clinics. Gestational age limits have been found to be associated with increased rates of maternal mortality and poor health outcomes. International human rights law requires States to reform law in order to prevent unsafe abortion and reduce maternal mortality and morbidity.

The studies also showed that where women requested an abortion and were denied care due to gestational age this could result in the unwanted continuation of pregnancy, especially among women with cognitive impairments or those who presented at 20 weeks' gestation or later. This outcome can be viewed as incompatible with the requirement in international human rights law to make abortion available when carrying a pregnancy to term would cause the woman substantial pain or suffering, regardless of pregnancy viability.

The evidence from these studies showed that women with cognitive impairments, adolescents, younger women, women living further from clinics, women who need to travel for abortion, women with lower educational attainment, women facing financial hardship and unemployed women were disproportionately impacted by gestational age limits. This points to the disproportionate impact of gestational age limits on certain groups of women, with implications for States' obligation to ensure non-discrimination and equality in provision of SRH services.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO GESTATIONAL AGE LIMITS

- Availability, accessibility, acceptability and quality must be central to the regulation of sexual and reproductive health (SRH) services.
- States may not regulate abortion in a manner that forces women to resort to unsafe abortion.
- States must take steps, including revising laws, to reduce maternal morbidity and mortality, and to effectively protect women and girls from the physical and mental risks associated with resorting to unsafe abortion.
- Everyone has a right to non-discrimination and equality in accessing SRH services.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

Chapter 3.
Recommendations and best practice statements across the continuum of abortion care

3.1 Background

As a standard approach to human rights-based health care, all norms, standards and clinical practice related to abortion should promote and protect:

- individuals' health and human rights
- informed and voluntary decision-making
- autonomy in decision-making
- non-discrimination (including intersectional discrimination) and equality
- confidentiality and privacy
- adequate referral mechanisms
- the continuum of care.

New and updated recommendations presented in this guideline were formulated by the expert panels formed for the development of this guideline, including expert human rights advisers (all contributors are listed in Annex 1, and the roles of the groups of contributors are described in Annex 4).[10] The evidence was first systematically reviewed for each prioritized topic and question, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology *(24, 119),* and the level of certainty of that evidence was assessed (i.e. based on the quality of the evidence, including the types and sizes of studies conducted and their various limitations).

The direction (in favour or against) and strength of each recommendation was determined by the panel of experts based on the six substantive criteria of the WHO-INTEGRATE framework as applied to each intervention for the specified population – balance of health benefits and harms; human rights and sociocultural acceptability; health equity, non-discrimination and equality; societal implications; financial and economic considerations; and feasibility and health system considerations – while also taking into account the meta-criterion: quality of evidence *(118)*. The methods are described in full in Annex 4, including the differences in the methods applied for the recommendations relating to law and policy issues (Recommendations 1,2,3,6,7,21,22) compared with the other types of recommendations. The full Evidence-to-Decision (EtD) frameworks are provided online as supplementary materials, and hyperlinked cross-references to these are supplied with the rationale for each new and updated recommendation presented.[11]

10 The expert panels included the Evidence and Recommendations Review Groups (ERRGs) for each of the three domains (Law and policy, Clinical services and Service delivery) and later the Guideline Development Group (GDG), and each phase and each meeting of these groups also involved at least one human rights adviser. For further details of the roles of these groups and the full methodology for the guideline development process, see Annex 4: Methods.

11 EtD frameworks for this guideline can be accessed online: Supplementary material 1: EtD frameworks for law and policy topics https://www.who.int/publications/i/item/9789240039483; Supplementary material 2: EtD frameworks for clinical service topics https://www.who.int/publications/i/item/9789240039483; Supplementary material 3: EtD frameworks for service delivery topics https://www.who.int/publications/i/item/9789240039483.

Recommendations in favour of an intervention are qualified as either strong or weak (with the conditions of use specified for the latter), with the third alternative being a recommendation against the intervention. To clearly indicate the strength and direction of each recommendation, the following wording is used:

- **Recommend** – a strong recommendation in favour of the intervention
- **Suggest** – a weak recommendation in favour of the intervention (requiring additional wording to qualify the recommendation, specifying the conditions of use)
- **Recommend against** – a strong recommendation against the intervention/in favour of the comparison.

New and updated recommendations resulted from the review of the PICO questions (i.e. population, intervention, comparator, outcomes) that had been identified during the scoping meetings for this guideline. While 10 recommendations in this guideline are completely "new" (as labelled in the Executive summary table and in this chapter), updated recommendations are those that had been published in prior WHO guidance but had undergone an updated process of scoping, search and review of relevant evidence, application of the GRADE methodology and reconsideration of the WHO-INTEGRATE criteria for the purposes of this guideline, which may or may not have resulted in any substantive change to the strength, direction or substance of the recommendation *(19, 23, 120)*. Finally, there are some existing recommendations that are carried forward unchanged from previous WHO guidance;[12] in these cases, the topic had not been scoped prior to the development of this guideline and thus no new search or review was conducted or, in some cases, an updated literature search *was* conducted to review the current evidence base but did not lead to any change in the existing recommendation. In particular it should be noted that the 2012 *Safe abortion* guidance provided a composite recommendation related to law and policy; in this guideline, this has been developed into seven separate recommendations using GRADE methodology, but they are not considered to be "new" (i.e. Recommendations 1,2,3,6,7,21,22). A summary table linking the topics covered, the research/PICO questions, the systematic reviews conducted and the recommendation numbers is provided in Annex 7.

3.1.1 Structure of information in this chapter

The information and recommendations in this chapter are presented in sections that reflect the continuum of abortion care and modes of service delivery: (i) services applicable across the continuum of care, (ii) pre-abortion, (iii) abortion, (iv) post-abortion, (v) service-delivery options and self-management approaches. In each section, the following aspects are covered as appropriate: "what" (specific clinical interventions), "who" (which type of health worker can provide the intervention, or self-management), "where" (facility-based versus off-site/ remote service-delivery models/no requirement for on-site versus off-site location), and "how" (service-delivery models, implementation considerations). It should be noted that four recommendations relating to law and policy considerations are presented in the pre-abortion section (section 3.3), while three were presented in Chapter 2, section 2.2.

For each topic covered in this chapter, brief background information is first supplied, followed by the recommendation boxes or tables, providing information on the "what" and the "who" for the intervention in question. Each recommendation is immediately followed by a list of related remarks (if any) from the expert panel that reviewed the evidence in detail, explaining the conditions and context in which the recommendation applies. When appropriate, there is also a section indicating where the intervention can be carried out – in particular whether the intervention must be undertaken at a particular level of health-care facility, or whether there is no such requirement and an "off-site" location (e.g. at home, or other location) would be appropriate if preferred by the individual or if that is the only option available (the "where" is often closely tied to the "who", e.g. tasks provided by pharmacists would be provided in a pharmacy). The remarks for existing unchanged recommendations are repeated from the original cited guidance where still relevant, including revisions as appropriate, based on the results of any relevant updated evidence reviews conducted.

12 Existing recommendations are presented exactly as in previous guidance or with wording updated to use the wording "recommend/ recommend against" for strong recommendations and "suggest" for weak recommendations (previously termed "conditional" recommendations), and reference is provided to the original guidance for further details.

For each of the new/updated recommendations, additional information is presented in the following order after the box presenting the recommendation(s) and remarks:

i. Rationale: This includes a brief summary of the type and extent of the evidence included in the review(s) that form the evidence base, and an explanation of the rationale for the direction (for or against) and strength of the recommendation (strong or weak), with reference to the key judgements on effects of the intervention (benefits and risks), the level of certainty of the evidence and any relevant information on the other criteria of the WHO-INTEGRATE framework. Any additional evidence of potential harms or unintended consequences is highlighted. Such considerations may have been derived from studies and additional evidence that may not directly address the PICO question but provide pertinent information in the absence of direct evidence. This may be extracted from single studies, systematic reviews or other relevant sources.

ii. Implementation considerations: Points to bear in mind regarding implementation, including those relating to "how".

Finally, in each topic section, a box is presented listing any key human rights considerations relevant to the recommendation or broader topic, as well as a box providing cross-references and hyperlinks to related topics within this guideline.

Full details for all related PICO questions can be found in Annexes 8, 9 and 10, and the summaries of the evidence (i.e. from the systematic reviews; listed in Annex 7) and the EtD frameworks relevant to each new or updated recommendation are made available online as supplementary material.

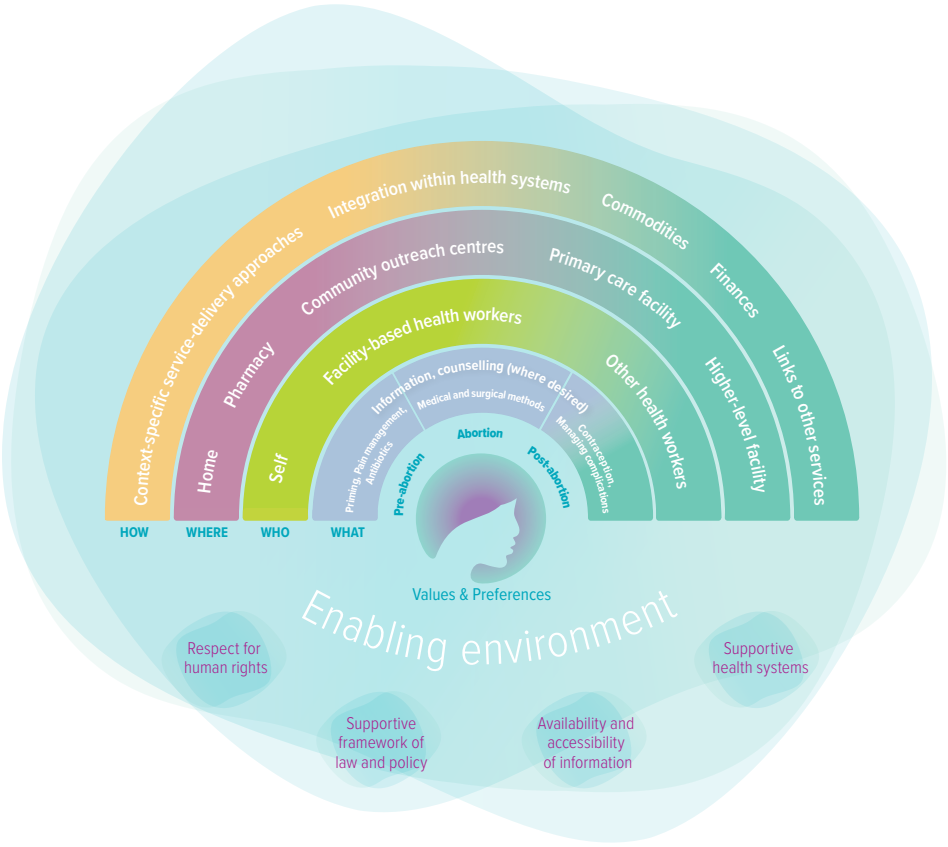
3.1.2 Underlying principles and assumptions relating to recommendations on health worker roles

Health workers are all people engaged in actions whose primary intent is to enhance health *(100)*. This includes all categories of health workers listed and described in Annex 5, from community health workers all the way through to specialist medical practitioners (e.g. obstetricians and gynaecologists), and including traditional and complementary medicine professionals (i.e. non-allopathic physicians). Abortions can be done safely using tablets (medical abortion) or a simple outpatient procedure, such that most no longer require a specialist or even a general practice doctor. The recommendations presented in this guideline provide guidance on how to involve a wider range of health workers and pregnant individuals themselves in the provision or self-management of abortion care, to encourage optimization of the available health workforce, address health system shortages of specialized health-care professionals, reduce costs and improve affordability, improve equity and equality in access to health care and increase the acceptability of health services for those who need them.

The following principles and assumptions apply to all health workers:

- The recommendations are appropriate for and intended for all resource settings, i.e. high-, middle- and low-resource settings.
- The recommendations refer to a range of types of health workers who can safely, effectively and satisfactorily perform some or all of the specific abortion-related tasks mentioned. The options for who can perform the same task are intended to be inclusive and do not imply either a preference for or an exclusion of any particular type of health worker. The choice of health worker for a specific task will depend upon the needs, preferences and conditions of the individual, and the local context.
- Training of health workers must ensure that they have the competencies to provide good-quality, gender-sensitive care in accordance with national standards and guidelines and human rights. Ensuring quality abortion care requires ongoing supervision, quality assurance, monitoring and evaluation, as well as access to the necessary equipment and commodities.
- It is assumed that any health worker discussed in this guideline has the basic training required of that type of health worker (and in the case of individuals acting as their own provider – i.e. self-management – that they have the appropriate information and understanding). In addition, the recommendations all assume that health workers who are in a category that is recommended or suggested to perform specific tasks will have received the appropriate task-specific training and information prior to performing that task.

3.2 Services applicable across the continuum of care



This section covers information, counselling and linkage to additional care or services, any or all of which may be needed or desired before, during and/or after the abortion procedure or process.

The provision of scientifically accurate and easy-to-understand information to all women undergoing an abortion, and non-directive voluntary counselling to anyone who requests it, is a core element of good-quality, human rights-compliant abortion services (see Chapter 1, section 1.3.2). The provision of information and counselling (where desired), as well as access or referrals to other related services, starts pre-abortion but should continue across the continuum of care. In addition, everyone should be provided with all the necessary information to make an informed decision regarding the use of contraception.

What

3.2.1 Providing information

Abortion-related information for individuals considering or seeking abortion or in the post-abortion period should include:

- the available options for abortion methods and pain management;
- information related to free and informed consent;
- what will occur before, during and after the abortion procedure or process, including any tests and/or pain relief that may be needed and any aspects of the care that could be self-managed if desired, with or without remote support;
- what the individual is likely to experience during and after the abortion procedure or process, and how long the procedure/process and the recovery are likely to take;

- when normal activities can be resumed, including sexual intercourse;
- how to recognize potential side-effects and symptoms of ongoing pregnancy (which may persist temporarily even when abortion has been successful, or which may indicate failure of the abortion), and other medical reasons to return for follow-up care, including complications such as prolonged heavy bleeding or fever; and
- when, where and how to access follow-up care or additional services that may be desired such as counselling (section 3.2.2), contraception (see section 3.5.4) and other services (section 3.2.3).

Who

SERVICE DELIVERY Recommendation 4: Provision of information on abortion care

Type of health worker	Recommendation	Rationale[a]
Community health workers (CHWs)	**Recommend**	Provision of health promotion interventions by CHWs is generally well accepted and feasible in many contexts where there is a strong CHW programme (moderate-certainty evidence). The potential to expand equitable access to information and quality abortion care by equipping CHWs to provide essential information on abortion is high.
Pharmacy workers	**Suggest** Condition: In contexts where the pharmacy worker is under the direct supervision of a pharmacist and there is access or referral to appropriate health services.	Insufficient direct evidence was found for the safety, effectiveness and acceptability of this option. However, in many contexts, pharmacy workers are often consulted by women seeking advice on how to deal with delayed menstruation (moderate-certainty evidence). Although the effectiveness of training interventions with pharmacy workers is uncertain, the potential benefits of equipping them to provide essential information outweighs the potential harms of them not providing information or providing incorrect information.
Pharmacists	**Recommend**	Pharmacists are qualified to provide information about the medicines they dispense. Evidence was found for the effectiveness of provision of education and counselling on chronic illnesses by pharmacists (low to moderate certainty). In many contexts, pharmacists are often consulted by women seeking advice on how to deal with delayed menstruation (moderate-certainty evidence).
Traditional and complementary medicine professionals **Auxiliary nurses/auxiliary nurse midwives (ANMs)** **Nurses** **Midwives** **Associate/advanced associate clinicians** **Generalist medical practitioners** **Specialist medical practitioners**	**Recommend**	Within their typical scope of practice,[b] therefore no assessment of the evidence was conducted.

Source: Recommendation from WHO (2015) *(23)*.

Note on updating of the recommendation: This was an existing recommendation for which evidence relating to pharmacy workers was reviewed using GRADE methodology, since that was the only category of health worker that didn't already have a strong recommendation ("recommend") for this task. After review, no change was made to the existing weak recommendation ("suggest"). A summary of the evidence is presented in Supplementary material 3, EtD framework on Information provision by pharmacy workers.

[a] For this and all health worker recommendations, given the limited evidence for many of the health worker–task combinations, the discussions of the expert panel focused on the competency framework in WHO's 2011 publication, *Sexual and reproductive health: core competencies in primary care (121)*, which provides information on the competencies (including skills and knowledge) required for each task, and also the WHO-INTEGRATE criteria, in particular on the feasibility, equity and acceptability of the intervention and women's values and preferences.

[b] For typical scope of work/practice, please refer to Annex 5: Health worker categories and roles.

Where

There is no requirement for location (on-site vs off-site), but privacy and confidentiality should be ensured during the provision of information, with particular attention needed to this requirement in the off-site (out-of-facility) settings, such as pharmacies and community-based sites, where infrastructure and procedures may make this more challenging.

How

Implementation considerations

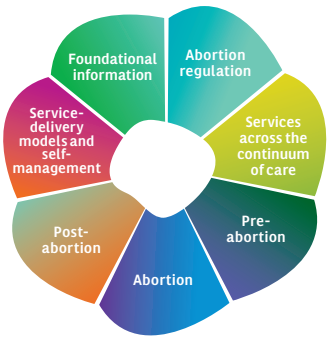
- Different modalities exist for the provision of information on abortion, e.g. remote access via hotlines and telemedicine, and through approaches such as harm reduction and community-based outreach (see section 3.6) as well as in-person interactions with health workers.
- Information should be accessible and understandable, including formats catering to low-literacy and differently abled populations.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO THE PROVISION OF INFORMATION

- Informed consent requires the provision of complete and accurate, evidence-based information.
- Accurate information on abortion must be available to individuals in a way that respects privacy and confidentiality.
- The right to refuse such information when offered must be respected.
- Abortion information should be available to all persons without the consent or authorization of a third party. This includes abortion information being available to adolescents without the consent or authorization of a parent, guardian or other authority.
- Information must be non-discriminatory and non-biased and presented in a respectful manner. It should not fuel stigma or discrimination.
- Dissemination of misinformation, withholding of information and censorship should be prohibited.
- Information should be acceptable to the person receiving it and of high quality; it should be presented in a way that can be understood and it must be accurate and evidence based.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

Links to related topics/recommendations



All recommendations related to law and policy (Recommendations 1,2,3,6,7,21,22)

Informed consent (section 1.3.1: Human rights)

Availability and accessibility of information (section 1.3.2)

What

3.2.2 Offering and providing counselling

Some individuals may wish to receive counselling before or after an abortion. Counselling is more than information provision. It is a focused, interactive process through which a person voluntarily receives support, information and non-directive guidance from a trained person *(122)*, in an environment that is conducive to openly sharing thoughts, feelings, perceptions and personal experiences. In addition to the specific knowledge about abortion services and care required for both information provision and counselling, the latter also requires specialized counselling training. Counselling is a core element of provision of abortion and post-abortion care.

When offering and providing counselling, it is essential to apply the following guiding principles:

- ensure that the individual is requesting the counselling and make it clear that counselling is not required;
- ensure privacy and confidentiality;
- ask the individual what they want or need, what their concerns are, given them the time they need, and actively listen to their expressed needs and preferences;
- highlight relevant information during the counselling session (such as the information provided in section 3.2.1);
- communicate information respectfully and non-judgementally, and in a manner understandable to/tailored to the individual;
- support the individual and check to ensure they receive adequate responses to their questions and that they understand the information provided;
- present all suitable options tailored to individual's needs, while avoiding imposing one's personal values and beliefs onto them; and
- make it clear that the individual will need to decide what services to receive.

Who

SERVICE DELIVERY Recommendation 5: Provision of counselling

Type of health worker	Recommendation	Rationale[a]
Community health workers (CHWs)	**Recommend**	Insufficient direct evidence was found for the safety, effectiveness or acceptability of this option, but indirect evidence did show that health promotion interventions by CHWs are generally well accepted, effective and feasible in many contexts, and that CHWs are often intermediaries between the health system and women seeking abortion-related care (moderate-certainty evidence). The expert panel affirmed the feasibility of this option and its ability to expand equitable access to quality abortion care.
Pharmacy workers	**Suggest** Condition: Balanced counselling is provided (i.e. about both medical and surgical methods) and there is access or referral to appropriate health services should the woman choose a surgical method.	Although no direct evidence was found on the safety, effectiveness or acceptability of this option, the skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] The expert panel affirmed the feasibility of this option and its ability to expand equitable access to quality abortion care.
Pharmacists	**Suggest** Condition: Balanced counselling is provided (i.e. about both medical and surgical methods) and there is access or referral to appropriate health services should the woman choose a surgical method.	Although no direct evidence was found on the safety, effectiveness or acceptability of this option, the skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.a Pharmacists are qualified to provide information about the medicines they dispense. There is evidence for the effectiveness of provision of counselling on the management of chronic illnesses by pharmacists (low certainty evidence). In many contexts, pharmacists are often consulted by women seeking advice on how to deal with delayed menstruation (moderate-certainty evidence). Pharmacists have been recommended to provide medical abortion at < 12 weeks across all three subtasks (Recommendation 28). Therefore, the expert panel affirmed that it is feasible for pharmacists to provide balanced counselling on abortion, including surgical options.
Traditional and complementary medicine professionals	**Recommend**	Although no direct evidence was found on the safety, effectiveness or acceptability of this option, the skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a]
Auxiliary nurses/ANMs **Nurses**	**Recommend**	Counselling is a core competency for these health workers[a] and this task is within their typical scope of practice.[b]
Midwives	**Recommend**	Counselling is a core competency for midwives[a] and this task is within their typical scope of practice.[b]
Associate/advanced associate clinicians	**Recommend**	Counselling is a core competency for these clinicians[a] and this task is within their typical scope of practice.[b]
Generalist medical practitioners **Specialist medical practitioners**	**Recommend**	Within their typical scope of practice,[b] therefore no assessment of the evidence was conducted.

Source: Recommendation updated from WHO (2015) *(23)*.

Note on updating of the recommendation: This was an existing recommendation for which evidence relating to traditional and complementary medicine professionals, pharmacists, pharmacy workers and community health workers was reviewed using GRADE methodology, since the other health workers already had a strong recommendation for this task. After review, the recommendations were upgraded for all four of those health worker categories, from "recommend against" to "suggest" for pharmacists and pharmacy workers, and from "suggest" to "recommend" for traditional and complementary medicine professionals and CHWs. A summary of the evidence is presented in Supplementary material 3, EtD framework on Pre- and post-abortion counselling.

[a] For this and all health worker recommendations, given the limited evidence for many of the health worker–task combinations, the discussions of the expert panel focused on the competency framework in WHO's 2011 publication, *Sexual and reproductive health: core competencies in primary care (121)*, which provides information on the competencies (including skills and knowledge) required for each task, and also the WHO-INTEGRATE criteria, in particular on the feasibility, equity and acceptability of the intervention and women's values and preferences.

[b] For typical scope of work/practice, please refer to Annex 5: Health worker categories and roles.

Where

There is no requirement for location (on-site vs off-site), but privacy and confidentiality should be ensured during counselling, with particular attention needed to this requirement in the off-site (out-of-facility) settings, such as the pharmacies and community-based sites, where infrastructure and procedures may make this more challenging.

How

Implementation considerations

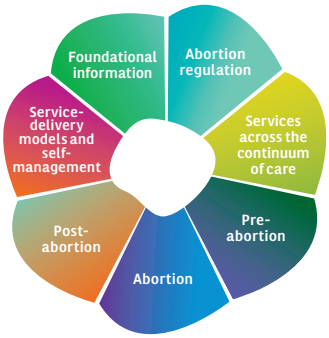
- Counselling can be provided to those seeking abortion services but also jointly to their partners, family members or other individuals, should the woman wish them to be present.
- While counselling should be made available and accessible, it should always be voluntary for women to choose whether or not they want to receive it.
- Counselling should be person-centred and may need to be tailored according to the needs of the individual; young people, survivors of sexual and gender-based violence or members of marginalized groups may have different information or counselling requirements.
- The content of and approach to counselling will need to be adjusted depending on the reason for seeking abortion services (e.g. induced abortion, intrauterine fetal demise [IUFD], fetal anomaly). Therefore, it is important for the counsellor to be aware of and sensitive to the individual's situation and needs.
- Different service-delivery models exist for pre- and post-abortion counselling, e.g. remote access via hotlines and telemedicine and through approaches such as harm reduction counselling and community-based outreach.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO COUNSELLING

- Counselling must be entered into freely and voluntarily, i.e. it should not be mandatory. The right to refuse counselling when offered must be respected.
- Where provided, counselling must be available to individuals in a way that respects privacy and confidentiality.
- Counselling must be acceptable and of good quality, i.e. it must be provided in a way that can be understood by the recipient and it must be accurate and evidence based.
- Counselling must be non-discriminatory and non-biased.
- Dissemination of misinformation, withholding of information, and censorship should be prohibited.
- Counselling should be available to all persons without the consent or authorization of a third party. This includes counselling being available to adolescents without the consent or authorization of a parent, guardian or other authority.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

Links to related topics/recommendations



All recommendations related to law and policy (Recommendations 1,2,3,6,7,21,22)

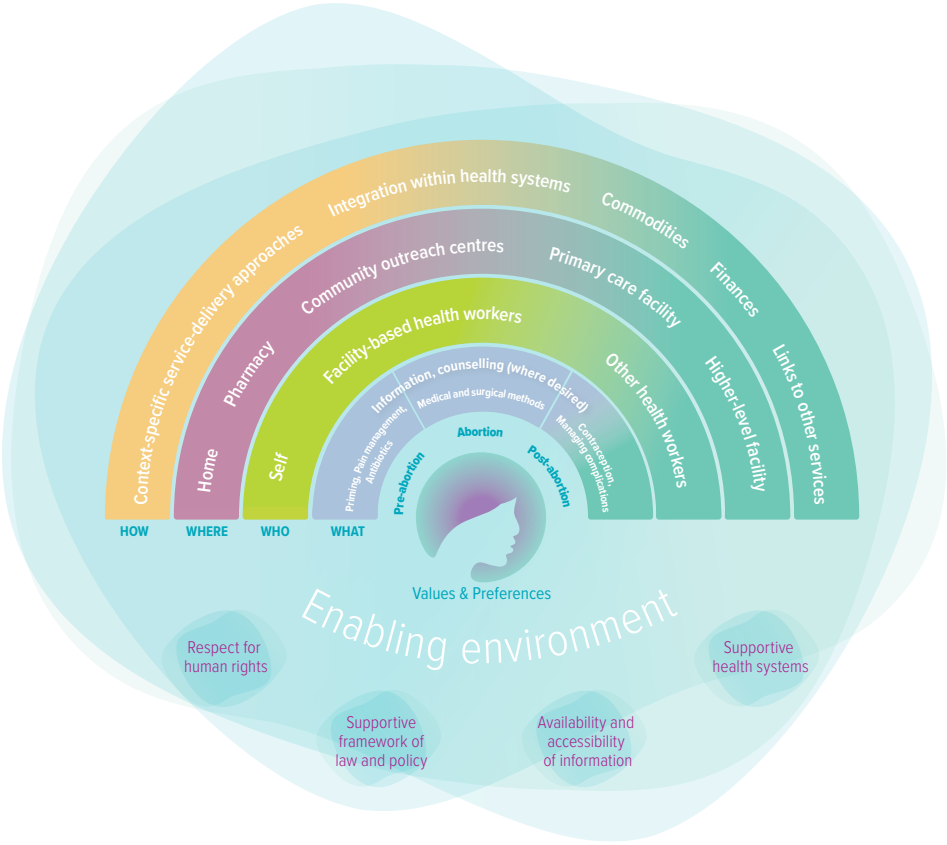
Information provision (section 3.2.1)

Recommendations 41, 42 and 43 on post-abortion contraception

3.2.3 Links to additional services

Individuals seeking abortion may require additional services *(122)*. As needed, provide management or referral to other service providers for other health conditions or urgent needs. This includes facilitating linkages (access or referrals) to counselling and testing for sexually transmitted infections including HIV, contraception where desired, and support services for survivors of gender-based violence.

3.3 Pre-abortion



This section includes information and recommendations first on the issues of mandatory waiting periods and third-party authorization, followed by recommendations on Rh isoimmunization, antibiotic prophylaxis, determination of gestational age of pregnancy, pain management, and cervical priming prior to surgical abortion, and finally also recommendations on the issues of restrictions on health workers who can provide abortions and conscientious objection.

3.3.1 Mandatory waiting periods imposed by States, health-care facilities or health workers

In a number of countries, health-care facilities or health workers require women to wait a specified amount of time between requesting and receiving an abortion. These imposed delays are known as mandatory waiting periods. In some cases, women must also receive (sometimes biased) counselling or advice (see sections 3.2.1 and 3.2.2), attend the facility at the start and end of the waiting period, and/or undergo mandated ultrasound during these waiting periods (see section 3.3.5, Recommendation 10 on pre-abortion ultrasound).

LAW & POLICY Recommendation 6: Mandatory waiting periods

Recommend against mandatory waiting periods for abortion.

Note on updating of the recommendation: This and other law and policy recommendations are not new recommendations. WHO's 2012 *Safe abortion* guidance provided a composite recommendation related to law and policy *(19)*; in this guideline, this has been developed into seven separate recommendations using GRADE methodology.

Rationale

In order to identify the impacts of mandatory waiting periods on abortion seekers and health workers, a systematic review of studies published between 2010 and 2020 was undertaken, identifying 33 studies all conducted in the USA. A summary of the evidence from these studies is presented in Supplementary material 1, EtD framework on Mandatory waiting periods. The evidence reviewed showed that mandatory waiting periods delayed access to abortion, sometimes to the extent that women's access to abortion or choice of abortion method was restricted in that setting.

The evidence also indicates that mandatory waiting periods increase the cost of abortion and they may make abortion unattainable, resulting in the continuation of pregnancy against the wishes of the abortion seeker, especially among women with fewer resources, adolescents, younger women, those from racial or ethnic minorities and those who need to travel further for an abortion.

Among those seeking an abortion, the studies showed that mandatory waiting periods were experienced negatively, as a restriction on their access to abortion. For some women, the logistical and economic challenges of completing a mandatory waiting period, such as the need for time off work or education, extra travel and/or childcare, meant that they were forced to disclose their pregnancy to others even though international human rights law requires States to ensure that SRH services are provided in a way that ensures privacy and confidentiality. The evidence did not establish any benefits of mandatory waiting periods for women.

For health-care facilities, mandatory waiting periods increase staffing costs and logistical difficulties, by mandating additional visits or interventions outside of standard clinical practice (e.g. unnecessary ultrasound, specific counselling that is not evidence-based).

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO MANDATORY WAITING PERIODS

- Availability, accessibility, acceptability and quality must be central to the regulation of sexual and reproductive health (SRH) services.
- States may not regulate abortion in a manner that forces women to resort to unsafe abortion.
- Everyone has a right to non-discrimination and equality in accessing SRH services.
- SRH services must be provided in a way that ensures privacy and confidentiality.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

3.3.2 Third-party authorization for abortion

Third-party authorization requirements exist where there is a requirement imposed by law or policy, or in practice, that a party other than the pregnant woman must authorize an abortion, even though other applicable legal requirements for lawful abortion have been met (e.g. grounds or gestational age limits, see sections 2.2.2 and 2.2.3). Common third parties required to provide authorization include a parent, guardian, spouse, partner, health worker, health authority or judicial authority. Third-party authorization requirements operate without regard to whether the person who seeks to end a pregnancy has capacity to consent to medical treatment.

Regardless of whether third-party authorization requirements apply, informed consent of the person availing of abortion is a prerequisite for the provision of abortion (refer to Chapter 1, section 1.3.1[v] for information on free and informed consent, and also Web annex A: Key international human rights standards on abortion).

LAW & POLICY Recommendation 7: Third-party authorization

Recommend that abortion be available on the request of the woman, girl or other pregnant person without the authorization of any other individual, body or institution.

Remark:

- While parental or partner involvement in abortion decision-making can support and assist women, girls or other pregnant persons, this must be based on the values and preferences of the person availing of abortion and not imposed by third-party authorization requirements.

Note on updating of the recommendation: This and other law and policy recommendations are not new recommendations. WHO's 2012 *Safe abortion* guidance provided a composite recommendation related to law and policy *(19)*; in this guideline, this has been developed into seven separate recommendations using GRADE methodology.

Rationale

In order to identify the impacts of third-party authorization requirements on abortion seekers and health workers, systematic reviews of studies published between 2010 and 2019 were undertaken. A total of 32 studies were included, conducted in Hong Kong Special Administrative Region (China), Turkey and the USA. A summary of the evidence from these studies is presented in Supplementary material 1, EtD framework for Third-party authorization. The reviewed evidence showed that third-party authorization requirements were associated with delays to abortion. For minors, these delays were sometimes, although not always, reduced when judicial authorization was used to bypass parental authorization requirements. However, bypass can be burdensome and time-consuming, and minors from ethnic minorities or of lower socioeconomic status are significantly more likely to need to use it. The evidence showed that adolescents and women sought to bypass parental/spousal authorization requirements to avoid anticipated violence, reproductive coercion and family disharmony.

A number of studies described "parental notification" or "parental involvement" rather than using the term "parental authorization". As these terms may encompass parental authorization requirements and mandate the disclosure of the fact that a minor is seeking an abortion, thus creating opportunities for parental veto, these studies were included within the evidence base for this topic. These studies reinforced the associations between mandated parental involvement (including authorization) and barriers to accessing abortion (including delay, continuation of pregnancy, anticipated interpersonal violence or exploitation, reproductive coercion, family disharmony and recourse to unsafe abortion).

Third-party authorization requirements are incompatible with international human rights law, which provides that States may not restrict women's access to health services on the ground that they do not have the authorization of husbands, partners, parents or health authorities, because they are unmarried, or because they are women. Therefore, the evidence underlines the importance of the requirements stated in international human rights law that SRH services be provided in a way that respects and maintains women's and girls' privacy and confidentiality, that States protect women and girls seeking abortion, and that States recognize adolescents' evolving capacity (see section 1.3.1[v], Box 1.2 and Web annex A: Key international human rights standards on abortion).

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO THIRD-PARTY AUTHORIZATION

- States may not restrict women's access to health services on the ground that they do not have the authorization of husbands, partners, parents or health authorities, because they are unmarried, or because they are women.
- Sexual and reproductive health (SRH) services must be provided in a way that ensures privacy and confidentiality.
- States may not regulate abortion in a manner that forces women to resort to unsafe abortion.
- States must take steps, including revising laws, to reduce maternal morbidity and mortality, and to effectively protect women and girls from the physical and mental risks associated with resorting to unsafe abortion.
- Everyone has a right to privacy and confidentiality in accessing SRH services.
- Availability, accessibility, acceptability and quality must be central to the regulation of SRH services.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

3.3.3 Rh isoimmunization

Rh isoimmunization is a type of haemolytic disease of the fetus and newborn (HDFN). Specifically, it is the development of antibodies against the Rh antigens on the surface of red blood cells of another individual (i.e. one's own fetus) *(123)*.

What

CLINICAL SERVICES Recommendation 8 (NEW):
Rh isoimmunization for abortion at gestational ages < 12 weeks

For both medical and surgical abortion at < 12 weeks: **Recommend against** anti-D immunoglobulin administration.

Remark:

- Standard of care applies for anti-D administration at gestational ages ≥ 12 weeks.

Who

Not applicable.

Rationale

A systematic review assessed the effect of routine anti-D administration among unsensitized Rh-negative individuals undergoing an abortion. There are few studies examining Rh isoimmunization in unsensitized Rh-negative individuals seeking abortion before 12 weeks of gestation. Only two studies, conducted in Israel and the USA, met the inclusion criteria for the review, both published in 1972 *(124, 125)*. A summary of the evidence is presented in Supplementary material 2, EtD framework on Rh isoimmunization.

The evidence on the effectiveness of the intervention may favour the intervention, because fewer women in the intervention group (anti-D administration) had antibody formation after the initial pregnancy compared to the women in the comparison group (no anti-D), and no harms (undesirable effects) of the intervention were noted. However, after consideration of the resources required, cost-effectiveness and feasibility of administering anti-D, as well as the very low certainty of the evidence on effectiveness, the expert panel concluded that overall, the evidence does not favour the intervention and decided to recommend against it for gestational ages < 12 weeks, rather than < 9 weeks, as mentioned in the 2012 guidance *(19)*. The justification for this new recommendation is outlined in the following points: (i) The presence of fetal blood in Rh-negative women at early gestational ages does not necessarily correlate with development of Rh alloimmunization and if we apply the results of an experimental study to this scenario, then theoretically there is zero chance of antibody formation if the Rh-negative woman is exposed to the Rh antigen of the fetal blood cells *(126)*; (ii) A study comparing Rh alloimmunization rates in two countries demonstrated the safety of not treating Rh-negative women with spontaneous abortion under 10 weeks of gestation *(127)*; (iii) WHO only recommends antenatal prophylaxis with anti-D immunoglobulin in non-sensitized Rh-negative pregnant women at 28 and 34 weeks of gestation to prevent RhD alloimmunization in the context of rigorous research *(128)*.

How

Implementation considerations

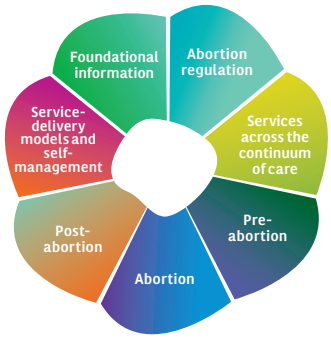
- Routine laboratory testing, including Rh testing, is not a requirement for abortion services at any gestational age.
- Determination of Rh status and the offer of anti-D prophylaxis are not considered prerequisites for early medical abortion at gestational ages before 12 weeks.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO Rh ISOIMMUNIZATION

- States must ensure access to up-to-date scientific technologies necessary for women.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

Links to related topics/recommendations



All recommendations related to law and policy (Recommendations 1,2,3,6,7,21,22)

3.3.4 Antibiotic prophylaxis

The role of antibiotics is pertinent for surgical abortion. The presence of infection in the lower reproductive tract at the time of surgical abortion is a risk factor for post-abortion reproductive tract infections *(129)*. Provision of antibiotics at the time of abortion (prophylaxis) is to prevent such complications after a surgical abortion.

What

CLINICAL SERVICES Recommendation 9: Antibiotic prophylaxis for surgical and medical abortion

a. For surgical abortion, regardless of the individual's risk of pelvic inflammatory infection: **Recommend** appropriate prophylactic antibiotics pre- or perioperatively.

b. For medical abortion: **Recommend against** the use of prophylactic antibiotics.

Remark:

- Lack of antibiotics should not limit access to abortion services.

Source: Recommendation 11 carried forward from WHO (2012) *(19)*. The wording has been revised to use the word "recommend" to clarify that these are strong recommendations, and the former wording "routine use" (in 9b) has been changed to "use", following discussion among the expert panel.

How

Implementation consideration

- Single-dose administration of nitroimidazoles, tetracyclines or penicillins has been shown to be effective when used as prophylactic antibiotics for surgical abortion.

Who

For information regarding which health workers can provide this intervention, refer to Recommendation 24 on vacuum aspiration (< 14 weeks) and Recommendation 26 on dilatation and evacuation (D&E) (≥ 14 weeks).

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO ANTIBIOTIC PROPHYLAXIS

- States must ensure adequate access to essential medicines in an affordable and non-discriminatory manner.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

Links to related topics/recommendations



Recommendations 24 (on vacuum aspiration) and 26 (on D&E)

3.3.5 Determining gestational age of pregnancy

Determining the gestational age of the pregnancy is a preliminary step before selecting the most appropriate abortion method. There are multiple ways to determine gestational age. Pregnancy dating can be done based on last menstrual period (LMP) alone or in combination with the use of a validated tool (i.e. mobile app, checklist or pregnancy wheel), thus enabling the option of self-assessment of gestational age. When LMP is uncertain, gestational age can be determined by way of a clinical/physical examination (i.e. bimanual pelvic and abdominal examination) or by ultrasound, both of which are used to assess the size of the uterus, estimated in weeks, that corresponds to a pregnant uterus of the same gestational age dated by LMP. In general, the least invasive method that is appropriate in the circumstances and available in the setting should be used.

Routine screening for ectopic pregnancy is not necessary prior to medical abortion. The incidence of ectopic pregnancy is lower in abortion seekers then in the general population *(130)*. Even for continuing pregnancies, WHO only recommends one ultrasound scan before 24 weeks of gestation (early pregnancy ultrasound) to estimate gestational age, improve detection of fetal anomalies and multiple pregnancies, reduce induction of labour for post-term pregnancy, and improve a woman's pregnancy experience *(128)*.

What

CLINICAL SERVICES Recommendation 10: Pre-abortion ultrasound scanning

For both medical and surgical abortion: **Recommend against** the use of ultrasound scanning as a prerequisite for providing abortion services.*

Remark:

- Legal regulation that limits the availability of abortion by gestational age may require or result in ultrasounds being used to verify gestational age prior to abortion, even though this is not necessary from a clinical perspective. Removing legal gestational age limits on access to abortion (see Recommendation 3) should result in unnecessary pre-abortion ultrasound being avoided, and increase the availability of abortion in settings where ultrasound is difficult to access.

* On a case-by-case basis, there may be clinical reasons for using ultrasound scanning prior to abortion.

Source: Recommendation 12 carried forward from WHO (2012) *(19)*. The wording has been revised to use the word "recommend against" to clarify that this is a strong recommendation against the intervention, and the former wording "routine" has been changed to use "prerequisite" for greater clarity, following discussion among the expert panel.

Who

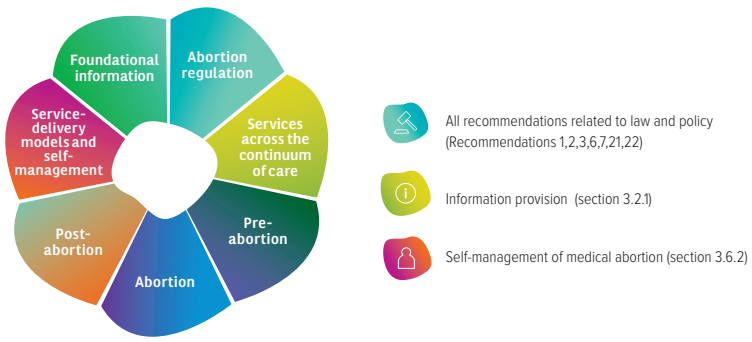
Not applicable.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO DETERMINING THE GESTATIONAL AGE OF PREGNANCY

- Any information on gestational age should be complete, accurate and evidence based. It should not be provided with the aim of directing decision-making.
- As a form of health information, information on gestational age should be of high quality, accurate and accessible. It should be presented a respectful manner and acceptable to the person receiving it. It should not fuel stigma and discrimination.
- Where information on gestational age is made available, it must be provided to individuals in a way that respects privacy and confidentiality.
- The right to refuse such information when offered must be respected. This includes the right to refuse to view ultrasound images.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

Links to related topics/recommendations



3.3.6 Pain management for abortion

There is generally some degree of pain with abortion. The need for pain management increases with gestational age. The degree of the pain varies with the age, parity, prior vaginal delivery, history of dysmenorrhoea and anxiety/fear level of the woman undergoing the abortion *(131-134).* A shorter procedure time has been associated with less pain *(131).* Neglecting this important element of care needlessly increases anxiety, discomfort and pain, thereby seriously compromising the quality of care and potentially increasing the difficulty of performing the procedure. Pain management should always be available and it should be administered in advance, in anticipation of the onset of pain, or provided to the woman in case it is needed for later use at home.

What

CLINICAL SERVICES Recommendations 11–14: Pain management for surgical abortion and for prior cervical priming

11. For pain management for surgical abortion at any gestational age:

a. Recommend that pain management should be offered routinely (e.g. non-steroidal anti-inflammatory drugs [NSAIDS]) and that it should be provided to those who want it; and

b. Recommend against the routine use of general anaesthesia**.**

NEW RECOMMENDATIONS BELOW INDICATE PAIN MANAGEMENT THAT IS *ADDITIONAL* TO NSAIDS.

12. (NEW) For pain management for surgical abortion at < 14 weeks:

a. Recommend the use of a paracervical block; and

b. Suggest that the option of combination pain management using conscious sedation[13] plus paracervical block should be offered, where conscious sedation is available.

13. (NEW) For pain management for cervical priming with osmotic dilators prior to surgical abortion at ≥ 14 weeks:

Suggest the use of a paracervical block. (See also section 3.3.7 on cervical priming prior to surgical abortion.)

Remark:

- For cervical priming (Recommendation 13), additional pain medication can be considered, such as the use of intravaginal gel.

14. (NEW) For pain management for surgical abortion at ≥ 14 weeks:

a. Recommend the use of a paracervical block; and

b. Suggest that the option of combination pain management using conscious sedation plus paracervical block should be offered, where conscious sedation is available.

Source: Recommendation 11 updated from WHO (2012) *(19).* Recommendations 12–14 are new.

Note on updating of the recommendation: Recommendation 11a was previously published as part of Recommendation 14 in WHO (2012) *(19),* and evidence for it was reviewed using GRADE methodology. After review, in this updated version, we have split the first part of the original recommendation wording to apply to surgical abortion here (11a) and medical abortion in a separate recommendation (15) and revised the wording to mention provision, and we have separated and revised the wording of the second part of the recommendation referring to general anaesthesia (Recommendation 11b).

13 Conscious sedation is also known as intravenous (IV) sedation or moderate sedation. See definition in Glossary.



In a health-care facility.

Rationale for Recommendations 11b and 12

An update of an existing Cochrane Review[14] served as the evidence base for assessing the pain management regimens for surgical abortions at < 14 weeks of gestation. Thirty studies reporting on pain management for surgical abortion were identified by the search strategy. Of these studies, nine studies – conducted in France, the Islamic Republic of Iran, Norway, Turkey and the USA – are the focus of the evidence base for these recommendations. Six studies compared the paracervical block (PCB) with a placebo. One study compared the PCB with general anaesthesia. Two studies compared conscious sedation[15] plus PCB versus PCB alone. A summary of the evidence is presented in Supplementary material 2, EtD framework for Pain management for surgical abortion < 14 weeks.

Combination pain management using conscious sedation plus PCB: Mean pain scores were lower in the group of women who received conscious sedation and PCB compared with the women who received a PCB alone, based on moderate-certainty evidence. In addition, satisfaction with their pain management was higher among the former group of women, based on high-certainty evidence.

Paracervical block (PCB): Both with and without conscious sedation, mean pain scores were lower in the group of women who received a PCB compared with the women who received a placebo, based on moderate-certainty evidence. Fewer women required additional analgesic medication, based on high-certainty evidence, and satisfaction in the former group of women was high, based on moderate-certainty evidence.

General anaesthesia: Pain scores were lower in the group of women who received general anaesthesia compared with PCB alone, based on moderate-certainty evidence. However, discussions on the resources required, cost effectiveness, feasibility and equity related to administering general anaesthesia resulted in a conclusion that did not favour the intervention. In addition, Recommendation 11b aligns with the existing statement that vacuum aspiration does not require an operating theatre *(19)*.

Rationale for Recommendations 13 and 14

A systematic review assessed the pain management regimens for surgical abortions at gestational ages ≥ 14 weeks. Three studies reporting on pain management for D&E were identified by the search strategy, all of which focused on pain management during the cervical priming prior to the surgical procedure. A summary of the evidence is presented in Supplementary material 2, EtD framework for Pain management for surgical abortion ≥ 14 weeks.

Mean pain scores were lower in the group of women who received a PCB compared with the women who received a placebo, based on high-certainty evidence. Satisfaction in the former group of women was high, based on moderate-certainty evidence. An intravaginal gel can be used as an alternative method of pain control; more women had a lower pain score after receiving the gel compared with those who had a PCB, based on low-certainty evidence. Cervical priming was performed with laminaria. Discussions on the values and preferences of women regarding pain management during surgical abortion, and on the resources required and the feasibility of PCB administration resulted in a determination that favoured the intervention.

No studies were identified that focused on pain management for the D&E procedure. Therefore, the expert panel came to a consensus to align the recommendations to those for pain management for surgical abortion at < 14 weeks of gestation (see Recommendation 12).



For information regarding which health workers can provide this intervention, refer to Recommendations 24 and 26 for surgical abortion (vacuum aspiration and D&E).

14 A Cochrane Review is a systematic review of research in health care and health policy that is published in the *Cochrane Database of Systematic Reviews*.

15 Conscious sedation is also known as intravenous (IV) sedation or moderate sedation. See definition in Glossary.

How

Implementation considerations

- Sufficient supplies and stocks of pain medications should be ensured.
- Training of providers in abortion care should include pain management, in particular the technique for administration of paracervical block.

What

CLINICAL SERVICES Recommendations 15 and 16: Pain management for medical abortion

15. For medical abortion at any gestational age:

Recommend that pain management should be offered routinely (e.g. non-steroidal anti-inflammatory drugs [NSAIDs]) and that it should be provided for the individual to use if and when wanted.

NEW RECOMMENDATION BELOW INDICATES PAIN MANAGEMENT THAT IS *ADDITIONAL* TO NSAIDS.

16. (NEW) For pain management for medical abortion at ≥ 12 weeks:

Suggest consideration of other methods to control pain or discomfort due to increased pain with increasing gestational age. Such methods include certain anti-emetics and epidural anaesthesia, where available.

Remark:

- For medical abortion at gestational ages < 14 weeks, if NSAIDS (e.g. ibuprofen) are not available or not an option, then acetaminophen can be considered for pain control.

Source: Recommendation 15 updated from WHO (2012) *(19).* Recommendation 16 is new.

Note on updating of the recommendation: Recommendation 15 was previously published as part of Recommendation 14 in WHO (2012) *(19),* and evidence for it was reviewed using GRADE methodology. After review, in this updated version, we have split the first part of the original recommendation wording to apply to surgical abortion (see Recommendation 11a) and medical abortion (here in Recommendation 15), and revised the wording to mention provision.

Where

No requirement for location (on-site vs off-site).

Rationale for Recommendation 15 (specifically for gestational ages < 14 weeks)

A Cochrane Review served as the evidence base for this key question. Five studies reporting on pain management for medical abortion at gestational ages < 14 weeks were identified by the search strategy, conducted in Israel, the United Kingdom and the USA. A summary of the evidence is presented in Supplementary material 2, EtD framework for Pain management for medical abortion < 14 weeks.

Of these studies, three were assessed using the following comparisons:

- ibuprofen versus placebo
- prophylactic versus therapeutic NSAIDs
- ibuprofen versus paracetamol.

Women who received NSAIDs had lower mean pain scores and fewer women from that group required additional analgesic medication, based on high-certainty evidence. Discussions on the values and preferences of women with pain management during medical abortion and the resources required, cost-effectiveness and feasibility for NSAID administration resulted in a determination that favoured the intervention.

Rationale for Recommendations 15 (specifically for gestational ages ≥ 14 weeks) and 16

A systematic review was undertaken to address this key question. Eleven studies reporting on pain management for medical abortion at gestational ages ≥ 14 weeks were identified by the search strategy, conducted in Belgium, Canada, Germany, Israel, Italy, Sweden, Thailand and the USA. A summary of the evidence is presented in Supplementary material 2, EtD framework for Pain management for medical abortion ≥ 14 weeks.

Using data from these studies, the following comparisons were made:

- paracervical block (PCB) versus oral pain medication
- NSAIDs versus non-NSAIDs/placebo
- anti-emetics versus placebo
- anti-epileptics versus anxiolytics
- intermittent versus continuous epidural
- patient controlled epidural versus patient-controlled intravenous (IV) fentanyl
- patient controlled fentanyl versus patient-controlled morphine
- patient controlled IV tramadol versus patient-controlled IV fentanyl.

Comparison of PCB versus oral pain medication: In the studies that assessed this comparison, fewer women experienced severe pain and there was a lower expulsion time with the use of oral pain medication compared with PCB, based on moderate-certainty evidence.

Comparison of NSAIDs versus non-NSAIDs/placebo: In the studies that assessed this comparison, fewer women required supplemental narcotics after the use of NSAIDs, based on high certainty of evidence. In addition, fewer women receiving NSAIDs experienced side-effects, based on moderate-certainty evidence.

Comparison of anti-emetics versus placebo: In the studies that assessed this comparison, there was lower use of supplemental narcotics and lower expulsion time with the use of anti-emetics, based on moderate-certainty evidence.

Comparison of anti-epileptics versus anxiolytics: In the studies that assessed this comparison, there were lower mean pain scores, lower use of additional analgesics and lower mean expulsion times with the use of anti-epileptics, based on moderate-certainty evidence.

Comparison of intermittent versus continuous epidural: In the studies that assessed this comparison, there were fewer side-effects with the use of intermittent epidural, based on low- to high-certainty evidence. Satisfaction was higher among women who had intermittent epidural for their pain management, based on high-certainty evidence.

Comparison of patient-controlled epidural (PCE) versus patient controlled IV fentanyl: In the studies that assessed this comparison, there were lower mean pain scores and fewer side-effects of vomiting and sedation with the use of PCE, based on moderate-certainty evidence. In addition, satisfaction was higher among women in the PCE group, based on moderate-certainty evidence.

Comparison of patient-controlled morphine versus patient-controlled IV fentanyl: In the studies that assessed this comparison, there were lower pain scores and fewer side-effects with the use of patient-controlled fentanyl (50 µg), based on moderate- to high-certainty evidence.

Comparison of patient controlled IV tramadol versus patient controlled IV fentanyl: In the studies that assessed this comparison, pain control was comparable with the use of patient-controlled tramadol and fentanyl, based on low- to moderate-certainty evidence. Satisfaction ratings were also similar between the two groups, based on high-certainty evidence.

Discussions on the values and preferences of women regarding pain management during medical abortion, and on the resources required, cost-effectiveness and feasibility for NSAID administration resulted in a determination that favoured the intervention.

Who

For information regarding which health workers can provide this intervention, refer to Recommendations 28 and 30 on medical abortion.

How

Implementation consideration for Recommendations 15 and 16

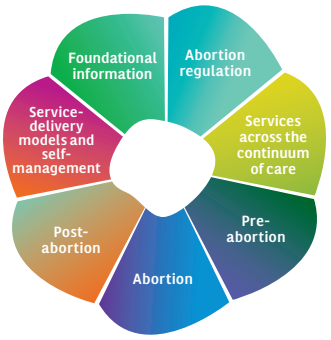
- Regardless of the service modality, there should be clear communication to the woman on the pain she may experience, which may vary based on pain perceptions and tolerance. In any event, she should be provided with information on pain management, and access to adequate pain medicines should be ensured.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO PAIN MANAGEMENT

- States must ensure adequate access to essential medicines in an affordable and non-discriminatory manner.
- Denial of pain medication may violate a wide range of human rights, including the right to health and autonomy in decision-making.
- Denial of pain medication as punishment for abortion or because it is part of abortion care may violate the right to equality and non-discrimination.
- Denial of pain medication may violate the right to be free from cruel, inhuman and degrading treatment.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

Links to related topics/recommendations



- Universal health coverage (UHC) (section 1.4.1)
- Commodities (section 1.4.4)
- Information provision (section 3.2.1)

3.3.7 Cervical priming prior to surgical abortion

Prior to surgical abortion, cervical priming (also known as cervical preparation) may be considered for all women with a pregnancy of any gestational age, in particular for women with a pregnancy over 12 weeks of gestation. Cervical priming before surgical abortion is especially beneficial for women with cervical anomalies or previous surgery, adolescents and those with advanced pregnancies, all of whom have a higher risk of cervical injury or uterine perforation that may cause haemorrhage *(135, 136)*. It may also facilitate the abortion procedure for inexperienced providers. However, cervical priming has disadvantages, including additional discomfort for the woman, and the extra cost and time required to administer it effectively.

Whether osmotic dilators or medication is used for cervical priming prior to the surgical abortion, this is done in advance of the procedure. As such, cervical priming may be initiated by a health worker other than the provider who will conduct the D&E.

What

CLINICAL SERVICES Recommendation 17: Cervical priming prior to surgical abortion at < 12 weeks of gestation

Prior to surgical abortion at < 12 weeks:

a. If cervical priming is used: **Suggest** the following medication regimens:

- Mifepristone 200 mg orally 24–48 hours prior to the procedure
- Misoprostol 400 µg sublingually 1–2 hours prior to the procedure
- Misoprostol 400 µg vaginally or buccally 2–3 hours prior to the procedure

b. Recommend against the use of osmotic dilators for cervical priming.

Remarks:

- The sublingual route is more effective for misoprostol administration.
- Appropriate pain medication should be provided.

Source: Recommendation updated from Recommendation 7.2 in WHO (2012) *(19)*.

Note on updating of the recommendation: This recommendation was reviewed using GRADE methods. The suggested mifepristone regimen is unchanged, but the misoprostol regimens have been updated, in terms of timing and route of administration, and laminaria is no longer a recommended option; these recommendations therefore replace the prior recommendation.

Rationale

An update of an existing Cochrane Review serves as the evidence base for this key question. The update identified 8 new studies, which makes a total of 61 included studies that assessed cervical priming methods for vacuum aspiration. From this review, approximately half of the included studies were evaluated to contribute towards the development of the Evidence-to-Decision (EtD) framework. The review includes the following cervical priming methods: medication with mifepristone and/or misoprostol and mechanical methods (i.e. natural or synthetic osmotic dilators). A summary of the evidence is presented in Supplementary material 2, EtD framework for Cervical priming prior to surgical abortion < 12.[16]

For Recommendation 17a, we suggest the option of misoprostol or mifepristone as a cervical priming agent prior to surgical abortion less than 12–14 weeks. For the studies that compared misoprostol versus mifepristone, time to complete the procedure was less for misoprostol, based on moderate-certainty evidence. However, the pre-procedure cervical dilation was greater with mifepristone use, based on moderate-certainty evidence. The side-effects profile was comparable between the two groups, based on very low-certainty evidence.

Regarding the timing of misoprostol administration, studies that compared the interval timing for administration of misoprostol for cervical priming revealed that the highest efficacy was seen (i.e. greater pre-procedure cervical

16 For the sake of consistency across the recommendations, the cut-off gestational age is 12 weeks, but evidence did include women with pregnancies up to 14 weeks of gestation who underwent vacuum aspiration.

dilation) with the 3-hour interval. This finding was based on high-certainty evidence. Although the 3-hour interval is considered optimal, the 1-hour interval is also included as a result of the expert panel members' discussions on the feasibility and acceptability of the shorter duration of waiting time prior to a woman's surgical abortion.

For Recommendation 17b, the reasoning is due to the longer time to complete the procedure if osmotic dilators are used compared with when misoprostol is used for cervical priming, based on high-certainty evidence. In addition, satisfaction rates were higher among those who received misoprostol compared with the laminaria group, based on moderate-certainty evidence.

The expert panel added the buccal route (this was added along with the vaginal route due to buccal and misoprostol concentration curves being similar in pharmacokinetics data), and their remark highlights the sublingual route as being the more effective route.

What

CLINICAL SERVICES Recommendation 18 (NEW): Cervical priming prior to surgical abortion (MVA or D&E) at ≥ 12 weeks of gestation

Prior to surgical abortion at later gestational ages:

a. For surgical abortion at ≥ 12 weeks: **Suggest** cervical priming prior to the procedure.

b. For surgical abortion between 12 and 19 weeks: **Suggest** cervical priming with medication alone (a combination of mifepristone plus misoprostol is preferred) or with an osmotic dilator plus medication (mifepristone, misoprostol, or a combination of both).

c. For surgical abortion between 12 and 19 weeks, when using an osmotic dilator for cervical priming: **Suggest** that the period between osmotic dilator placement and the procedure should not extend beyond two days.

d. For surgical abortion at ≥ 19 weeks: **Recommend** cervical priming with an osmotic dilator plus medication (mifepristone, misoprostol, or a combination of both).

Remark:

- There was limited evidence for cervical priming for gestational ages between 12 and 14 weeks and therefore health workers should use clinical judgement to decide on the most convenient method for cervical priming prior to vacuum aspiration for this gestational age range.

Note: These are new recommendations and they replace Recommendations 8.1 and 8.2 in WHO (2012) *(19)*, which were for D&E after 14 weeks; these new recommendations now include information on methods/regimens for cervical priming at different gestational age ranges.

Rationale

A Cochrane Review provided the evidence base on cervical priming methods for surgical abortion at later gestational ages. From this review, 16 studies were included in the development of the EtD framework relating to the following cervical priming methods: medication with mifepristone and/or misoprostol; mechanical methods with osmotic dilators and synthetic dilators; one-day versus two-day procedures with laminaria. The study settings included Israel, South Africa, Spain, the United Kingdom and the USA. A summary of the evidence is presented in Supplementary material 2, EtD framework for Cervical priming prior to surgical abortion ≥ 12 weeks.

The inclusion of all medication options for cervical priming was based on the expert panel's discussion of the feasibility and acceptability of these interventions. The use of mifepristone with misoprostol is favoured over misoprostol alone for cervical priming due to higher pre-procedure cervical dilatation and shorter time to complete the procedure, based on moderate-certainty evidence. The combined use of medication and laminaria is favoured over laminaria alone due to the higher pre-procedure cervical dilatation, decreased need for further dilatation and shorter time to complete the procedure. This is based on high-certainty evidence. Sub-analyses of the included studies showed that the combined use of medication and laminaria appears to be more effective at higher gestational ages.

How

Implementation consideration

- The use of medication for cervical priming prior to surgical abortion beyond 12–14 weeks of gestation can be self-managed and can save travel time for the woman and staff time spent on insertion of osmotic dilators.

Who

SERVICE DELIVERY Recommendation 19: Cervical priming with medication prior to surgical abortion at any gestational age

Type of health worker	Recommendation	Rationale[a]
Community health workers (CHWs)	**Suggest** Condition: Provision of medication for the purpose of cervical priming is part of the surgical abortion process so the health worker needs to ensure continuity of care of the woman obtaining the medicines prior to the abortion procedure	Although no direct evidence was found on the safety, effectiveness or acceptability of this option, the skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] In addition, CHWs have been recommended to provide medical abortion at < 12 weeks (see Recommendation 28), which requires similar skills and knowledge as for this task.
Pharmacy workers	**Suggest** Condition: Provision of medication for the purpose of cervical priming is part of the surgical abortion process so the health worker needs to ensure continuity of care of the woman obtaining the medicines prior to the abortion procedure	Although no direct evidence was found on the safety, effectiveness or acceptability of this option, the skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] In addition, pharmacy workers have been recommended to provide medical abortion at < 12 weeks (see Recommendation 28), which requires similar skills and knowledge as for this task.
Pharmacists	**Suggest** Condition: Provision of medication for the purpose of cervical priming is part of the surgical abortion process so the health worker needs to ensure continuity of care of the woman obtaining the medicines prior to the abortion procedure	Although no evidence was found on the safety, effectiveness or acceptability of this option, dispensing medicines with a prescription is within the typical scope of practice of pharmacists. The skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] In addition, pharmacists have been recommended to provide medical abortion at < 12 weeks (see Recommendation 28), which requires similar skills and knowledge as for this task.
Traditional and complementary medicine professionals **Auxiliary nurses/ANMs** **Nurses** **Midwives**	**Recommend**	Evidence was found for the safety and effectiveness of this option (low-certainty evidence). Cervical priming is part of the training for provision of manual vacuum aspiration. The skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a]
Associate/advanced associate clinicians	**Recommend**	Evidence was found for health workers with similar or less comprehensive basic training (e.g. midwives, nurses, ANMs) using such medicines to provide medical abortion (moderate-certainty evidence). Cervical priming is part of the training for provision of manual vacuum aspiration. The skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a]
Generalist medical practitioners **Specialist medical practitioners**	**Recommend**	Within their typical scope of practice,[b] therefore no assessment of the evidence was conducted.

Source: Recommendation updated from WHO (2015) *(23)*.

Note on updating of the recommendation: This was an existing recommendation for which evidence relating to all types of health workers was reviewed using GRADE methodology, except for specialist and generalist medical practitioners, which were already "recommend". After review, the recommendations were upgraded for all reviewed health workers, from "recommend against" to "suggest" for pharmacists, pharmacy workers and CHWs, and from "suggest" to "recommend" for all other health worker categories. The gestational age for this recommendation was also amended from "beyond 12 weeks" to "at any gestational age" after conferring with the expert panel. A summary of the evidence is presented in Supplementary material 3, EtD framework for Cervical priming using medication and osmotic dilators.

[a] For this and all health worker recommendations, given the limited evidence for many of the health worker–task combinations, the discussions of the expert panel focused on the competency framework in WHO's 2011 publication, *Sexual and reproductive health: core competencies in primary care (121)*, which provides information on the competencies (including skills and knowledge) required for each task, and also the WHO-INTEGRATE criteria, in particular on the feasibility, equity and acceptability of the intervention and women's values and preferences.

[b] For typical scope of work/practice, please refer to Annex 5: Health worker categories and roles.

Where

No requirement for location (on-site vs off-site).

How

Implementation consideration

- Given that cervical priming initiates the process and is done prior to a surgical procedure, with an interval of up to 1–2 days, it is important that the health worker ensures the continuity of care for the woman by ensuring that there is a clear plan for the surgical abortion prior to the woman taking the priming agent and she has access to the existing health system should she desire or need additional support during that interval.

Who

SERVICE DELIVERY Recommendation 20: Cervical priming with osmotic dilators prior to D&E at gestational ages ≥ 12 weeks

Type of health worker	Recommendation	Rationale[a]
Traditional and complementary medicine professionals	**Suggest** Condition: Health worker ensures continuity of care from the time of cervical priming to the D&E	Although insufficient direct evidence was found for the safety and effectiveness of this option, these health workers have been suggested to do other transcervical procedures (e.g. inserting an IUD and vacuum aspiration; see Recommendations 43 and 24). The skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] The expert panel affirmed that this option has the potential to increase equitable access to quality abortion care in regions where these professionals constitute a significant proportion of the health workforce.
Auxiliary nurses/ANMs	**Recommend**	Although insufficient direct evidence was found for the safety and effectiveness of this option, ANMs have been recommended to do other transcervical procedures (e.g. inserting an IUD; see Recommendation 43), and auxiliary nurses have been recommended in certain contexts to do other transcervical procedures (e.g. inserting an IUD; see Recommendation 43). The skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] The expert panel affirmed that this option may help optimize workflow within a facility and decrease waiting times for women.
Nurses	**Recommend**	Although insufficient direct evidence was found for the safety or effectiveness of this option, nurses have been recommended to do other transcervical procedures (e.g. inserting an IUD; see Recommendation 43), and there is evidence that provision of manual vacuum aspiration by nurses is safe and effective (moderate-certainty evidence). The skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] The expert panel affirmed that this option may help optimize workflow within a facility and decrease waiting times for women.
Midwives	**Recommend**	Although insufficient direct evidence was found for the safety or effectiveness of this option, midwives have been recommended to do other transcervical procedures (e.g. inserting an IUD; see Recommendation 43), and there is evidence that provision of manual vacuum aspiration by midwives is safe and effective (moderate-certainty evidence). The skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] The expert panel affirmed that this option may help optimize workflow within a facility and decrease waiting times for women.

Table Continues

Table Continued

Type of health worker	Recommendation	Rationale[a]
Associate/advanced associate clinicians	**Recommend**	Indirect evidence was found for the safety and effectiveness of these clinicians providing vacuum aspiration (moderate-certainty evidence), which includes cervical priming with osmotic dilators for select cases. The skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] The expert panel affirmed that this option may help optimize workflow within a facility and decrease waiting times for women.
Generalist medical practitioners **Specialist medical practitioners**	**Recommend**	Within their typical scope of practice,[b] therefore no assessment of the evidence was conducted.

Source: Recommendation updated from WHO (2015) *(23)*.

Note on updating of the recommendation: This was an existing recommendation for which evidence relating to all types of health workers was reviewed using GRADE methodology, except for specialist and generalist medical practitioners, which were already "recommend". After review, the recommendations were upgraded for associate/advanced associate clinicians, midwives and nurses from "suggest" to "recommend", for auxiliary nurses and ANMs from "recommend against" to "recommend", and for traditional and complementary medicine professionals from "recommend against" to "suggest". For pharmacists, pharmacy workers and community health workers, the recommendations remain "recommend against" (not listed). The gestational age for this recommendation was also amended from "beyond 12 weeks" to "12 weeks and above" (≥ 12 weeks) to align this recommendation with Recommendation 18. A summary of the evidence is presented in Supplementary material 3, EtD framework for Cervical priming using medication and osmotic dilators.

[a] For this and all health worker recommendations, given the limited evidence for many of the health worker–task combinations, the discussions of the expert panel focused on the competency framework in WHO's 2011 publication, *Sexual and reproductive health: core competencies in primary care (121)*, which provides information on the competencies (including skills and knowledge) required for each task, and also the WHO-INTEGRATE criteria, in particular on the feasibility, equity and acceptability of the intervention and women's values and preferences.

[b] For typical scope of work/practice, please refer to Annex 5: Health worker categories and roles.

Where

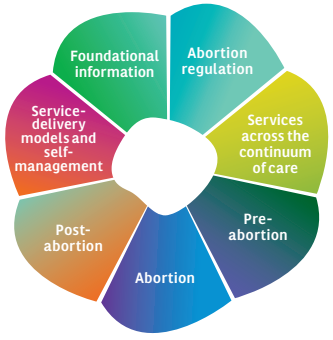
In a health-care facility.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO CERVICAL PRIMING

- Denial of cervical priming as punishment for abortion or because it is part of abortion care may violate the right to non-discrimination and equality.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

Links to related topics/recommendations



Recommendations 11–15: Pain management

Recommendation 23–26: Surgical abortion (vacuum aspiration and dilatation and evacuation)

3.3.8 Restrictions (in law or policy) on health workers who may lawfully provide abortion care

In a number of countries, law and policy restrict which type of health workers may lawfully provide abortion care *(137),* most often limiting this to gynaecologists. Since the advent of vacuum aspiration and medical abortion, however, abortion can be safely provided by a wide range of health workers in diverse settings, and safely self-managed in earlier pregnancy (see Recommendations 24, 28, 30, 33). Provider restrictions are inconsistent with WHO's support for the optimization of the roles of health workers; such restrictions are arbitrary and not evidence based *(138)*. Reflecting States' obligation to respect, protect and fulfil the right to health, health-care facilities, goods and services must be available, accessible, adequate and of good quality *(46)*. This includes facilities, goods and services for SRH care. Thus, States must ensure an adequate number of medical and professional personnel and skilled providers in the health system as well as adequate stocks of essential medicines *(46)*. Furthermore, the Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health, has stressed that abortion law must be evidence based *(37)* (see Chapter 1, section 1.3.1[i], and also Web annex A: Key international human rights standards on abortion).

LAW & POLICY Recommendation 21: Provider restrictions

Recommend against regulation on who can provide and manage abortion that is inconsistent with WHO guidance.

Remark:

- Where law or policy regulate who may provide or manage abortion, that regulation should be consistent with WHO guidance, which is presented throughout this chapter.

Note on updating of the recommendation: This and other law and policy recommendations are not new recommendations. WHO's 2012 *Safe abortion* guidance provided a composite recommendation related to law and policy *(19)*; in this guideline, this has been developed into seven separate recommendations using GRADE methodology.

Rationale

In order to identify the impacts of provider restrictions on abortion seekers and health workers, a systematic review of studies published between 2010 and 2019 was undertaken, identifying seven studies conducted in Australia, Ethiopia, Nepal and the USA. A summary of the evidence from these studies is presented in Supplementary material 1, EtD framework for Provider restrictions. The reviewed evidence showed that restrictions on who can provide and manage abortion resulted in delays to and burdens in accessing abortion. By contrast, expanding the range of health workers who can provide abortion care improved timely access to early medical and surgical abortion; reduced costs, travel and waiting time; shifted components of care away from physicians; made abortion more available including in rural areas and at primary health care level; prevented unsafe self-management of abortion; and reduced system costs. This evidence indicates that provider restrictions produce inefficiencies, administrative burdens and workload burdens within health systems, and reduce in practice the number of available providers.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO PROVIDER RESTRICTIONS

- Availability, accessibility, acceptability and quality must be central to the regulation of sexual and reproductive health care.
- Abortion regulation should be based on human rights and evidence.
- States must ensure an adequate number of medical and professional personnel and skilled providers in the health system as well as adequate stocks of essential medicines.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

3.3.9 Conscientious objection or refusal by health workers to provide abortion care

Refusal of abortion care on the basis of conscience operates as a barrier to access to safe and timely abortion *(3 [para. 14], 36 [para. 8], 139 [para. 109], 140 [para. 353], 141 [paras 42, 43])*, and unregulated conscientious refusal/objection can result in human rights violations, or lead women to seek unsafe abortion *(142 [para. 23], 143 [para. 106], 144)*. In some countries conscientious objection is expressly regulated through employment law, employment contracts or the law on abortion. As a matter of international human rights law, States that allow conscientious objection must organize their health system and abortion provision in a way that ensures that conscientious objection does not result in the refusal of legally available abortion care, and regulate the exercise of conscientious objection in a way that reflects best international clinical practice, protects abortion seekers, and ensures that provider refusal does not undermine or hinder access to quality abortion care *(145 [para. 12], 146 [para. 28])*. WHO has also advised that "health services should be organized in such a way as to ensure that an effective exercise of the freedom of conscience of health professionals in the professional context does not prevent patients from obtaining access to services to which they are entitled under the applicable legislation" *(19)*.

LAW & POLICY Recommendation 22: Conscientious objection

Recommend that access to and continuity of comprehensive abortion care be protected against barriers created by conscientious objection.

Remarks:

- In spite of the human rights obligation to ensure conscientious objection does not hinder access to quality abortion care, and previous WHO recommendations aimed at ensuring conscientious objection does not undermine or hinder access to abortion care, conscientious objection continues to operate as a barrier to access to quality abortion care. It is critical that States ensure compliance with regulations and design/organize health systems to ensure access to and continuity of quality abortion care. If it proves impossible to regulate conscientious objection in a way that respects, protects and fulfils abortion seekers' rights, conscientious objection in abortion provision may become indefensible.
- The evidence reviewed considered the impact of conscientious objection on access to and availability of abortion care and not the effectiveness of regulating conscientious objection in terms of improvements in those outcomes. However, international human rights law provides some guidance as to how States can ensure that human rights of abortion seekers are respected, protected and fulfilled. These include:
    - organizing the health system to ensure that sufficient, non-objecting providers are employed and distributed fairly across the country *(3)*;
    - putting in place clear and enforceable regulation of conscientious objection *(147 [paras 30, 31], 148 [para. 41(f)], 149 [para. 37(b)])*;
    - ensuring adequate enforcement of the regulation of conscientious objection, including identifying, addressing and sanctioning non-compliance *(147 [paras 30, 31], 148 [para. 41(f)], 149 [para. 37(b)])*;
    - outlining clearly who may object to what components of care *(150 [paras 30-31], 148 [para. 41(f)], 3 [para. 43])*;
    - prohibiting institutional claims of conscience *(147, 150 [para. 33(c)], 148 [para. 41(f)])*;
    - requiring objectors to provide prompt referral to accessible, non-objecting providers *(3 [para. 43], 37 [para. 65(m)], 39 [para. 11], 150 [para. 33(c)], 146 [para. 28])*;
    - requiring conscientious objection to be exercised in a respectful and non-punitive manner; and
    - prohibiting conscientious objection in urgent or emergency situations *(3, para. 43)*.

Note on updating of the recommendation: This and other law and policy recommendations are not new recommendations. WHO's 2012 *Safe abortion* guidance provided a composite recommendation related to law and policy *(19)*; in this guideline, this has been developed into seven separate recommendations using GRADE methodology.

Rationale

In order to identify the impacts of conscientious objection on abortion seekers and health workers, a systematic review of studies published between 2010 and 2020 was undertaken, identifying 26 studies conducted in Australia, Brazil, Colombia, Ghana, Italy, Mexico, Nigeria, Norway, Portugal, South Africa, Slovakia, Switzerland, Tunisia, the United Kingdom, the USA and Zambia. A summary of the evidence from these studies is presented in Supplementary material 1, EtD framework for Conscientious objection. The evidence reviewed established that conscientious objection may delay timely access to abortion and abortion care. Delay in care is exacerbated where there is a higher proportion of objecting health workers, and sometimes even in emergency cases where abortion is needed to save a woman's life. Delays are sometimes deliberately imposed by objectors. The evidence also suggests that conscientious objection contributes to increased abortion-related morbidity and mortality, and that some health workers claim conscientious objection and refuse abortion in the public sector, while providing abortion for payment in their private practices.

The studies showed that conscientious objection imposes increased barriers on populations in specific settings: rural areas; settings where abortion law has recently been changed and there is insufficient clarity on who may object to what aspects of abortion care; places where conscientious objection is not effectively regulated; and settings where objecting health workers intentionally refuse referrals or use biased counselling, or inaccurate legal and medical information to try to dissuade and obstruct people from accessing abortion (refer to section 3.2.1: Provision of information).

Refusal of abortion on the basis of conscience has been shown to impose significant burdens on women and girls, especially uncertainty about whether and where they can access abortion. Some objectors decide whether to provide abortion on a case-by-case basis depending on their view of the reason a woman seeks abortion, which means availability is not clear or consistent. Furthermore, objectors' referral practices are highly variable. The evidence demonstrated that while most objectors were willing to refer, this was not true for all, with some objectors referring on a case-by-case basis. Additionally, referral pathways may be circuitous and burdensome, which imposes additional difficulties and delays.

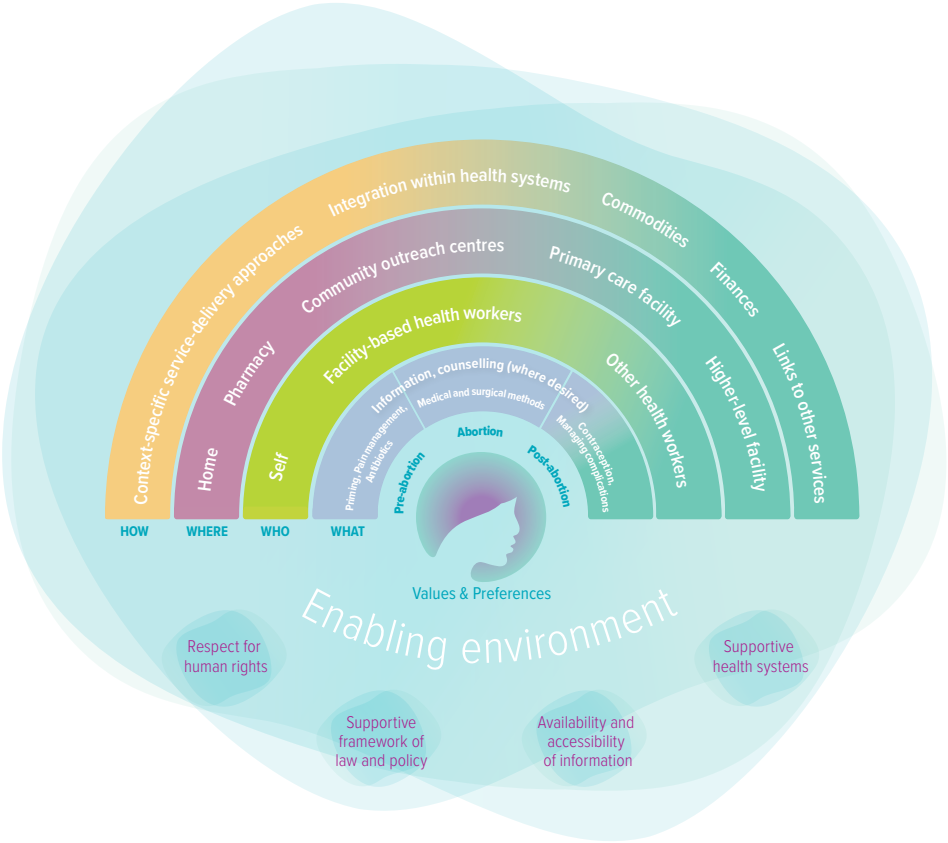
Conscientious objection has significant workload implications for health workers. Where there are many objectors, non-objecting health workers have an increased workload, abortion provision is often stigmatized, and those who do provide abortion care may experience career limitation or discrimination. Unclear, unenforced or non-existent regulation and legal frameworks for conscientious objection can create burdens on health workers, including in navigating challenges associated with their conscience or ethics, cause workplace conflicts, result in non-clinical staff attempting to claim conscientious objection, and undermine organizational models for the delivery of abortion.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO CONSCIENTIOUS OBJECTION

- Availability, accessibility, acceptability and quality must be central to the regulation of sexual and reproductive health (SRH) services.
- States that allow conscientious objection must organize their health system and abortion provision in a way that ensures that conscientious objection does not hinder access to or result in the refusal of legally available abortion care.
- States that allow conscientious objection should regulate the exercise of conscientious objection in a way that reflects best international clinical practice, protects abortion seekers, and ensures that provider refusal does not undermine or hinder access to quality abortion.
- Everyone has the right to accurate information on SRH.
- Everyone has a right to privacy and confidentiality in SRH services.
- Everyone has a right to non-discrimination and equality in accessing SRH services.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

3.4 Abortion



Abortion management is needed for both induced and spontaneous abortion, including for clinical indications such as missed abortion and intrauterine fetal demise (fetal death).

Recommended management options include medical management, or surgical management using manual or electric vacuum aspiration (MVA or EVA) or dilatation and evacuation (D&E). The method of surgical abortion would depend on gestational age: generally vacuum aspiration at < 14 weeks of gestation and D&E at ≥ 14 weeks, but there is flexibility in the use of these methods between 12 and 16 weeks. Medical abortion regimens include sequential use of mifepristone followed by misoprostol or, in settings where mifepristone is not available (or is restricted for certain clinical indications), the use of misoprostol alone. A new alternative medical method, in particular using letrozole in combination with misoprostol, is also available.

For missed abortion and intrauterine fetal demise (see sections 3.4.5 and 3.4.6), in addition to the options of medical and surgical management, expectant management can be offered as an option on the condition that the woman is first informed of the longer time for expulsion of the pregnancy tissue and the increased risk of incomplete emptying of the uterus (the same applies in the case of incomplete abortion, which is addressed in section 3.5.2 on post-abortion care).

Medical abortion care for all indications plays a crucial role in providing wider access to safe, effective and acceptable abortion care. This may increase the availability and accessibility of abortion and realization of the right to SRH. Across all resource settings, the use of medical abortion has contributed to the expansion of health worker roles, more efficient use of resources and reduced maternal mortality and morbidity from unsafe abortions. Moreover, medical abortion – particularly in early pregnancy – can now be provided at the primary-care level and on an outpatient basis, or from a pharmacy, which further increases access to abortion care. Medical abortion care

reduces the need for skilled surgical abortion providers and offers a non-invasive and highly acceptable and safe option to pregnant women. As a matter of international human rights law, States must provide essential medicines listed under WHO's Action Programme on Essential Drugs, which include abortion medicines *(46, para. 12a)*.

The recommendations presented below address surgical and medical management of abortion. Implementation of all of the recommendations in this section are conditional upon women's values and preferences, the acceptability of each intervention, and the availability of resources to provide the chosen method safely. It should be noted that a woman's choice of method for abortion management may be limited or not applicable if she has medical contraindications to one of the methods. The recommendations below relate only to the method of abortion, and should not be read as suggesting gestational age limits for the availability of abortion.

3.4.1 Methods of surgical abortion

The provision of vacuum aspiration includes the assessment of gestational age, cervical priming (if needed), the actual procedure, pain management including the provision of a paracervical block and the assessment of completeness of abortion through the visual inspection of products of conception. Health workers with the skills to perform a bimanual pelvic examination to diagnose and date a pregnancy, and to perform a transcervical procedure such as intrauterine device (IUD) insertion, can be trained to perform vacuum aspiration.

Recommended methods of surgical abortion at later gestational ages are vacuum aspiration and dilatation and evacuation (D&E). Although the recommendations in this section indicate differences before and after 14 weeks of gestation, it should be noted that there is flexibility in the use of one surgical method versus the other between the gestational ages of 12 and 16 weeks.



CLINICAL SERVICES Recommendation 23: Vacuum aspiration for induced abortion at gestational ages < 14 weeks

For surgical abortion at < 14 weeks:

a. Recommend vacuum aspiration.

b. Recommend against the practice of dilatation and sharp curettage (D&C), including sharp curette checks (i.e. to "complete" the abortion) following vacuum aspiration.

Remarks:

- Observational studies indicate that vacuum aspiration is associated with fewer complications than D&C; however, randomized controlled trials were underpowered to detect a difference in complication rates.
- No evidence supports the use of sharp curette checks following vacuum aspiration.
- The quality of the evidence based on randomized controlled trials is low to moderate.

Source: Recommendation 1 carried forward from WHO (2012) *(19)*. Some of the wording has been revised, and the gestational age range has been changed from "up to 12 to 14 weeks" to "before 14 weeks" (< 14 weeks).

Who

SERVICE DELIVERY Recommendation 24: Vacuum aspiration for induced abortion at gestational ages < 14 weeks

Type of health worker	Recommendation	Rationale[a]
Traditional and complementary medicine professionals	**Recommend**	Very low-certainty evidence was found for the effectiveness of this option for components of the task (e.g. assessing uterine size with bimanual examination as part of medical abortion provision). The skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] These professionals perform transcervical procedures (e.g. IUD insertion) in some settings. The expert panel affirmed that the benefits outweigh possible harms and this option has the potential to increase equitable access to quality abortion care in regions where these professionals constitute a significant proportion of the health workforce.
Auxiliary nurses/ANMs	**Suggest** Condition: In contexts where established health system mechanisms involve auxiliary nurses/ANMs in providing basic emergency obstetric care, and where referral and monitoring systems are strong.	Although insufficient direct evidence was found for the safety and effectiveness of this option, the benefits outweigh any possible harms. This option has been shown to be feasible, including at scale in low-resource settings, and has the potential to decrease inequities by extending quality abortion care to rural and underserved populations.
Nurses	**Recommend**	Evidence was found for the safety and effectiveness (low certainty) and for women's satisfaction (low certainty) with this option. Women often consider care received from nurses as more supportive compared with other health workers (moderate-certainty evidence). This option is feasible and may decrease inequities by extending quality abortion care to underserved populations.
Midwives	**Recommend**	This task is recognized as a core competency in midwifery.[a] Evidence was found for the safety and effectiveness (moderate certainty) and for women's satisfaction with the overall abortion experience (low certainty) with this option. Women often consider care received from midwives as more supportive compared with other health workers (moderate-certainty evidence). This option has been shown to be feasible, including in low-resource settings.
Associate/advanced associate clinicians	**Recommend**	Evidence was found for the safety and effectiveness (moderate certainty) and for women's satisfaction with the overall abortion experience (low certainty) with this option. This option is feasible in all resource settings, and may decrease inequities by extending quality abortion care to underserved populations.
Generalist medical practitioners **Specialist medical practitioners**	**Recommend**	Within their typical scope of practice,[b] therefore no assessment of the evidence was conducted.

Source: Recommendation updated from WHO (2015) *(23)*.

Note on updating of the recommendation: This was an existing recommendation for which evidence relating to traditional and complementary medicine professionals, auxiliary nurses and auxiliary nurse midwives was reviewed using GRADE methodology. After review, only the recommendation for traditional and complementary medicine professionals was upgraded, from "suggest" to "recommend"; the recommendations for all the other health worker categories remained unchanged. A summary of the evidence is presented in Supplementary material 3, EtD framework for Vacuum aspiration for all indications < 14 weeks.

[a] For this and all health worker recommendations, given the limited evidence for many of the health worker–task combinations, the discussions of the expert panel focused on the competency framework in WHO's 2011 publication, *Sexual and reproductive health: core competencies in primary care (121)*, which provides information on the competencies (including skills and knowledge) required for each task, and also the WHO-INTEGRATE criteria, in particular on the feasibility, equity and acceptability of the intervention and women's values and preferences.

[b] For typical scope of work/practice, please refer to Annex 5: Health worker categories and roles.

Where

In a health-care facility. Both types of vacuum aspiration can be performed in a primary care facility and on an outpatient basis.

How

Implementation considerations

- While MVA is more commonly used and more likely in primary care settings, the skills required for EVA are similar, thus the recommendations above apply to the provision of either form of vacuum aspiration.
- MVA is used earlier in pregnancy and in the absence of access to a stable source of electricity.
- Dilatation and sharp curettage (D&C) should be replaced with MVA.

What

CLINICAL SERVICES Recommendation 25: Methods of surgical abortion at gestational ages ≥ 14 weeks

For surgical abortion at ≥ 14 weeks: **Recommend** dilatation and evacuation (D&E).

Remark:

- Vacuum aspiration can be used during a D&E (i.e. for the purpose of amniotomy or tissue removal at the end of the D&E).

Source: Recommendation 5 carried forward from WHO (2012) *(19)*. The wording has been revised to use the word "recommend" to indicate that this is a strong recommendation, and the gestational age has been changed from "over 12 to 14 weeks" to "14 weeks and above" (≥ 14 weeks), and medical methods were removed (medical methods at later gestational ages are covered in Recommendation 29 in this guidance).

Who

SERVICE DELIVERY Recommendation 26: Dilatation and evacuation (D&E) for surgical abortion at gestational ages ≥ 14 weeks

Type of health worker	Recommendation	Rationale[a]
Traditional and complementary medicine professionals	**Suggest** Condition: In settings where established health system mechanisms exist to include these health workers in other tasks related to maternal and reproductive health.	Although no direct evidence was found for the safety, effectiveness or acceptability of this option, the skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] This type of health worker has been suggested (weak recommendation) to do other transcervical procedures, such as cervical priming with osmotic dilators, vacuum aspiration and inserting an IUD (see Recommendations 20, 24 and 43). The expert panel affirmed that this option has the potential to increase equitable access to quality abortion care in regions where these professionals constitute a significant proportion of the health workforce.
Midwives	**Suggest** Condition: In settings where established health system mechanisms exist to include these health workers in other tasks related to maternal and reproductive health.	Although no direct evidence was found on the safety, effectiveness or acceptability of this option, the skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] This type of health worker has been recommended to do other transcervical procedures, such as cervical priming with osmotic dilators, vacuum aspiration and inserting an IUD (see Recommendations 20, 24 and 43).
Associate/advanced associate clinicians	**Suggest** Condition: In settings where established health system mechanisms exist to include these health workers in other tasks related to maternal and reproductive health.	Although no direct evidence was found on the safety or effectiveness of this option, the skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] The expert panel affirmed that the potential benefits outweigh the possible harms, and this option has the potential to increase equitable access to quality abortion care beyond 14 weeks of gestation.

Table Continues

Table Continued

Type of health worker	Recommendation	Rationale[a]
Generalist medical practitioners	**Recommend**	No direct evidence was found on the safety or effectiveness of this option as compared with provision by specialist medical practitioners. However, it appears to be feasible in both high- and low-resource settings where D&E use is common. Such doctors routinely perform other surgical procedures, such as caesarean section, vacuum aspiration and tubal ligation. The potential benefits of this option outweigh the harms. A specialist provider may not always be available on-site and this option may therefore increase equitable access to quality abortion care.
Specialist medical practitioners	**Recommend**	Within their typical scope of practice,[b] therefore no assessment of the evidence was conducted.

Source: Recommendation updated from WHO (2015) *(23)*.

Note on updating of the recommendation: This was an existing recommendation for which evidence relating to associate/advanced associate clinicians (previously only suggested in the context of rigorous research), midwives and traditional and complementary medicine professionals (both previously recommended against) was reviewed using GRADE methodology. After review, the recommendations were upgraded for all of them to a weak recommendation ("suggest"). The gestational age range was also amended from "beyond 12 weeks" to "14 weeks and above" (≥ 14 weeks) to align with Recommendation 25 on this topic. A summary of the evidence is presented in Supplementary material 3, EtD framework for D&E for surgical abortion ≥ 14 weeks.

[a] For this and all health worker recommendations, given the limited evidence for many of the health worker–task combinations, the discussions of the expert panel focused on the competency framework in WHO's 2011 publication, *Sexual and reproductive health: core competencies in primary care (121)*, which provides information on the competencies (including skills and knowledge) required for each task, and also the WHO-INTEGRATE criteria, in particular on the feasibility, equity and acceptability of the intervention and women's values and preferences.

[b] For typical scope of work/practice, please refer to Annex 5: Health worker categories and roles.

Where

In a health-care facility. The procedure can be provided on an outpatient basis.

How

Implementation considerations

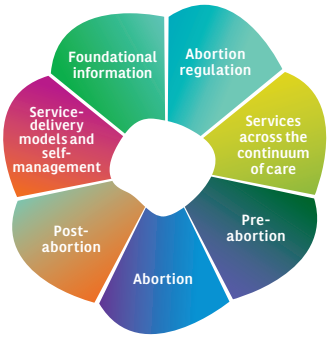
- For all providers, skills needed for D&E provision are greater than for a vacuum aspiration done in earlier pregnancy and training needs are higher.
- D&E includes the use of vacuum aspiration and therefore skills and knowledge of vacuum aspiration are relevant for this task.
- Health workers providing abortion or caring for women undergoing abortion at gestational ages ≥ 12 weeks may have additional needs for professional and mentoring support.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO SURGICAL ABORTION

- Health-care facilities, commodities and services must be available, accessible, acceptable and of good quality. This means they must be evidence-based and scientifically and medically appropriate and up to date.
- **AT < 14 WEEKS OF GESTATION:** As dilatation and sharp curettage (D&C) causes pain and suffering to women and is not recommended for use, its use is incompatible with numerous human rights including the right to health.
- **AT ≥ 14 WEEKS OF GESTATION:** States must ensure adequate access to essential medicines in an affordable and non-discriminatory manner.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

Links to related topics/recommendations



All recommendations related to law and policy (Recommendations 1,2,3,6,7,21,22)

Health financing (section 1.4.2)

Commodities (section 1.4.4)

Recommendations 11–15 on pain management

3.4.2 Medical management of induced abortion

Medical management of spontaneous and induced abortion (for both viable and non-viable pregnancies) at early or later gestational ages involves the use of a single-dose regimen or a combination regimen of medicines used in sequence, with specific dosages and routes of administration.

The medicines that have been used for some decades for medical abortion are mifepristone in combination with misoprostol, or misoprostol alone. Similar to mifepristone, letrozole can be used in combination with misoprostol for medical abortion at early gestational ages. Letrozole is a third-generation selective aromatase inhibitor. Its mechanism of action involves suppression of estrogen levels, which modifies the progesterone receptor concentration, subsequently leading to pregnancy loss.

Medical abortion is a process that takes place over a period of up to several days rather than being a discrete procedure. In addition to information provision (including reasons to seek urgent care at any point during the process), medical abortion includes the following components or subtasks:

i. assessing eligibility for medical abortion (diagnosing and dating the pregnancy, ruling out medical contraindications);

ii. administering the abortion medicines with instructions on their appropriate use and managing the common side-effects;

iii. assessing whether the abortion process has had a successful outcome and whether any further intervention is required.

One health worker can provide the whole package of care for medical abortion, but it is equally possible for the subtasks to be carried out by different health workers and at different locations, including remotely. In addition, given the nature of the medical abortion process, it is also possible for women to manage the process by themselves outside of a health-care facility (e.g. at home), with support if and when needed. Such self-assessment and self-management approaches can be empowering for women and help to triage care, leading to a more woman-centred and more optimal use of health resources.

Routes of administration for misoprostol used for medical abortion:

- Oral – pills are swallowed immediately
- Buccal – pills are placed between the cheek and gums and swallowed after 20 to 30 minutes
- Sublingual – pills are placed under the tongue and swallowed after 30 minutes
- Vaginal – pills are placed in the vagina

What

CLINICAL SERVICES Recommendation 27: Medical management of induced abortion at gestational ages < 12 weeks

For medical abortion at < 12 weeks:

a. **Recommend** the use of 200 mg mifepristone administered orally, followed 1–2 days later by 800 µg misoprostol administered vaginally, sublingually or buccally. The minimum recommended interval between use of mifepristone and misoprostol is 24 hours.*

b. When using misoprostol alone: **Recommend** the use of 800 µg misoprostol administered buccally, sublingually or vaginally.*

c. **(NEW) Suggest** the use of a combination regimen of letrozole plus misoprostol (letrozole 10 mg orally each day for 3 days followed by misoprostol 800 µg sublingually on the fourth day) as a safe and effective option.*‡

Remarks:

- Evidence from clinical studies demonstrates that the combination regimen (Recommendation 27a) is more effective than misoprostol alone.
- All routes are included as options for misoprostol administration, in consideration of patient and provider preference.
- The suggested combination regimen of letrozole plus misoprostol may be safe and effective up to 14 weeks of gestation.

* Repeat doses of misoprostol can be considered when needed to achieve success of the abortion process. In this guideline we do not provide a maximum number of doses of misoprostol.

‡ Further evidence is needed to determine the safety, effectiveness and acceptability of the letrozole plus misoprostol combination regimen at later gestational ages, especially in comparison with that of the mifepristone plus misoprostol combination regimen (the available evidence focused on comparison with the use of misoprostol alone).

Source: Recommendations 27a and 27b carried forward from WHO (2018) where they were Recommendation 3a *(120)*. Recommendation 27c is new.

Rationale for Recommendation 27c (combination regimen of letrozole plus misoprostol)

A systematic review assessed the efficacy, safety and acceptability of alternative methods of medical abortion to the standard regimens using mifepristone and/or misoprostol. The literature search identified seven studies, all of which reported on the combination of letrozole plus misoprostol (intervention) versus misoprostol alone (comparison) for medical abortion. No studies were identified that compared letrozole plus misoprostol versus mifepristone plus misoprostol. The study settings included China, Egypt and the Islamic Republic of Iran. A summary of the evidence is presented in Supplementary material 2, EtD framework for New medical methods for abortion.

Overall, the evidence favoured the intervention. The use of letrozole in combination with misoprostol showed lower rates of ongoing pregnancy and higher rates of successful abortion, based on low- to very low-certainty evidence. In addition, fewer women experienced side-effects, based on moderate-certainty evidence.

Discussion on the cost-effectiveness, equity, feasibility and acceptability favoured the intervention. Letrozole's typical use for infertility and cancer treatment makes it more readily accessible than mifepristone in certain parts of the world. In addition, the low cost of letrozole is another contributing factor to making this an alternative method for medical abortion.

Who

SERVICE DELIVERY Recommendation 28: Medical management of induced abortion at gestational ages < 12 weeks,* in whole or in part (i.e. performing all or some of the subtasks; see list at start of section 3.4.2) using mifepristone plus misoprostol, or misoprostol alone‡

Type of health worker	Recommendation	Rationale[a]
Community health workers (CHWs)	**Recommend**	Evidence was found for the safety, effectiveness and acceptability of this option, for all three subtasks of medical abortion (moderate certainty). The skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] Indirect evidence also demonstrated the feasibility and acceptability of CHWs facilitating assessment of eligibility and outcome.
Pharmacy workers	**Recommend**	Limited evidence was found for the safety, effectiveness, acceptability or feasibility of this option (non-comparative studies). The skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] Indirect evidence on CHWs was applied to support the feasibility of this option.
Pharmacists	**Recommend**	Although insufficient evidence was found for the safety, effectiveness and acceptability of pharmacists performing the three subtasks of medical abortion, the skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] Dispensing medicines on prescription is within their typical scope of practice. The expert panel affirmed that, with the aid of tools for assessment of eligibility and outcome, it would be feasible for pharmacists to provide all three subtasks of medical abortion.
Traditional and complementary medicine professionals	**Recommend**	Evidence was found for the safety and effectiveness of this option, and for women's satisfaction with this type of provider and services provided by them (very low certainty). The skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] The expert panel affirmed that the benefits outweigh any possible harms, and the potential to increase equitable access to quality abortion care in regions where these professionals constitute a significant proportion of the health workforce is high.
Auxiliary nurses/ANMs	**Recommend**	Evidence was found for the safety and effectiveness of this option (moderate certainty). This option is feasible and is already being implemented in some low-resource settings.
Nurses	**Recommend**	Evidence was found for the safety and effectiveness of this option, and for women's satisfaction with abortion services with this option (moderate certainty).
Midwives	**Recommend**	Evidence was found for the safety and effectiveness of this option (moderate certainty). More women are satisfied with the provider when midwives provide medical abortion (moderate-certainty evidence). This option is feasible and is already being implemented in several countries.
Associate/advanced associate clinicians	**Recommend**	Insufficient direct evidence was found for the effectiveness of these clinicians carrying out components of the task, e.g. assessing gestational age as part of provision of manual vacuum aspiration. Evidence was also found that health worker types with similar or less comprehensive basic training (e.g. midwives, nurses, auxiliary nurse midwives) can provide medical abortion safely and effectively (moderate certainty). This option is feasible and the potential to expand access to underserved populations is high.
Generalist medical practitioners **Specialist medical practitioners**	**Recommend**	Within their typical scope of practice,[b] therefore no assessment of the evidence was conducted.

Table Continues

Table Continued

Type of health worker	Recommendation	Rationale[a]
Individual/self		
Pregnant woman, girl or other pregnant person	**Recommend**	Please refer to Recommendation 50 in section 3.6.2 for rationale, remarks and implementation considerations for this recommendation and further information on self-management approaches.

Source: Recommendation updated from WHO (2015) *(23)*.

Note on updating of the recommendation: This was an existing recommendation for which evidence relating to traditional and complementary medicine professionals (previously only recommended in contexts with established health system mechanisms for the participation of these health workers in other tasks related to maternal and reproductive health), pharmacists (previously only suggested in the context of rigorous research), pharmacy workers (previously "recommend against"), community health workers (previously only suggested in the context of rigorous research) and individual/self (self-management; previously "suggest") was reviewed using GRADE methodology. After review, the recommendations were upgraded for all of those health worker categories to "recommend", including all three subtasks of this intervention. A summary of the evidence is presented in Supplementary material 3, EtD framework for Medical abortion at < 12 weeks.

[a] For this and all health worker recommendations, given the limited evidence for many of the health worker–task combinations, the discussions of the expert panel focused on the competency framework in WHO's 2011 publication, *Sexual and reproductive health: core competencies in primary care (121)*, which provides information on the competencies (including skills and knowledge) required for each task, and also the WHO-INTEGRATE criteria, in particular on the feasibility, equity and acceptability of the intervention and women's values and preferences.

[b] For typical scope of work/practice, please refer to Annex 5: Health worker categories and roles.

* Available evidence for the independent provision of medical abortion by non-physicians is for pregnancy durations up to 10 weeks (70 days).

‡ For this recommendation, the medical abortion regimens covered in the available evidence were mifepristone plus misoprostol, or misoprostol alone (the regimen using letrozole was not included).



No requirement for location (on-site vs off-site).



Implementation considerations

- It is not essential that the person providing the medical abortion should also be trained and competent in vacuum aspiration provision.
- Restrictions on prescribing and dispensing authority for some categories of health workers may need to be modified within the regulatory framework of the health system or other mechanisms put in place to allow these providers to make the medicines available to abortion seekers.
- Privacy should be ensured in all settings, in particular in places where a private space may be challenging (e.g. pharmacies).
- Support tools can be used to assess eligibility and outcome (e.g. high-sensitivity pregnancy tests, checklists).
- A range of service-delivery models exist to facilitate the medical abortion process, such as telemedicine or community outreach (see section 3.6.1).
- Mechanisms to ensure access to quality medicines need to be set up. Development of tools like point-of-care tests to assess quality could support both the pharmacy worker and the individual.
- It is important to note that as with all other medicines, pharmacy workers should dispense mifepristone and misoprostol as indicated by prescription.
- The person undergoing medical abortion should have access/referral to emergency care in case this becomes necessary.
- As part of the enabling environment, health workers should recognize self-management as a legitimate pathway to abortion care and to adapt health systems to facilitate and support women in their self-management of abortion, e.g. adapting clinical protocols.
- Mechanisms need to be established to ensure access or referrals to post-abortion contraception services and provision of contraceptives for women who want them.

What

CLINICAL SERVICES Recommendation 29: Medical management of induced abortion at gestational ages ≥ 12 weeks

For medical abortion at ≥ 12 weeks:

a. **Suggest** the use of 200 mg mifepristone administered orally, followed 1–2 days later by repeat doses of 400 µg misoprostol administered buccally, sublingually or vaginally every 3 hours.*‡ The minimum recommended interval between use of mifepristone and misoprostol is 24 hours.

b. When using misoprostol alone: **Suggest** the use of repeat doses of 400 µg misoprostol administered vaginally, sublingually or buccally every 3 hours.*‡

Remarks:

- The combination regimen (Recommendation 29a) is more effective than use of misoprostol alone.
- Evidence suggests that the vaginal route is the most effective. Consideration for patient and provider preference suggests the inclusion of all routes.
- Pregnancy tissue should be treated in the same way as other biological material unless the individual expresses a desire for it to be managed otherwise.

* Misoprostol can be repeated at the noted interval as needed to achieve success of the abortion process. Providers should use caution and clinical judgement to decide the maximum number of doses of misoprostol in pregnant individuals with a prior uterine incision. Uterine rupture is a rare complication; clinical judgement and health system preparedness for emergency management of uterine rupture must be considered with later gestational age.

‡ The dose of misoprostol should be reduced for induced abortion beyond 24 weeks due to limited data. Clinical judgement should be used to determine the appropriate dosage, recognizing the greater sensitivity of the uterus to prostaglandins.

Source: Recommendation 3b carried forward from WHO (2018) *(120).*

Who

SERVICE DELIVERY Recommendation 30: Medical management of induced abortion at gestational ages ≥ 12 weeks

Type of health worker	Recommendation	Rationale[a]
Traditional and complementary medicine professionals	**Suggest** Condition: In contexts where established and easy access to appropriate surgical backup and proper infrastructure is available to address incomplete abortion or other complications.	Although no direct evidence was found on the safety, effectiveness or acceptability of this option, the skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] In addition, these professionals have been recommended to provide medical abortion at < 12 weeks (Recommendation 28). The potential to increase equitable access to quality abortion care in regions where these professionals form a significant proportion of the health workforce is high.
Auxiliary nurses/ANMs	**Suggest** Condition: In contexts where established and easy access to appropriate surgical backup and proper infrastructure is available to address incomplete abortion or other complications.	Although no direct evidence was found on the safety, effectiveness or acceptability of this option, the skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] In addition, these health workers have been recommended to provide medical abortion at < 12 weeks (Recommendation 28). This option is feasible and acceptable and has the potential to increase equitable access to quality abortion care.

Table Continues

Table Continued

Type of health worker	Recommendation	Rationale[a]
Nurses	**Suggest** Condition: In contexts where established and easy access to appropriate surgical backup and proper infrastructure is available to address incomplete abortion or other complications.	Although insufficient direct evidence was found for the safety and effectiveness of nurses providing this intervention as a whole, these health workers are often responsible for the monitoring and care of women from the time of misoprostol administration to completion of the abortion. Women often find abortion care provided by nurses to be more acceptable (moderate-certainty evidence).
Midwives	**Suggest** Condition: In contexts where established and easy access to appropriate surgical backup and proper infrastructure is available to address incomplete abortion or other complications.	Although insufficient direct evidence was found for the safety and effectiveness of midwives providing this intervention as a whole, these health workers are often responsible for the monitoring and care of women from the time of misoprostol administration to completion of the abortion. Women often find abortion care provided by midwives to be more acceptable (moderate-certainty evidence).
Associate/advanced associate clinicians	**Suggest** Condition: In contexts where established and easy access to appropriate surgical backup and proper infrastructure is available to address incomplete abortion or other complications.	Although insufficient direct evidence was found for the safety of effectiveness of this option, these clinicians routinely carry out tasks of similar complexity (e.g. vacuum aspiration and manual removal of placenta) *(138)*. These clinicians are often present at higher-level facilities where care during advanced gestation is provided. A trained specialist medical practitioner may not always be present at higher-level facilities and the potential to sustain services for advanced gestational ages is increased with more than one trained provider on site.
Generalist medical practitioners	**Recommend**	Although insufficient direct evidence was found for the safety and effectiveness of this option, generalist medical practitioners routinely carry out tasks of similar or greater complexity (e.g. conducting deliveries, manual removal of placenta, vacuum aspiration). The potential benefits of this option outweigh the harms and the intervention has proven feasible in several settings. A specialist medical practitioner may not always be available on-site and therefore this option may increase equitable access to quality abortion care.
Specialist medical practitioners	**Recommend**	Within their typical scope of practice,[b] therefore no assessment of the evidence was conducted.

Source: Recommendation updated from WHO (2015) *(23)*.

Notes on updating of the recommendation: This was an existing recommendation for which evidence relating to all health worker categories was reviewed using GRADE methodology, except for specialist and generalist medical practitioners, for whom there was already a strong recommendation for this task. After review, the recommendations were upgraded for traditional and complementary medicine professionals and auxiliary nurses/ANMs from "recommend against" to "suggest" with specified conditions. For the other health worker categories reviewed, the recommendations remain unchanged. A summary of the evidence is presented in Supplementary material 3, EtD framework for Medical abortion at ≥ 12 weeks.

[a] For this and all health worker recommendations, given the limited evidence for many of the health worker–task combinations, the discussions of the expert panel focused on the competency framework in WHO's 2011 publication, *Sexual and reproductive health: core competencies in primary care (121)*, which provides information on the competencies (including skills and knowledge) required for each task, and also the WHO-INTEGRATE criteria, in particular on the feasibility, equity and acceptability of the intervention and women's values and preferences.

[b] For typical scope of work/practice, please refer to Annex 5: Health worker categories and roles.



Medical abortion for pregnancies at gestational ages ≥ 12 weeks has been practised and researched as a facility-based procedure during which women should remain under observation until the process is complete.



Implementation consideration

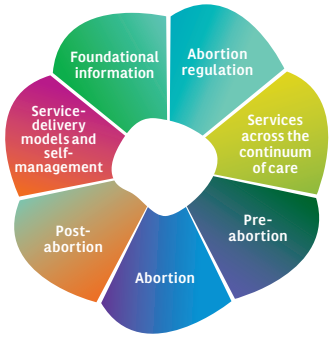
- Health workers providing abortion or caring for women undergoing abortion at gestational ages ≥ 12 weeks may have additional needs for professional and mentoring support.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO MEDICAL ABORTION

- Everyone has a right to privacy and confidentiality in sexual and reproductive health (SRH) care.
- Abortion regulation should be human rights and evidence based.
- States must ensure adequate access to essential medicines in an affordable and non-discriminatory manner.
- Everyone has the right to scientific progress and right to health, which requires the availability and accessibility, acceptability, and quality of medical abortion. This means that States should ensure access to abortion medicines, and that evidence-based standards and guidelines for the provision and delivery of SRH services, are (i) in place and (ii) routinely updated to incorporate medical advancements.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

Links to related topics/recommendations



All recommendations related to law and policy (Recommendations 1,2,3,6,7,21,22)

Information provision and counselling (section 3.2.1 and 3.2.2)

Determining gestational age (section 3.3.5)

Pain management for abortion (section 3.3.6)

Self-management of medical abortion (section 3.6.2)

3.4.3 Missed abortion

Missed abortion is when a pregnancy stops developing, where the embryo/fetus/embryonic tissue or empty gestation sac remains in the uterus and the cervical os is closed. Symptoms may include pain, bleeding or no symptoms at all. If an ultrasound is done, the scan may show an embryo or fetus without cardiac activity, or what appears to be an early developing pregnancy, with only a fluid-filled sac visible within the uterus *(151)*. Medical, surgical (vacuum aspiration) and expectant management are all options for management of missed abortion.

What

CLINICAL SERVICES Recommendation 31 (NEW): Medical management of missed abortion at gestational ages < 14 weeks

For missed abortion at < 14 weeks, for individuals preferring medical management: **Recommend** the use of combination mifepristone plus misoprostol over misoprostol alone.

- Recommended regimen: 200 mg mifepristone administered orally, followed by 800 µg misoprostol administered by any route (buccal, sublingual, vaginal).*
- Alternative regimen: 800 µg misoprostol administered by any route (buccal, sublingual, vaginal).‡

Remarks:

- The decision about the mode of management (expectant, medical or surgical) of missed abortion should be based on the individual's clinical condition and preference for treatment.
- Expectant management can be offered as an option on the condition that the woman, girl or other pregnant person is informed of the longer time for expulsion of the pregnancy tissue and the increased risk of incomplete emptying of the uterus.
- Pregnancy tissue should be treated in the same way as other biological material unless the individual expresses a desire for it to be managed otherwise.

* The minimum recommended interval between use of mifepristone and misoprostol is 24 hours.

‡ If using the alternative regimen (misoprostol alone), it should be noted that at gestational ages ≥ 9 weeks, evidence shows that repeat dosing of misoprostol is more effective to achieve success of the abortion process. In this guideline we do not provide a maximum number of doses of misoprostol.

Rationale

A systematic review was undertaken to address this key question. Twenty studies reporting on management for missed abortion were identified by the search strategy. These studies were conducted in China, Germany, India, Israel, Malaysia, Pakistan, Sweden, Thailand, United Kingdom, USA and Yemen. A summary of the evidence is presented in Supplementary material 2, EtD framework for Medical management of missed abortion at < 14 weeks.

Of these studies, 19 were assessed that included one of the following comparisons:

- Mifepristone and misoprostol versus misoprostol alone
- Medical versus expectant management
- Surgical versus medical/expectant management

Medical management in comparison to expectant management produced lower rates of ongoing pregnancy and higher rates of successful abortion (uterine evacuation without surgical intervention), based on moderate- to high-certainty evidence. When comparing the combination regimen with misoprostol alone, the combination regimen produced higher rates of successful abortion. This recommendation is based on moderate-certainty evidence. Complications and side-effects were also fewer, based on moderate- to high-certainty evidence. Women expressed greater satisfaction with the combination mifepristone plus misoprostol regimen, based on high-certainty evidence. Surgical management in comparison to medical and expectant management produced higher rates of successful abortion, based on low- to moderate-certainty evidence. Discussion of women's values and preferences underlined the importance of offering the option of all three types of management to the woman. For the medical regimen, the expert panel determined that given the varied regimens of the included studies, the recommended and suggested regimens for induced abortion at < 12 weeks of gestation can be applied (see Recommendation 27).

Who

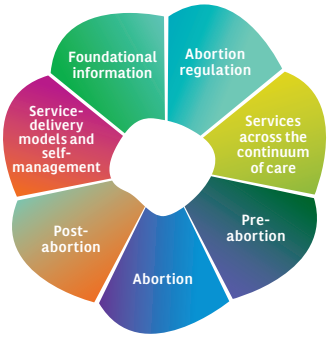
Regarding who is recommended to provide medical management of missed abortion at < 14 weeks of gestation, refer to Recommendation 28 for medical management of induced abortion at gestational ages < 12 weeks.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO MANAGEMENT OF MISSED ABORTION

- Everyone has a right to privacy and confidentiality in sexual and reproductive health (SRH) care.
- Abortion regulation should be human rights and evidence based.
- States must ensure adequate access to essential medicines in an affordable and non-discriminatory manner.
- Everyone has the right to scientific progress and right to health, which requires the availability and accessibility, acceptability, and quality of medical abortion. This means that States should ensure access to abortion medicines, and that evidence-based standards and guidelines for the provision and delivery of SRH services, are (i) in place and (ii) routinely updated to incorporate medical advancements.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

Links to related topics/recommendations



Commodities (section 1.3.4)

Information provision and counselling (sections 3.2.1 and 3.2.2)

Recommendation 27: Medical management of induced abortion < 12 weeks

3.4.4 Intrauterine fetal demise (IUFD)

Fetal demise (fetal death) refers to situations in which the fetus is no longer alive, but the uterus has not yet started to expel its contents and the cervical os remains closed *(152)*. The diagnosis is made by ultrasound scan following the clinical findings, which can include vaginal bleeding, absent fetal heart sounds on electronic auscultation, a failure to feel fetal movements or a uterus that is significantly smaller than the expected size *(152)*. IUFD may be managed expectantly, or treated surgically (D&E) or medically.

What

CLINICAL SERVICES Recommendation 32: Medical management of IUFD at gestational ages ≥ 14 to ≤ 28 weeks

For medical management of IUFD at ≥ 14 to ≤ 28 weeks: **Suggest** the use of combination mifepristone plus misoprostol over misoprostol alone.

- Suggested regimen: 200 mg mifepristone administered orally, followed 1–2 days later by repeat doses of 400 µg misoprostol administered sublingually or vaginally every 4–6 hours.*‡ The minimum recommended interval between use of mifepristone and misoprostol is 24 hours.
- Alternative regimens: repeat doses of 400 µg misoprostol administered sublingually or vaginally every 4–6 hours.*‡

Remarks:

- Evidence from clinical studies indicates that the combination regimen is more effective than the use of misoprostol alone.
- Pregnancy tissue should be treated in the same way as other biological material unless the individual expresses a desire for it to be managed otherwise.

* Misoprostol can be repeated at the noted interval as needed to achieve success of the abortion process. Providers should use caution and clinical judgement to decide the maximum number of doses of misoprostol in pregnant individuals with prior uterine incision. Uterine rupture is a rare complication; clinical judgement and health system preparedness for emergency management of uterine rupture must be considered with later gestational age.

‡ The dose of misoprostol should be reduced for IUFD beyond 28 weeks due to limited data. Clinical judgement should be used to determine the appropriate dosage, recognizing the greater sensitivity of the uterus to prostaglandins.

Source: Recommendation 2 carried forward from WHO (2018) *(120)*. Wording has been revised to match that used for Recommendation 31 on missed abortion.

Who

SERVICE DELIVERY Recommendation 33 (NEW): Medical management of intrauterine fetal demise (IUFD) at gestational ages ≥ 14 to ≤ 28 weeks

Type of health worker	Recommendation	Rationale[a]
Traditional and complementary medicine professionals	**Suggest** Condition: In contexts where established and easy access to appropriate surgical backup and proper infrastructure is available to address incomplete abortion or other complications.	Although no direct evidence was found on the safety, effectiveness or acceptability of this option, the skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] In addition, these professionals have been recommended to provide medical abortion at < 12 weeks (Recommendation 28). The expert panel affirmed that the potential to increase equitable access to quality abortion care in regions where such professionals constitute a significant proportion of the health workforce is high.
Auxiliary nurses/ANMs	**Suggest** Condition: In contexts where established and easy access to appropriate surgical backup and proper infrastructure is available to address incomplete abortion or other complications.	Although no direct evidence was found on the safety, effectiveness or acceptability of this option, the skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] In addition, these health workers have been recommended to provide medical abortion at < 12 weeks (Recommendation 28). The expert panel determined that this option is feasible and acceptable with the potential to increase equitable access to quality abortion care.

Table Continues

Table Continued

Type of health worker	Recommendation	Rationale[a]
Nurses	**Suggest** Condition: In contexts where established and easy access to appropriate surgical backup and proper infrastructure is available to address incomplete abortion or other complications.	Although insufficient direct evidence was found for the safety and effectiveness of this option, these health workers are often responsible for the monitoring and care of women from the time of misoprostol administration to completion of the abortion. Women often find abortion care provided by nurses to be more acceptable compared with other health workers (moderate-certainty evidence).
Midwives	**Suggest** Condition: In contexts where established and easy access to appropriate surgical backup and proper infrastructure is available to address incomplete abortion or other complications.	Although insufficient direct evidence was found for the safety and effectiveness of this option, these health workers are often responsible for the monitoring and care of women from the time of misoprostol administration to completion of the abortion. Women often find abortion care provided by midwives to be more acceptable compared with other health workers (moderate-certainty evidence).
Associate/advanced associate clinicians	**Suggest** Condition: In contexts where established and easy access to appropriate surgical backup and proper infrastructure is available to address incomplete abortion or other complications.	Although insufficient direct evidence was found for the safety and effectiveness of this option, these clinicians routinely carry out tasks of similar complexity, such as vacuum aspiration and manual removal of placentas *(138)*. These clinicians are often present at higher-level facilities where care is provided in advanced gestation. A trained specialist medical practitioner may not always be present at a higher-level facility and the potential to sustain services for advanced gestational ages is increased with more than one trained provider on site.
Generalist medical practitioners	Recommend	Although insufficient direct evidence was found for the safety and effectiveness of this option, these professionals routinely carry out tasks of similar or greater complexity (e.g. conducting deliveries, manual removal of placentas, vacuum aspiration). The potential benefits of this option outweigh the harms, and the intervention has proven feasible in several settings. A specialist medical practitioner may not always be available on site and therefore this option may increase equitable access to quality abortion care.
Specialist medical practitioners	Recommend	Within their typical scope of practice,[b] therefore no assessment of the evidence was conducted.

Note: This is a new recommendation. There was no recommendation on medical management of IUFD in WHO's 2015 guideline on health worker roles *(23)*, but a clinical services recommendation on this intervention was provided in WHO's 2018 guideline, *Medical management of abortion (120)*. Due to the lack of direct evidence on this topic and the similarity between the two tasks, Recommendation 30 for medical abortion at ≥ 12 weeks of gestation was applied here. A summary of the evidence is presented in Supplementary material 3, EtD framework on Medical management of intrauterine fetal demise.

[a] For this and all health worker recommendations, given the limited evidence for many of the health worker–task combinations, the discussions of the expert panel focused on the competency framework in WHO's 2011 publication, *Sexual and reproductive health: core competencies in primary care (121)*, which provides information on the competencies (including skills and knowledge) required for each task, and also the WHO-INTEGRATE criteria, in particular on the feasibility, equity and acceptability of the intervention and women's values and preferences.

[b] For typical scope of work/practice, please refer to Annex 5: Health worker categories and roles.

Where

Medical abortion for pregnancies at gestational ages ≥ 12 weeks has been practised and researched as a facility-based procedure during which women should remain under observation until the process is complete.

How

Implementation consideration

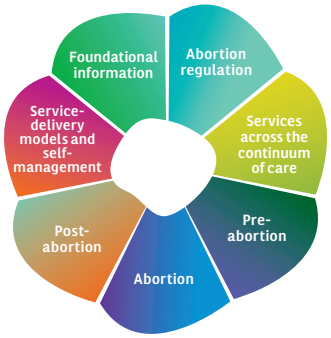
- Any regulation around the management/disposal of pregnancy remains and birth or death certificates should not pose a burden or a breach of confidentiality for women or providers.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO MANAGEMENT OF IUFD

- Everyone has a right to privacy and confidentiality in sexual and reproductive health (SRH) care.
- Abortion regulation should be human rights and evidence based.
- States must ensure adequate access to essential medicines in an affordable and non-discriminatory manner.
- Everyone has the right to scientific progress and right to health, which requires the availability and accessibility, acceptability, and quality of medical abortion. This means that States should ensure access to abortion medicines, and that evidence-based standards and guidelines for the provision and delivery of SRH services, are (i) in place and (ii) routinely updated to incorporate medical advancements.

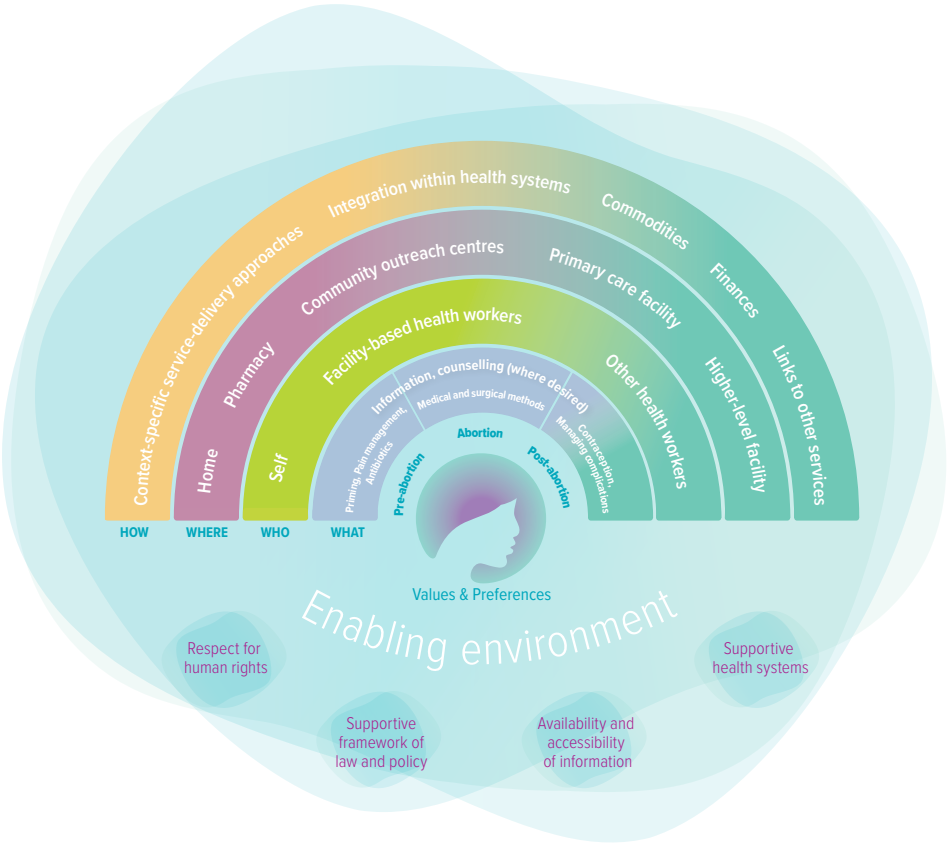
For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

Links to related topics/recommendations



All recommendations relating to law and policy (Recommendations 1,2,3,6,7,21,22)

3.5 Post-abortion



The post-abortion period is the third and final part of the continuum of care for abortion. Post-abortion care includes any or all of the following, as needed or desired: optional follow-up check-up, management of residual side-effects or complications, and contraception services. When done safely, abortion complications are rare, but they can include incomplete abortion, haemorrhage, infection, uterine perforation, anaesthesia-related complications, uterine rupture. In line with international human rights law and medical best practice, post-abortion care should always be provided regardless of whether abortion is restricted in a particular setting.

3.5.1 Follow-up care after abortion

Routine follow-up is not necessary following an uncomplicated surgical or medical abortion, if the individual has adequate information about when to seek care for complications and has received any appropriate supplies or information to meet contraceptive needs. However, an optional follow-up visit 7–14 days after the procedure may be offered to provide contraceptive services, emotional support or management of any medical concerns.

If the woman chooses to attend a follow-up appointment, then use the contact to:

- assess the individual's recovery and inquire about any signs or symptoms of ongoing pregnancy;
- review any available medical records and referral documents;
- ask about any symptoms experienced since the procedure;
- perform a focused physical examination if needed to assess any complaints; and
- assess the individual's fertility goals and need for contraceptive services.
    - If no contraceptive method was provided or started at the time of the abortion, provide information on contraception and offer contraceptive counselling and provision of contraceptive services, if desired by the woman.
    - If a contraceptive method was already started, assess the method used and address any concerns or resupply as needed *(122)*.

What

CLINICAL SERVICES Recommendation 34: Follow-up care or additional services after abortion

Following uncomplicated surgical abortion or medical abortion: **Recommend** that there is no medical need for a routine follow-up visit. However, information should be provided about the availability of additional services if they are needed or desired.

Remarks:

- Women, girls and other pregnant persons must be adequately informed about symptoms of ongoing pregnancy (which may or may not indicate failure of the abortion) and other medical reasons to return for follow-up, such as prolonged heavy bleeding, no bleeding at all with medical management of abortion, pain not relieved by medication, or fever.
- The quality of the evidence was low (observational studies and indirect evidence).

Source: Recommendation 9 updated from WHO (2012) *(19)*.

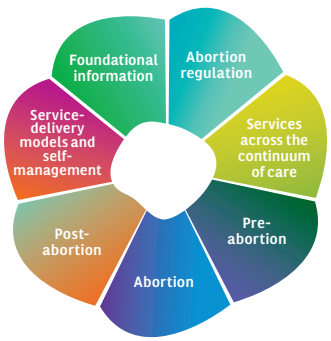
Note on updating of the recommendation: This was an existing recommendation for which an updated literature search was conducted, but GRADE methodology was not applied. The wording of the recommendation was revised to remove the medical abortion regimen that was mentioned (this recommendation now applies to all abortion methods and regimens, see section 3.4) and to use the word "recommend" to make clear this is a strong recommendation.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO FOLLOW-UP CARE

- Regardless of whether abortion is legal, States are required to ensure access to post-abortion care where it is needed.
- Post-abortion care must be available on a confidential basis, including in situations where abortion is illegal.
- Post-abortion care must be available without the threat of criminal prosecution or punitive measures. States must not require health workers to report persons suspected of undertaking unlawful abortion, or require them to provide any potentially incriminating information during or as a prerequisite to receiving post-abortion care.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

Links to related topics/recommendations



All recommendations relating to law and policy (Recommendations 1,2,3,6,7,21,22)

Information provision (section 3.2.1)

3.5.2 Incomplete abortion

Incomplete abortion is defined by clinical presence of an open cervical os and bleeding, whereby all products of conception have not been expelled from the uterus, or the expelled products are not consistent with the estimated duration of pregnancy. Common symptoms include vaginal bleeding and abdominal pain. Uncomplicated incomplete abortion can result after an induced or spontaneous abortion (i.e. miscarriage); the management in both cases is the same. Incomplete abortion may be managed expectantly, medically or surgically (vacuum aspiration). Managing uncomplicated incomplete abortion with vacuum aspiration (when uterine size is less than 14 weeks) includes recognizing the condition, assessing uterine size, the actual procedure and pain management.

What

CLINICAL SERVICES Recommendation 35 and 36:
Management of incomplete abortion

35. For incomplete abortion at < 14 weeks: **Recommend** either vacuum aspiration or medical management.

36a. For the medical management of incomplete abortion at < 14 weeks uterine size: **Suggest** the use of 600 µg misoprostol administered orally or 400 µg misoprostol administered sublingually.

36b. For the medical management of incomplete abortion at ≥ 14 weeks uterine size: **Suggest** the use of repeat doses of 400 µg misoprostol administered sublingually, vaginally or buccally every 3 hours.*

Remarks:

- The decision about the mode of management of incomplete abortion should be based on the individual's clinical condition and preference for treatment.
- Expectant management of incomplete abortion can be as effective as misoprostol; it can be offered as an option on the condition that the woman, girl or other pregnant person is informed of the longer time for expulsion of the pregnancy tissue and the increased risk of incomplete emptying of the uterus.
- Recommendation 35 was extrapolated from research conducted in women with reported spontaneous abortion.

* Misoprostol can be repeated at the noted interval as needed to achieve success of the abortion process. At gestational ages ≥ 14 weeks, providers should use caution and clinical judgement to decide the maximum number of doses of misoprostol in pregnant individuals with prior uterine incision. Uterine rupture is a rare complication; clinical judgement and health system preparedness for emergency management of uterine rupture must be considered with advanced gestational age.

Source: Recommendation 35 carried forward from WHO (2012) where it was Recommendation 10 *(19)*. The wording has been revised to amend the gestational age from "13 weeks or less" to "before 14 weeks" (< 14 weeks). Recommendations 36a and 36b carried forward from WHO (2018) where they were Recommendations 1A and 1B *(120)*. The gestational ages have also been updated to change the cut-off point from 13 weeks to 14 weeks.

Who

SERVICE DELIVERY Recommendation 37: Medical management of uncomplicated incomplete abortion with misoprostol at gestational ages < 14 weeks

Type of health worker	Recommendation	Rationale[a]
Community health workers (CHWs)	**Recommend**	No direct evidence was found for this option, but some indirect evidence was found that CHWs can use simple tools and checklists to determine gestational age (based on patient history), and to assess eligibility for and the outcome of medical abortion (low to moderate certainty). CHWs are often involved in advising women seeking abortion care (moderate-certainty evidence). In general, CHW interventions are acceptable and have proved feasible in many contexts. The skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a]
Pharmacy workers **Pharmacists**	**Recommend**	Although insufficient evidence was found for the safety and effectiveness of this option, the skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] In addition, the skills required for managing incomplete abortion with misoprostol are similar to those for provision of medical abortion at < 12 weeks, which is a recommended task for these health workers (see Recommendation 28).
Traditional and complementary medicine professionals	**Recommend**	Evidence was found for the safety and effectiveness of these professionals providing medical abortion at gestational ages < 12 weeks (low certainty), and the skills required for managing incomplete abortion with misoprostol are similar. In addition, the skills and knowledge for this task (according to the competency framework) align with the competencies of this type of health worker.[a]
Auxiliary nurses/ANMs	**Recommend**	Evidence was found for the safety and effectiveness of these health workers providing medical abortion at gestational ages < 12 weeks (moderate certainty), and the skills required for managing incomplete abortion with misoprostol are similar.
Nurses	**Recommend**	Indirect evidence was found for the safety, effectiveness and acceptability of nurses providing medical abortion (moderate certainty), and the skills required for managing incomplete abortion with misoprostol are similar. The option is feasible and has the potential to increase equitable access to quality abortion care.
Midwives	**Recommend**	Evidence was found from a low-resource setting for the safety and effectiveness of this option (moderate to high certainty). Women's overall satisfaction with the provider was high when midwives manage incomplete abortion (moderate-certainty evidence). This option is feasible and has the potential to increase equitable access to quality abortion care.
Associate/advanced associate clinicians	**Recommend**	Moderate-certainty indirect evidence was found for the safety and effectiveness of medical management of incomplete abortion by midwives, and moderate-certainty evidence was also found for the safety and effectiveness of medical abortion provision by health worker types with similar or less comprehensive basic training. Additionally, direct evidence was found that these clinicians can assess gestational age (by uterine size) as part of provision of manual vacuum aspiration. This option is feasible and the potential to increase equitable access to quality abortion care is high.
Generalist medical practitioners **Specialist medical practitioners**	**Recommend**	Within their typical scope of practice,[b] therefore no assessment of the evidence was conducted.

Source: Recommendation updated from WHO (2015) *(23)*.

Note on updating of the recommendation: This was an existing recommendations for which evidence relating to traditional and complementary medicine professionals (previously "suggest"), pharmacists and pharmacy workers (both previously "recommend against") and community health workers (previously "within the context of rigorous research") was reviewed using GRADE methodology, since the other health workers already had a strong recommendation for this task. After review, the recommendations were upgraded to "recommend" for all of the reviewed health worker categories. A summary of the evidence is presented in Supplementary material 3, EtD framework on Medical management of incomplete abortion.

[a] For this and all health worker recommendations, given the limited evidence for many of the health worker–task combinations, the discussions of the expert panel focused on the competency framework in WHO's 2011 publication, *Sexual and reproductive health: core competencies in primary care (121)*, which provides information on the competencies (including skills and knowledge) required for each task, and also the WHO-INTEGRATE criteria, in particular on the feasibility, equity and acceptability of the intervention and women's values and preferences.

[b] For typical scope of work/practice, please refer to Annex 5: Health worker categories and roles.

Where

No requirement for location (on-site vs off-site).

How

Implementation considerations

- Restrictions on prescribing authority for some categories of providers may need to be modified or other mechanisms put in place for making the medicines available for these providers within the regulatory framework of the health system.
- The evacuation of retained products is a signal function of basic emergency obstetric care (EmOC); thus training and implementation of these tasks can be integrated with EmOC services.

Who

SERVICE DELIVERY Recommendation 38: Vacuum aspiration for management of uncomplicated incomplete abortion at gestational ages < 14 weeks

Type of health worker	Recommendation	Rationale[a]
Traditional and complementary medicine professionals	**Recommend**	Evidence was found for the effectiveness of these professionals carrying out components of the task, such as assessing uterine size with bimanual examination as part of medical abortion provision (very low certainty). The skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] These professionals perform other transcervical procedures (e.g. IUD insertion) in some settings. This option has the potential to increase equitable access to quality abortion care in regions where these professionals constitute a significant proportion of the health workforce.
Auxiliary nurses/ANMs	**Suggest** Condition: In contexts where established health system mechanisms involve auxiliary nurses/ANMs in providing basic emergency obstetric care, and where referral and monitoring systems are strong.	Insufficient direct evidence was found for the safety and effectiveness of this option. However, the option of this type of health worker delivering emergency obstetric care (which includes removing retained products as a signal function) or post-abortion care using manual vacuum aspiration has been shown to be feasible in programmes in several low-resource settings.
Nurses	**Recommend**	Evidence was found for the safety and effectiveness of these health workers providing vacuum aspiration for induced abortion (low certainty), and the skills required for the management of uncomplicated incomplete abortion with vacuum aspiration are similar. The option is feasible, including in low-resource settings.
Midwives	**Recommend**	Indirect evidence was found for the safety and effectiveness of these health workers providing vacuum aspiration for induced abortion (moderate certainty), and the skills required for the management of uncomplicated incomplete abortion with vacuum aspiration are similar. The option is feasible, including in low-resource settings.

Table Continues

Table Continued

Type of health worker	Recommendation	Rationale[a]
Associate/advanced associate clinicians	**Recommend**	Indirect evidence was found for the safety and effectiveness of these clinicians providing of vacuum aspiration for induced abortion (moderate certainty), and the skills required for the management of uncomplicated incomplete abortion with vacuum aspiration are similar.
Generalist medical practitioners **Specialist medical practitioners**	**Recommend**	Within their typical scope of practice,[b] therefore no assessment of the evidence was conducted.

Source: Recommendation updated from WHO (2015) *(23)*.

Note on updating of the recommendation: This was an existing recommendation for which evidence relating to traditional and complementary medicine professionals and for auxiliary nurses and auxiliary nurse midwives was reviewed using GRADE methodology. After review, only the recommendation for traditional and complementary medicine professionals was upgraded from "suggest" to "recommend". For all the other health worker categories, the recommendations remain unchanged from the previous guidance. A summary of the evidence is presented in Supplementary material 3, EtD framework on Vacuum aspiration for management of incomplete abortion.

[a] For this and all health worker recommendations, given the limited evidence for many of the health worker–task combinations, the discussions of the expert panel focused on the competency framework in WHO's 2011 publication, *Sexual and reproductive health: core competencies in primary care (121)*, which provides information on the competencies (including skills and knowledge) required for each task, and also the WHO-INTEGRATE criteria, in particular on the feasibility, equity and acceptability of the intervention and women's values and preferences.

[b] For typical scope of work/practice, please refer to Annex 5: Health worker categories and roles.

Where

In a health-care facility.

How

Implementation considerations

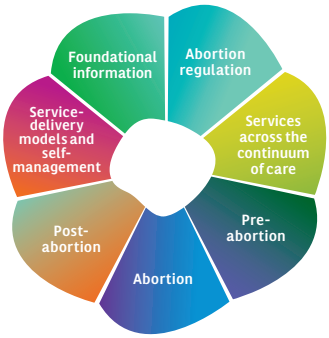
- The skills required for the provision of both MVA and EVA are similar, so the recommendations above apply to both. MVA is more commonly used and more likely to be used in primary care settings.
- Uncomplicated incomplete abortion can result after an induced or spontaneous abortion (i.e. miscarriage). The management is identical and the above recommendations apply to both.
- The evacuation of retained products is also a signal function of basic emergency obstetric care (EmOC) and training and implementation can be integrated with EmOC services.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO MANAGEMENT OF INCOMPLETE ABORTION

- States must ensure adequate access to essential medicines in an affordable and non-discriminatory manner.
- Regardless of whether abortion is legal, States are required to ensure access to post-abortion care where it is needed.
- Post-abortion care must be available on a confidential basis, including in situations where abortion is illegal.
- Post-abortion care must be available without the threat of criminal prosecution or punitive measures. States must not require health workers to report persons suspected of undertaking unlawful abortion, or require them to provide any potentially incriminating information during or as a prerequisite to receiving post-abortion care.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

Links to related topics/recommendations



All recommendations relating to law and policy (Recommendations 1,2,3,6,7,21,22)

Commodities (section 1.4.4)

3.5.3 Management of non-life-threatening complications: infection and haemorrhage

Initial and basic management includes recognizing the complication, stabilizing the woman, providing oral or parenteral antibiotics and intravenous fluids prior to referral to an appropriate health worker/facility.

Who

SERVICE DELIVERY Recommendation 39: Initial management of non-life-threatening post-abortion infection*

Type of health worker	Recommendation	Rationale[a]
Traditional and complementary medicine professionals	**Recommend**	Although no direct evidence was found for the management of post-abortion infection by these health workers, their basic training covers the skills required for this task. The skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] The expert panel affirmed that this option is feasible and that it has the potential to increase equitable access to post-abortion care.
Auxiliary nurses/ANMs **Nurses** **Midwives** **Associate/advanced associate clinicians**	**Recommend**	Although no direct evidence was found for the management of post-abortion infection by these health workers, the management of puerperal sepsis with intramuscular antibiotics, which requires similar skills, is within their typical scope of practice *(138)*.[b]
Generalist medical practitioners **Specialist medical practitioners**	**Recommend**	Within their typical scope of practice,[b] therefore no assessment of the evidence was conducted.

Source: Recommendation updated from WHO (2015) *(23)*.

Note on updating of the recommendation: This was an existing recommendation for which evidence relating to traditional and complementary medicine professionals, pharmacists, pharmacy workers and community health workers was reviewed using GRADE methodology. After review, the recommendation was only upgraded for traditional and complementary medicine professionals, from "suggest" to "recommend." For all other health worker categories reviewed, the recommendations remain "recommend against" (not listed). A summary of the evidence is presented in Supplementary material 3, EtD framework on Diagnosis and management of abortion-related complications.

[a] For this and all health worker recommendations, given the limited evidence for many of the health worker–task combinations, the discussions of the expert panel focused on the competency framework in WHO's 2011 publication, *Sexual and reproductive health: core competencies in primary care (121)*, which provides information on the competencies (including skills and knowledge) required for each task, and also the WHO-INTEGRATE criteria, in particular on the feasibility, equity and acceptability of the intervention and women's values and preferences.

[b] For typical scope of work/practice, please refer to Annex 5: Health worker categories and roles.

* For the pharmacists, pharmacy workers and community health workers, it is important that they are equipped with the knowledge to recognize signs and symptoms of this complication.

Where

No requirement for location (on-site vs off-site).

How

Implementation considerations

- It is important that pharmacists, pharmacy workers and community health workers are equipped with the knowledge to recognize signs and symptoms of the complications of unsafe abortion and to know where to refer women in their communities.
- Restrictions on prescribing authority for some categories of providers may need to be modified or other mechanisms put in place for allowing such providers to administer the antibiotics within the regulatory framework of the health system.

Who

SERVICE DELIVERY Recommendation 40: Initial management of non-life-threatening post-abortion haemorrhage*

Type of health worker	Recommendation	Rationale[a]
Traditional and complementary medicine professionals	**Recommend**	No direct evidence was found for the management of post-abortion haemorrhage by these professionals, but their basic training covers the skills required for this task. The skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a]
Auxiliary nurses/ANMs	**Recommend**	Although no direct evidence was found for the management of post-abortion haemorrhage by these health workers, the initial management of post-partum haemorrhage with intravenous (IV) fluids, which requires similar skills, is a task that these health workers are recommended to do *(138)*.
Nurses **Midwives** **Associate/advanced associate clinicians**	**Recommend**	Although no direct evidence was found for the management of post-abortion haemorrhage by these health workers, the initial management of post-partum haemorrhage with IV fluids, which requires similar skills, is within their typical scope of practice *(138)*.
Generalist medical practitioners **Specialist medical practitioners**	**Recommend**	Within their typical scope of practice,[b] therefore no assessment of the evidence was conducted.

Source: Recommendation updated from WHO (2015) *(23)*.

Note on updating of the recommendation: This was an existing recommendation for which evidence relating to traditional and complementary medicine professionals, pharmacists, pharmacy workers and community health workers was reviewed using GRADE methodology. After review, the recommendation was only upgraded for traditional and complementary medicine professionals, from "suggest" to "recommend". For all other health worker categories reviewed, the recommendations remain "recommend against" (not listed). A summary of the evidence is presented in Supplementary material 3, EtD framework on Diagnosis and management of abortion-related complications.

[a] For this and all health worker recommendations, given the limited evidence for many of the health worker–task combinations, the discussions of the expert panel focused on the competency framework in WHO's 2011 publication, *Sexual and reproductive health: core competencies in primary care (121)*, which provides information on the competencies (including skills and knowledge) required for each task, and also the WHO-INTEGRATE criteria, in particular on the feasibility, equity and acceptability of the intervention and women's values and preferences.

[b] For typical scope of work/practice, please refer to Annex 5: Health worker categories and roles.

* For the pharmacists, pharmacy workers and community health workers, it is important that they are equipped with the knowledge to recognize signs and symptoms of this complication.

Where

No requirement for location (on-site vs off-site).

How

Implementation consideration

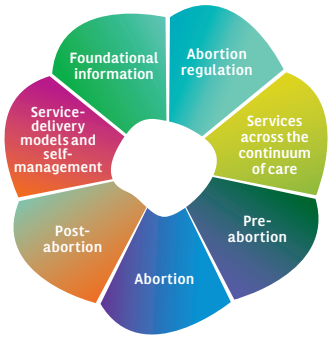
- Initial management of haemorrhage and infection is also a signal function of basic emergency obstetric care (EmOC) and training and implementation can be integrated with EmOC services.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO NON-LIFE-THREATENING COMPLICATIONS

- Regardless of whether abortion is legal, States are required to ensure access to post-abortion care where it is needed.
- Post-abortion care must be available on a confidential basis, including in situations where abortion is illegal.
- Post-abortion care must be available without the threat of criminal prosecution or punitive measures. States must not require health workers to report persons suspected of undertaking unlawful abortion, or require them to provide any potentially incriminating information during or as a prerequisite to receiving post-abortion care.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

Links to related topics/recommendations



All recommendations relating to law and policy (Recommendations 1,2,3,6,7,21,22)

3.5.4 Post-abortion contraception

Following an induced or spontaneous abortion, ovulation can return as early as 8–10 days later and usually within one month, and thus contraception initiation as soon as possible within the first month is important for women who desire to delay or prevent a future pregnancy *(153, 154)*. All contraceptive options may be considered after an abortion. The client's wishes are paramount; if the individual wishes to start or resume a contraceptive method, then all contraceptive options may be considered at any point in care and some methods can be initiated at the time of the abortion *(155)*. States are required to ensure there is access to a wide range of modern, safe and affordable contraceptive methods *(36 [para. 8], 49 [para. 33])*. Criteria laid out in the WHO publications *Ensuring human rights in the provision of contraceptive information and services* and *Medical eligibility criteria for contraceptive use* should be adhered to *(156, 157)*. In-depth consideration of all methods of post-abortion contraception is outside the scope of this guideline.

This section addresses the timing of contraception and the health workers who can provide certain methods. The role of self-management approaches with post-abortion contraception will be discussed further in section 3.6.3.



CLINICAL SERVICES Recommendation 41: Medical eligibility criteria for post-abortion contraception

The following contraceptive methods may be started immediately (MEC Category 1 – no restrictions) after a surgical or medical abortion (first and second trimester, and also after a septic abortion): combined hormonal contraceptives (CHCs), progesterone-only contraceptives (POCs) and barrier methods (condoms, spermicide, diaphragm, cap – note: The diaphragm and cap are unsuitable until 6 weeks after second-trimester abortion)

Intrauterine devices (IUDs) may be started immediately after a first-trimester surgical or medical abortion (MEC Category 1 – no restrictions) or after second-trimester abortion (MEC Category 2 – the advantages generally outweigh the risks), but should not be started immediately after septic abortion (MEC Category 4 – insertion of an IUD may substantially worsen the condition).

Fertility-awareness-based (FAB) methods: Symptom-based methods should only be started after abortion with "caution" (special counselling may be needed to ensure correct use of the method in this circumstance) and the use of calendar-based methods should be delayed (until the condition is evaluated; alternative temporary methods of contraception should be offered).

Notes:

- Refer to the box below for an explanation of the MEC categories.
- CHCs include combined oral contraceptives (COCs), the contraceptive patch (P), the combined vaginal ring (CVR) and combined injectable contraceptives (CICs).
- POCs include progesterone-only pills (POPs), levonorgestrel (LNG) or etonogestrel (ETG) implants, depot medroxyprogesterone acetate (DMPA) injectables, and norethisterone enanthate (NET-EN) injectables.
- IUDs include copper-bearing IUDs (Cu-IUD) and levonorgestrel-releasing IUDs (LNG-IUD).
- Symptoms-based methods include the cervical mucus method (also called the ovulation method) and the TwoDay Method, which are both based on the evaluation of cervical mucus, and the sympto-thermal method, which is a double-check method based on evaluation of cervical mucus to determine the first fertile day and evaluation of cervical mucus and temperature to determine the last fertile day.
- Calendar-based methods include the Calendar Rhythm Method (avoiding unprotected intercourse from the first to the last estimated fertile days, after recording the length of several menstrual cycles as a basis for calculation) and the Standard Days Method (avoiding unprotected intercourse on cycle days 8–19, for people whose cycles are usually 26–32 days long).

Source: Recommendations brought in from WHO's *Medical eligibility criteria for contraceptive use* (2015) *(157)*. The wording has been revised to narrative format from the tables in the source guideline.

Key to MEC categories for contraceptive eligibility

- Category 1 – A condition for which there is no restriction for the use of the contraceptive method
- Category 2 – A condition where the advantages of using the method generally outweigh the theoretical or proven risks
- Category 3 – A condition where the theoretical or proven risks usually outweigh the advantages of using the method
- Category 4 – A condition which represents an unacceptable health risk if the contraceptive method is used.

CLINICAL SERVICES Recommendation 42: Timing of contraception and surgical abortion

For individuals undergoing surgical abortion and wishing to use contraception: **Recommend** the option of initiating the contraception at the time of surgical abortion.

Remark:

- The quality of evidence based on randomized controlled trials was very low.

Source: Part of Recommendation 13 carried forward from WHO (2012) *(19)*. Only the component of the existing recommendation that is relevant to surgical abortion has been retained, with the word "recommend" used to clarify that it is a strong recommendation and revisions made to include all contraceptive methods).

CLINICAL SERVICES Recommendation 43: Timing of contraception and medical abortion

For individuals undergoing medical abortion with the combination mifepristone and misoprostol regimen or with misoprostol alone:

a. For those who choose to use **hormonal contraception** (oral contraceptive pills, contraceptive patch, contraceptive ring, contraceptive implant or contraceptive injections): **Suggest** that they be given the option of starting hormonal contraception immediately after the first pill of the medical abortion regimen.

b. For those who choose to have an **IUD** inserted: **Suggest** IUD placement at the time that success of the abortion procedure is determined.

Remark (for Recommendations 43a and b):

- This recommendation applies to the combination mifepristone plus misoprostol regimen and the use of misoprostol alone. The letrozole plus misoprostol combination regimen is not mentioned here because the included studies informing these recommendations did not assess this regimen.

Remarks (for Recommendation 43a only):

- Immediate initiation of intramuscular depot medroxyprogesterone acetate (DMPA) is associated with a slight decrease in the effectiveness of medical abortion regimens *(158)*. However, immediate initiation of DMPA should still be offered as an available contraceptive method after an abortion.
- Indirect evidence was used as a basis for decision-making on initiation of hormonal contraception as an option for individuals undergoing medical abortion with misoprostol alone.
- No data were available on the use of combined hormonal contraception (pills or injections) by those undergoing medical abortion.
- Individuals who choose to initiate the contraceptive ring should be instructed to check for expulsion of the ring in the event of heavy bleeding during the medical abortion process.

Source: Recommendations 4a and 4b carried forward from WHO (2018) *(120)*.

Who

SERVICE DELIVERY Recommendation 44: Insertion and removal of intrauterine devices (IUDs)

Type of health worker	Recommendation	Rationale
Traditional and complementary medicine professionals	**Suggest** Condition: In contexts with established health system mechanisms for the participation of these professionals in other tasks related to maternal and reproductive health.	Their basic training generally covers the relevant skills needed for this task. This option is probably feasible and may promote continuity of care for women and increase access in regions where these professionals constitute a significant proportion of the health workforce.
Auxiliary nurses	**Suggest** Condition: In the context of rigorous research.	The recommendation comes originally from the *OptimizeMNH* guideline *(138).*
ANMs **Nurses** **Midwives**	**Recommend**	The recommendation comes originally from the *OptimizeMNH* guideline *(138).*
Associate/advanced associate clinicians **Generalist medical practitioners** **Specialist medical practitioners**	**Recommend**	The recommendation comes originally from the *OptimizeMNH* guideline *(138),* where this task was considered to be within their typical scope of practice.[a]

Source: Recommendation carried forward from WHO (2015) *(23).*

[a] For typical scope of work/practice, please refer to Annex 5: Health worker categories and roles.

Who

SERVICE DELIVERY Recommendation 45: Insertion and removal of implants

Type of health worker	Recommendation	Rationale
Community health workers	**Suggest** Condition: In the context of rigorous research.	The recommendation comes originally from the *OptimizeMNH* guideline *(138).*
Traditional and complementary medicine professionals	**Suggest** Condition: In contexts with established health system mechanisms for the participation of these professionals in other tasks related to maternal and reproductive health and where training in implant removal is given along with training in insertion.	Although insufficient direct evidence was found for the safety and effectiveness of this option, their basic training covers the relevant skills needed for this task. This option may promote continuity of care for women.
Auxiliary nurses/ANMs	**Suggest** Condition: In the context of targeted monitoring and evaluation.	The recommendation comes originally from the *OptimizeMNH* guideline *(138).*
Nurses **Midwives**	**Recommend**	The recommendation comes originally from the *OptimizeMNH* guideline *(138).*
Associate/advanced associate clinicians **Generalist medical practitioners** **Specialist medical practitioners**	**Recommend**	The recommendation comes originally from the *OptimizeMNH* guideline *(138),* where this task was considered to be within their typical scope of practice.[a]

Source: Recommendation carried forward from WHO (2015) *(23).*

[a] For typical scope of work/practice, please refer to Annex 5: Health worker categories and roles.

How

Implementation consideration

- The removal of implants can require greater skills than insertion; any health worker trained to independently insert implants should also be well trained on implant removal *(23)*.

Where

In a health-care facility or other setting with sterile conditions.

Who

SERVICE DELIVERY Recommendation 46: Administration of injectable contraceptives (initiation and continuation)

Type of health worker	Recommendation	Rationale[a]
Community health workers (CHWs)	**Recommend**	Limited evidence was found for the safety, effectiveness and feasibility of this option. The skills and knowledge for this task (according to the competency framework) align with the competencies for CHWs.[a] This option is feasible and acceptable given that CHWs provide other components of abortion care. In addition, this option has the potential to increase women's choices and reduce inequities in contraceptive access.
Pharmacy workers	**Recommend**	Although no evidence was found for the safety, effectiveness, acceptability or feasibility of this option, administering injections is within their typical scope of practice[b] and the additional training needs for this task would be minimal. The skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] This option has the potential to increase women's choices and reduce inequities in contraceptive access.
Pharmacists	**Recommend**	Although the available evidence for the safety and effectiveness of this option is of very low certainty, administering injections is within their typical scope of practice[b] and the additional training needs for this task would be minimal. This option has the potential to increase women's choices and reduce inequities in contraceptive access.
Traditional and complementary medicine professionals	**Recommend**	Their basic training covers the relevant skills needed for this task, hence additional training needs would be minimal. The skills and knowledge for this task (according to the competency framework) align with the competencies for this type of health worker.[a] This option is feasible and acceptable given that these professionals provide similar services in the existing health system, and thus it may promote continuity of care for women.
Auxiliary nurses/ANMs	**Recommend**	The recommendation comes originally from the *OptimizeMNH* guideline *(138)*.
Nurses **Midwives** **Associate/advanced associate clinicians** **Generalist medical practitioners** **Specialist medical practitioners**	**Recommend**	The recommendation comes originally from the *OptimizeMNH* guideline *(138)*, where this task was considered to be within their typical scope of practice.[b]

Table Continues

Table Continued

Type of health worker	Recommendation	Rationale[a]
Individual/self		
Pregnant woman, girl or other pregnant person	**Recommend**	Refer to Recommendation 51 in section 3.6.2 for the rationale, remark, implementation considerations and further information about self-management approaches.

Source: Recommendation updated from WHO (2015) *(23)*.

Note on updating of the recommendation: This was an existing recommendation for which evidence relating to traditional and complementary medicine professionals, pharmacy workers, community health workers and individuals/self (self-administration) was reviewed using GRADE methodology. After review, recommendations for all three of those health worker categories were upgraded from "suggest" to "recommend". The recommendations for the other health worker categories were not reviewed and remain unchanged, such that all health worker categories and the individual/self now have a strong recommendation for this task. A summary of the evidence is presented in Supplementary material 3, EtD framework on Delivery of injectable contraceptives.

[a] For this and all health worker recommendations, given the limited evidence for many of the health worker–task combinations, the discussions of the expert panel focused on the competency framework in WHO's 2011 publication, *Sexual and reproductive health: core competencies in primary care (121)*, which provides information on the competencies (including skills and knowledge) required for each task, and also the WHO-INTEGRATE criteria, in particular on the feasibility, equity and acceptability of the intervention and women's values and preferences.

[b] For typical scope of work/practice, please refer to Annex 5: Health worker categories and roles.

No requirement for location (on-site vs off-site).

Implementation considerations

- The administration of an injectable contraceptive involves using a syringe and may be intramuscular or subcutaneous.
- It is important to have adequate mechanisms for the disposal of used sharps, syringes and needles.
- It is important to ensure a consistent supply of the injectables, especially at the point of sale for women to obtain and use on their own.
- The investment in initial training is a consideration where the health worker is not already certified to provide injections. It is important to have mechanisms to link the health worker to the health system and ensure a referral pathway.

SERVICE DELIVERY Recommendation 47: Tubal ligation

Type of health worker	Recommendation	Rationale
Nurses	**Suggest** Condition: In the context of rigorous research.	The recommendation comes originally from the *OptimizeMNH* guideline *(138)*.
Midwives	**Suggest** Condition: In the context of rigorous research.	The recommendation comes originally from the *OptimizeMNH* guideline *(138)*.
Associate/advanced associate clinicians **Generalist medical practitioners** **Specialist medical practitioners**	**Recommend**	The recommendation comes originally from the *OptimizeMNH* guideline *(138)*, where this task was considered to be within their typical scope of practice.[a]

Source: Recommendation carried forward from WHO (2015) *(23)*. The recommendations will be reviewed for the next update of the WHO guidance on optimizing health worker roles *(138)*.

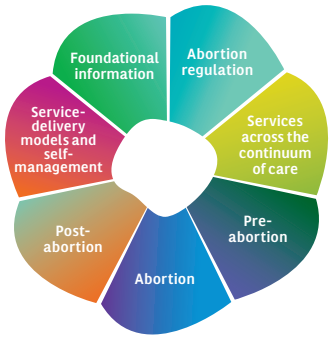
[a] For typical scope of work/practice, please refer to Annex 5: Health worker categories and roles.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO POST-ABORTION CONTRACEPTION

- Contraception should be provided only where the person has given free and informed consent to receive it.
- States must ensure availability of the full range of contraceptive options, including a wide range of modern, safe and affordable methods.
- States must ensure adequate access to essential medicines, including contraceptives, in an affordable and non-discriminatory manner.
- Everyone has a right to evidence-based information on all aspects of SRH, including contraceptives.
- Contraceptive information and services must be provided without discrimination, coercion or violence.
- Everyone has a right to privacy and confidentiality in the receipt of contraceptive information and services.
- Post-abortion contraceptive information and services should be available and accessible to adolescents without requiring parental or guardian authorization.
- States must guarantee that practices of conscientious refusal/objection do not infringe on the right to contraceptive information and services.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

Links to related topics/recommendations



Free and informed consent (section 1.3.1[v])

Commodities (section 1.4.4)

Information provision and counselling (sections 3.2.1 and 3.2.2)

3.6 Service-delivery options and self-management approaches

As indicated throughout this chapter so far, abortion care services can be provided by a range of health workers and some tasks can be managed by individuals themselves. Even for procedures that take place at a health-care facility, some elements of the care (e.g. pre-abortion information and counselling, cervical priming or post-abortion follow-up care) can take place in other locations.

Unlike surgical abortion, medical abortion is a process that takes place over a period of several hours or days rather than being a discrete procedure. The process as a whole or its components can take place at different locations including through self-management and/or with the support of different health workers at various stages of the process, making it possible – and in some cases desirable – to obtain care in a range of different settings, through a wide range of different options.

This section addresses supported service-delivery approaches (section 3.6.1) and self-management approaches. Self-management approaches addressed in this section include self-management of medical abortion (section 3.6.2), and self-management of post-abortion contraception (section 3.6.3).

3.6.1 Supported service-delivery approaches

Medical abortion services can be obtained from and provided or supported by a multitude of actors within the health system. Services may be delivered through a comprehensive model that addresses the full spectrum of abortion care or may include only specific components on the care pathway. Services could be delivered through the public or private sectors or nongovernmental organizations (NGOs), and may be received at a community-based, off-site location or even at home, and a variety of service-delivery models can co-exist at national, subnational and local levels.

Approaches to service delivery are not static and as the role of digital technologies grows and the science and evidence on effective interventions evolves, innovations will also continue to evolve. For this guideline, available evidence on various modalities of providing and/or supporting abortion care were reviewed. Examples of service-delivery approaches that were identified in the systematic reviews conducted for this guideline included:

- **Accompaniment models:** Where a community health worker provides support by accompanying the individual through the medical abortion process (by phone, secure technological platform, or in person), including providing information, counselling, emotional/moral support and/or logistical support (including referrals to and support interacting with local health-care facilities in the event that care is needed or desired).
- **Community outreach:** This includes health services that mobilize health workers to provide services to the population or to other health workers, away from the location where they usually work and live *(159)*. This is a strategy to mobilize health workers to remote or rural areas, such as mobile clinics. However, documented evidence on the use of this model for abortion care provision is limited.
- **Digital support tools:** These included apps providing information, text messaging reminders, and tools to assist in the assessment of pregnancy duration.
- **Harm reduction models:** Service models in the clinic setting, in which women are supported with pre-abortion information, are told where to find the medicines and how to use them and can return for post-abortion support if needed, but are not actually provided with the medicines to terminate the pregnancy.
- **Hotlines:** This typically refers to telephonic information services that can support women in accessing quality abortion care. Abortion hotlines may be limited to providing evidence-based information about services or may be linked to other service-delivery models that facilitate access to medicines and support women through the abortion process and after the abortion.
- **Social marketing:** Broadly defined as the application of marketing techniques to social problems and aims to persuade or motivate people to adopt specific sources of action or behaviour which are generally accepted as being beneficial. This approach to marketing has been well studied as a successful model for distribution of health interventions/commodities (e.g. condoms), however, documentation related to quality abortion care (i.e. abortion medicines and instructions) is more limited. It may be an option for increasing access and making care more affordable.

- **Social franchising:** This is described as a system of contractual relationships usually run by an NGO which uses the structure of a commercial franchise to achieve social goals. The overarching difference between social and commercial franchising is that social franchising seeks to fulfil a social benefit whereas commercial franchising is driven by profit. However, the limited evidence illustrates the potential inequities of such models *(160)*.
- **Telemedicine:** This is a mode of health service delivery where providers and clients, or providers and consultants, are separated by distance. The interaction may take place in real time (synchronously), using telephone or video link, or asynchronously using a store-and-forward method, when a query is submitted and an answer is provided later (e.g. by email, text or voice/audio message) *(161)*.

Across the range of service-delivery options, interactions between an abortion seeker and a health worker can take place in person or remotely. After review and assessment of the evidence by the expert panel, it was agreed that there was sufficient quantity and quality of evidence to support the formulation of a specific recommendation in relation to using telemedicine approaches as an alternative to in-person interactions for provision of medical abortion (see Recommendation 48).

The available evidence was inadequate to support the formulation of recommendations on any of the other service-delivery models. Instead, given the contextual nature of service-delivery approaches, the heterogeneity of the types of interventions and the overlaps between the approaches, a two-part best practice statement was developed to apply to all of them, with reference to service delivery in general, rather than any specific modality/model of service delivery (see Best Practice Statement 49).

What Who

SERVICE DELIVERY Recommendation 48 (NEW):
Telemedicine approaches to delivering medical abortion care

Recommend the option of telemedicine as an alternative to in-person interactions with the health worker to deliver medical abortion services in whole or in part.

Remarks:

- The above recommendation applies to assessment of eligibility for medical abortion, counselling and/or instruction relating to the abortion process, providing instruction for and active facilitation of the administration of medicines, and follow-up post-abortion care, all through telemedicine.
- Hotlines, digital apps or one-way modes of communication (e.g. reminder text messages) that simply provide information were not included in the review of evidence for this recommendation.

Rationale

A systematic review was undertaken to address this key question. Ten studies reporting on medical abortion provision through telemedicine were identified by the search strategy. Four randomized controlled trials were conducted in Bangladesh, Cambodia, Egypt and Indonesia, and six observational studies took place in Canada, Peru and the USA. In studies comparing telemedicine with in-person medical abortion care services, there was no difference between the two groups in rates of successful abortion or ongoing pregnancies (based on very low-certainty evidence). Referrals for surgical intervention were fewer among women who used telemedicine (based on low-certainty evidence). Satisfaction with telemedicine services was high and comparable to the usual clinical services (based on very low-certainty evidence). A summary of the evidence is presented in Supplementary material 3, EtD framework on Telemedicine.

How

Implementation consideration

- Telemedicine services should include referrals (based on the woman's location) for medicines (abortion and pain control medicines), any abortion care or post-abortion follow-up required (including for emergency care if needed), and for post-abortion contraceptive services, which may apply to both medical and surgical abortion.

What Who

SERVICE DELIVERY Best Practice Statement 49 (NEW)

Part 1: There is no single recommended approach to providing abortion services. The choice of specific health worker(s) (from among the recommended options) or management by the individual themself, and the location of service provision (from among the recommended options) will depend on the values and preferences of the woman, girl or other pregnant person, available resources, and the national and local context. A plurality of service-delivery approaches can co-exist within any given context.

Part 2: Given that service-delivery approaches can be diverse, it is important to ensure that for the individual seeking care, the range of service-delivery options taken together will provide:

- access to scientifically accurate, understandable information at all stages;
- access to quality-assured medicines (including those for pain management);
- back-up referral support if desired or needed;
- linkages to an appropriate choice of contraceptive services for those who want post-abortion contraception.

A summary of the evidence is presented in Supplementary material 3, EtD framework on Medical abortion provided in different settings.

How

Implementation considerations

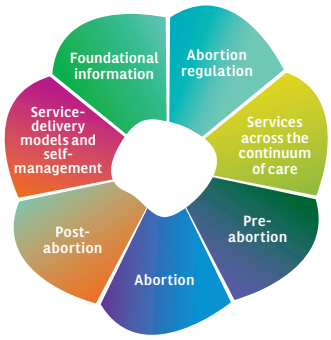
- Service-delivery approaches should, where feasible, be co-created with the people who will benefit from the intervention.
- All models should be tested and adapted for the local context in which they will operate.
- Not all service-delivery approaches may function at scale but for those that are being considered for national programmes, appropriate pilot testing is needed prior to scaling up.
- All service-delivery models should have mechanisms for monitoring quality and ensuring accountability.

KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO SERVICE-DELIVERY MODELS

- States should develop and enforce evidence-based standards and guidelines for the provision and delivery of sexual and reproductive health (SRH) services, and such guidance must be routinely updated to incorporate medical advancements. At the same time, States are required to provide age-appropriate, evidence-based, scientifically accurate comprehensive education for all on SRH.
- SRH services must be available, accessible, affordable, acceptable and of good quality. This means that delivery of services must be respectful of the culture of individuals, minorities, peoples and communities, and sensitive to gender, age, disability, sexual diversity and life-cycle requirements.
- States must take steps to reduce maternal mortality and morbidity.
- States must make accurate, evidence-based abortion information available to individuals on a confidential basis
- States must ensure delivery of services on the basis of non-discrimination and equality.
- States must ensure delivery of services in a way that respects the right to scientific progress, meaning that States should ensure access to modern and safe forms of contraception, including emergency contraception, abortion medicines, assisted reproductive technologies, and other SRH goods and services, on the basis of non-discrimination and equality.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

Links to related topics/recommendations



All recommendations related to law and policy (Recommendations 1,2,3,6,7,21,22)

3.6.2 Self-management approaches for medical abortion in whole or in part

Self-care, as defined in the Glossary, is a broad-based concept and can encompass numerous actions that are intended to empower the individual to enhance their own health. Self-management approaches are one component of self-care. Given the nature of the medical abortion process, it is possible for women to manage the process by themselves in whole or part. While individuals may conduct some or all elements related to the abortion process (self-assessment of eligibility, self-administration of medicines and self-assessment of the success of the abortion) entirely on their own, more typically, self-management co-exists with interactions with trained health workers or with a health-care facility and in conjunction with service-delivery approaches described in section 3.6.1. It is the individual (i.e. the "self") who drives the process of deciding which aspects of the abortion care will be self-managed and which aspects will be supported or provided by trained health workers or in a health-care facility.

Women may self-manage parts or all of the abortion process for a variety of reasons related to individual circumstances and preferences. For some women, this may be the only feasible option within their context and for others it may represent an active choice. However, from the perspective of the health system, self-management should not be considered a "last resort" option or a substitute for a non-functioning health system. Self-management must be recognized as a potentially empowering and active extension of the health system and task-sharing approaches. A supportive enabling environment as described in Chapter 1, section 1.3, is equally applicable to self-management approaches as it is to other elements of care provision.



SELF-MANAGEMENT Recommendation 50:
Self-management of medical abortion in whole or in part at gestational ages < 12 weeks

For medical abortion at < 12 weeks (using the combination of mifepristone plus misoprostol or using misoprostol alone): **Recommend** the option of self-management of the medical abortion process in whole or any of the three component parts of the process:

- self-assessment of eligibility (determining pregnancy duration; ruling out contraindications)
- self-administration of abortion medicines and management of the abortion proces outside of a health-care facility and without the direct supervision of a trained health worker
- self-assessment of the success of the abortion.

Remarks:

- There was more evidence for self-management of medical abortion (with either of the regimens) for pregnancies before 10 weeks of gestation.
- This recommendation applies to the combination regimen of mifepristone plus misoprostol, and the use of misoprostol alone. The included studies informing these recommendations did not assess the letrozole plus misoprostol regimen.
- All individuals engaging in self-management of medical abortion must also have access to accurate information, quality-assured medicines including for pain management, the support of trained health workers and access to a health-care facility and to referral services if they need or desire it.
- Restrictions on prescribing and dispensing authority for abortion medicines may need to be modified or other mechanisms put in place for self-management within the regulatory framework of the health system.

Source: Recommendation updated from WHO (2015) *(23)*.

Note on updating of the recommendation: This was an existing recommendation for which evidence for all of the subtasks was reviewed using GRADE methodology. After review, the recommendations for all subtasks were upgraded to "recommend" – from "suggest" for self-administration and self-assessment of outcome, and from "only in the context of rigorous research" for self-assessment of eligibility.

Where

No requirement for location (on-site vs off-site).

Rationale

Two systematic reviews were undertaken to address this key question. The first review focused on the self-assessment of eligibility and self-assessment of success. A total of 14 studies reporting on these two sub-tasks were identified by the search strategy. The four studies on self-assessment of eligibility took place in South Africa, the United Kingdom and the USA. Ten studies on self-assessment of success took place in Austria, Finland, India, Mexico, Nepal, Norway, South Africa, Sweden, Uzbekistan and Viet Nam. The second review was on the self-administration of medicines and included 18 studies, which took place in Albania, Bangladesh, China, France, India, Nigeria, Tunisia, Turkey and Viet Nam. A summary of the evidence is presented in Supplementary material 2, EtD framework on Self-management of medical abortion.

Self-assessment of eligibility: There is low-certainty evidence on the safety, effectiveness and acceptability of self-assessment of eligibility for a medical abortion, using the start date of last menstrual period (LMP) alone or in combination with other tools (e.g. checklists). The expert panel discussed the feasibility of this intervention in certain scenarios such as the woman having regular menses, a known LMP and the availability of validated tools. When they have the necessary information, women are able to determine their eligibility for medical abortion. Given this and taking into account the values and preferences and high acceptability of this approach, the panel determined that the intervention was favoured.

Self-administration of medicines: There is evidence that the option of self-administering medicines for medical abortion is effective (moderate certainty) and safe (low certainty). Women reported high satisfaction with taking their own medicines for the abortion (very low-certainty evidence). There was high adherence to the medical abortion regimen (low-certainty evidence). The high acceptability and feasibility favoured this intervention.

Self-assessment of success: There is high-certainty evidence that self-assessment of abortion outcome/success (using tools such as a low-sensitivity pregnant test or multi-level pregnancy test) is as effective as assessment by a trained health worker. Low-certainty evidence indicated that more women in the self-assessment group expressed satisfaction with the process.

How

Implementation considerations

- Every individual must have access to accurate information about the self-management process as well as other options available within their local context, to enable informed decision making on whether to self-manage all or parts of the process.
- Self-assessment of eligibility includes the assessment of pregnancy duration based on LMP. Paper or digital tools to assist recall and calculate duration or checklists may assist in the self-assessment of eligibility. When menstrual cycles are irregular or women have other concerns, she should be encouraged to seek support from a trained health worker where possible.
- Self-administration of medicines and management of the medical abortion process involves taking all or some of the abortion medicines without the direct supervision of a health worker. It is important that all sources from which medicines are procured provide quality-assured medicines.
- Women should also have information about pain during the process and should be able to obtain medicines for pain management.
- Women should also have information about the requirements of managing abortion-related bleeding at home, and should have access/referral to emergency care if this becomes necessary.

- Self-assessment of the success of abortion can be done using check lists of signs and symptoms. Other tools (e.g. low-sensitivity pregnancy tests), if available, may be used to assist the woman in self-assessing completion. Low-sensitivity urine pregnancy tests are different from ordinary pregnancy tests. The use of a high-sensitivity pregnancy test (a multi-level pregnancy test [MLPT]) alone or in conjunction with checklists has been shown to have a higher sensitivity for detecting successful abortion. Access should be available to a health worker or health-care facility to confirm the success of abortion or to manage side-effects or complications.
- As part of the enabling environment, health workers and managers should recognize self-management as a legitimate pathway to abortion care, and should work to adapt health systems to facilitate and support women in their self-management of abortion – for example, by adapting clinical protocols used at their facility.
- Mechanisms need to be established to ensure access or referrals to post-abortion contraception services and provision of contraception for women who want them.
- While self-management can support efficiencies within health systems in the long term, it should not mean that the burden of the cost of health services is simply transferred from the provider or facility to the woman herself.

3.6.3 Self-management approaches for post-abortion contraception

All contraceptive options may be considered after an abortion. For further information, refer to section 3.5.4: Post-abortion contraception. Many family planning methods are entirely self-managed (i.e. self-procured over the counter or online and self-administered) and generally available without a prescription, including barrier methods and some hormonal contraceptives, including some oral contraceptive pills (OCPs), and also emergency contraceptive pills. For methods that have traditionally required a prescription from a doctor and/or administration by a health worker, shifting to include the option of using self-management approaches, such as over-the counter OCPs and self-injection of hormonal contraceptives, may improve continuation of contraceptive use by removing barriers, such as the need to return to a health-care facility every three months for a repeat injection. These approaches could expand access to contraception for those facing challenges in accessing health-care settings regularly, and in places where there are shortages of health workers, thus potentially greatly reducing the incidence of unintended pregnancy.

What Who

SELF-MANAGEMENT Recommendation 51: Self-administration of injectable contraception (initiation and continuation)[17]

Recommend the option of self-administration of injectable contraception in the post-abortion period.

Remark:

- The administration of an injectable contraceptive involves using a syringe and may be intramuscular or subcutaneous. Compact pre-filled auto-disable devices have been developed to facilitate the self-administration process.

Source: Recommendation updated from WHO (2015) *(23)*.

Note on updating of the recommendation: This was an existing recommendation for which evidence was reviewed using GRADE methodology. After review, the recommendation was upgraded from "suggest" to "recommend".

Where

No requirement for location (on-site vs off-site).

17 Including a recommendation only on injectable contraception here does not imply that post-abortion contraceptive options for women should be limited to this method, or indeed to the methods covered by recommendations presented in section 3.5.4; all contraceptive methods can be considered after an abortion.

Rationale

A systematic review was undertaken to address this key question. Studies with indirect populations (i.e. women of reproductive age willing to initiate or continue with injectable contraceptive) were also considered for inclusion. Seven studies reporting on self-administered injectable contraceptives were identified by the search strategy and included in the reviewed evidence; three randomized controlled trials were conducted in Malawi and the USA and four observational studies were conducted in Senegal, Uganda, the United Kingdom and the USA. The evidence was considered indirect since none of the women included in the reviewed studies were described as seeking contraception post-abortion. A summary of the evidence is presented in Supplementary material 3, EtD framework on Self-administration of injectable contraception.

There is evidence that continuation rates for self-administered injectable contraceptives are higher compared with injectable contraceptives being provided by clinic-based providers (very low- to low-certainty evidence). Satisfaction was higher among the self-administration group (very low- to moderate-certainty evidence). The option may result in time and financial savings for women. In addition, this option may increase choice and autonomy in contraceptive use within a rights-based framework.

How

Implementation considerations

- There must be training in the technique for self-injection.
- There must be training in and the provision of mechanisms for the safe and secure storage and disposal of sharps (used injectable contraceptives), especially in settings with high HIV prevalence.
- The client must be able to procure injectable contraceptives on a regular basis without needing to repeatedly visit a health-care facility.

What Who

SELF-MANAGEMENT Recommendation 52: Over-the-counter oral contraceptive pills

Recommend that over-the-counter oral contraceptive pills (OCPs) should be made available without a prescription for individuals using OCPs.

SELF-MANAGEMENT Recommendation 53: Over-the-counter emergency contraceptive pills

Recommend making over-the-counter emergency contraceptive pills available without a prescription to individuals who wish to use emergency contraception.

SELF-MANAGEMENT Recommendation 54: Condom use

The consistent and correct use of male and female condoms is highly effective in preventing the sexual transmission of HIV; reducing the risk of HIV transmission both from men to women and women to men in serodiscordant couples; reducing the risk of acquiring other STIs and associated conditions, including genital warts and cervical cancer; and preventing unintended pregnancy.

Source: Recommendations 15, 16 and 18 brought in from WHO (2021) *(26)*.



No requirement for location (on-site vs off-site).



Implementation considerations for OCPs

- Provide up to one year's supply of pills, depending on the woman's preference and anticipated use.
- Programmes must balance the desirability of giving women maximum access to pills with concerns regarding contraceptive supply and logistics.
- The resupply system should be flexible, so that the woman can obtain pills easily in the amount and at the time she requires them.[18]

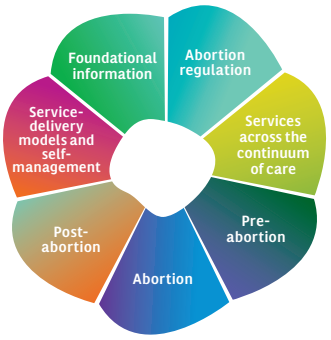
KEY HUMAN RIGHTS CONSIDERATIONS RELEVANT TO SELF-MANAGEMENT APPROACHES

- Sexual and reproductive health (SRH) care must be available, accessible, acceptable and of good quality.
- States must ensure availability of a wide range of modern, safe and affordable contraceptive methods.
- States must ensure adequate access to essential medicines in an affordable and non-discriminatory manner.
- States must respect autonomous decision-making, non-discrimination and equality. This means that States should repeal or reform laws and policies that nullify or impair the ability of certain individuals and groups to realize their right to SRH, including the criminalization of abortion or restrictive abortion laws.
- States must make accurate, evidence-based abortion information available to individuals on a confidential basis
- States must take steps to reduce maternal mortality and morbidity.
- In line with human rights requirements, self-management of abortion should not be criminalized. Criminalization of self-management of abortion may result in delays in or barriers to seeking assistance or post-abortion care where needed. Self-management of medical abortion should be available as an option on the basis of clinical appropriateness. It should not be restricted for non-clinical reasons such as age.

For further information and sources, please refer to Box 1.2 and Web annex A: Key international human rights standards on abortion.

18 These are Recommendations 20a, b and c from WHO (2021) *(26)*.

Links to related topics/recommendations



All recommendations related to law and policy (Recommendations 1,2,3,6,7,21,22)

Informed consent (in section 1.3.1: Human rights)

Provision of information on quality abortion care (section 3.2.1)

Provision of counselling (section 3.2.2)

Pain management for abortion (section 3.3.6)

Chapter 4.

Dissemination, applicability, research gaps and future updates of the guideline and recommendations

4.1 Dissemination

This guideline will be published digitally (both an interactive web-based version and a traditional document available online for download) and in print; see further information in Annex 11.

Translation of the guideline into Spanish (in collaboration with the Pan American Health Organization [PAHO]), French and Portuguese is planned. Translations into other United Nations languages will be developed as needed.

Several derivative products will be developed based on this updated and consolidated guideline:*

- operational guidance containing details on implementation of the recommendations, including strategic considerations for improving access to quality abortion care for youth;
- informational materials, such as posters highlighting selected recommendations, which can be placed in health-care facilities and other appropriate places;
- pocket charts/cards for health workers, providing the updated recommendations for medical and surgical abortion and post-abortion contraception, and referral cards for referring individuals to other health-care services (adapted for use by different types of health workers and for different literacy levels);
- user-friendly decision-support tools for health workers and policy-makers, created with the input of end-users who will be engaged in the process of determining how best to translate the guidance for this purpose (the tools may include digital decision tools in the format of a mobile application [app]);
- case studies on quality abortion care in different humanitarian settings, to demonstrate and highlight the relevant considerations and requirements;
- operational guidance on medical management of select clinical indications, such as miscarriage.

* *Note:* Where applicable, WHO will collaborate with relevant United Nations agencies in the dissemination efforts. For example, WHO will collaborate with the Office of the United Nations High Commissioner for Human Rights (OHCHR) to disseminate guidance and tools to support application of a human rights-based approach to sexual and reproductive health, as well as respond to country requests for technical assistance to implement these approaches.

4.2 Implementation and impact evaluation of the guideline

Implementation of this guideline requires a multifaceted approach. After the initial publication, translation and dissemination efforts on regional, national and local levels (see Annex 11), it will be important to apply active techniques such as conducting workshops and training programmes to familiarize users with the guideline. Engagement by WHO team members with managers and staff of health-care facilities to build reminders about

the latest guidance into their clinical support systems will also be crucial. With regard to policy and programme planning, it will be important to work with policy-makers and national and local health officials to ensure implementation of the adopted recommendations at all levels of the health system. Engaging with national ministries and WHO country offices to contextualize the guidelines may facilitate adaptation of the guideline. It is anticipated that the main barrier to implementation of this guideline will be the subject matter – quality abortion care – which is a sensitive and stigmatized topic. This means that it is all the more important to work with stakeholders, including government, policy-makers and advocates for safe and legal abortion, to inform them about the guideline and facilitate open dialogue about the realities of abortion in their country. Using the Global Abortion Policies Database will facilitate these discussions *(116)*.

Process and impact evaluation will be ongoing during the first year of implementation of this guideline, focusing on the accessibility, acceptance, use, impact and generalizability of the guideline and its recommendations. As an assessment of document uptake, the engagement with the interactive online version of the guideline, the number of downloads of the document from the WHO website, and the number of hard copies of the guidance requested and distributed through the document centre will be monitored.

A year after publication, an evaluation of the immediate impact of the guidelines will be undertaken in the form of an online survey. This will be conducted through WHO regional and country offices and through selected respondents from other user groups (e.g. professional societies, NGOs) in order to gauge utilization in-country and whether and how any of the recommendations in the guideline have been implemented or have influenced policy decisions. This short-term impact evaluation will also include an assessment of barriers to effective implementation, which will be important feedback for derivative products and future modifications.

4.3 Research gaps/topics for further research

In the course of developing this guideline, during the meetings of the Evidence and Recommendation Review Groups (ERRGs) and the Guideline Development Group (GDG), several evidence gaps and areas for further research were identified.

Law and policy

- Impact of abortion laws and policies on people with disabilities and people with diminished capacity who seek abortion
- Impact of abortion laws and policies on groups in vulnerable situations and groups with marginalized identities, specifically adolescents and transgender individuals
- Impacts, effects and rights-related implications of procedural barriers to abortion in various contexts
- Impacts, effects and rights-related implications of making abortion available on the request of the woman, girl or other pregnant person, with no additional restrictions
- Impacts, effects, and rights-related implications of the decriminalization of self-management of abortion and of assistance with self-management of abortion

Clinical services

- Efficacy, safety and acceptability of the letrozole plus misoprostol combination regimen across gestational ages and compared with the mifepristone plus misoprostol combination regimen
- Effectiveness of using misoprostol alone (i.e. typical/real use outside of study conditions, optimal number of repeat doses)
- Efficacy, safety and acceptability of the use of misoprostol alone across gestational ages
- Effectiveness, safety and acceptability of outpatient medical abortion at gestational ages ≥ 12 weeks
- Safety, effectiveness and acceptability of anti-epileptics and anxiolytics for pain management for medical abortion at gestational ages ≥ 14 weeks
- Management of cervical priming prior to dilatation and evacuation (D&E) at gestational ages ≥ 18 weeks in settings where osmotic dilators are not available

- Optimal antibiotic regimens for post-abortion infection prophylaxis
- Effective methods for diagnosis and treatment of non-symptomatic ectopic pregnancy
- Safety and effectiveness of screening and antibiotic treatment for pelvic inflammatory disease before surgical abortion versus provision of pre- or perioperative prophylactic antibiotics without screening or risk assessment for pelvic inflammatory infection
- Effectiveness of telemedicine for medical abortion at gestational ages < 6 weeks
- Efficacy, safety and acceptability of all abortion methods and related clinical interventions across gestational ages in transgender, nonbinary and intersex individuals seeking abortion care
- Development and adaptation of validated materials to provide individuals engaging in self-management of abortion with the information they need to make informed decisions about the risks/benefits of and the alternatives to the use of different medical abortion regimens
- Development of effective and user-friendly information for abortion seekers, e.g. leaflets and web pages or information for use in the context of hotlines and telemedicine services
- Development and validation of quality training materials for use in training of providers on a range of abortion care services (e.g. to train pharmacists, pharmacy workers and community health workers to effectively provide – or support self-management of – all tasks involved in medical abortion at gestational ages < 12 weeks)
- Safety, convenience and acceptability of re-using manual vacuum aspiration (MVA) equipment

Service delivery

- Safety, effectiveness and feasibility of expansion of health worker roles for certain abortion care tasks in low- and middle-income settings (e.g. surgical abortion at gestational ages ≥ 12 weeks, vacuum aspiration for incomplete abortion)
- Feasibility of pharmacists administering injectable contraception in low- and middle-resource settings (implementation research)
- Impact of social marketing and social franchising approaches in abortion care assessed through evaluation research
- The most appropriate prescribing and dispensing authorities for abortion medicines, including comparison of self-sourced abortion medicines versus medicines prescribed and/or dispensed by trained health workers
- Mechanisms for ensuring individuals who manage medical abortion on their own have access to medicines for pain management and to contraceptive methods
- Acceptability of and satisfaction with a range of service-delivery approaches for quality abortion care for transgender, nonbinary and intersex individuals

Universal health coverage (UHC), health financing and commodities

- Impact of the WHO Model Lists of Essential Medicines changes to the mifepristone plus misoprostol combination regimen assessed through evaluation research

Indicators for use in monitoring and evaluation (M&E) of care

- Development and validation of indicators that include social and economic disability in addition to physical disability when calculating years living with abortion-related disability (in line with the growing focus on global burden of disease and disability estimation)
- Development and validation of standardized data-verification methods, so that abortion-related data can be presented with a verification score (as part of efforts to address the underreporting of abortion-related data as a result of abortion-related stigma)
- Development and increased use of qualitative methods for M&E of quality abortion care to assess barriers to progress and enablers for strengthening health system performance

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Annexes

Annex 1. External experts and WHO staff involved in guideline development

Members of the Evidence and Recommendation Review Groups (ERRGs)

There were three ERRGs (expert panels), one for each domain of this guidance: Clinical services, Service delivery, Law and policy. Below each list of ERRG members, additional contributors to the pre-ERRG scoping meetings are listed per domain.

Clinical services domain ERRG members

Name	Affiliation City, country	WHO region of residence	Expertise	Declarations/ conflicts of interest
Laura Castleman	Planned Parenthood Michigan and University of Michigan Ann Arbor, MI, United States of America (USA)	Americas	Obstetrics and gynaecology	None
Suchitra Dalvie	Sexual and reproductive health programme consultant Mumbai, India	South-East Asia	Abortion, advocacy	None
Michalina Drejza	International Youth Alliance for Family Planning (IYAFP) Poznań, Poland	Europe	Obstetrics and gynaecology, youth	None
Kristina Gemzell Danielsson[a]	Department of Women's and Children's Health, Karolinska Institutet Stockholm, Sweden	Europe	Obstetrics and gynaecology, abortion research	None
Laura Gil[a]	Fundación Educación Para la Salud Reproductiva (ESAR) (Education Foundation for Reproductive Health) Bogotá, Colombia	Americas	Abortion, contraception	None
Selma Hajri[a]	TAWHIDA Group for Research and Action on Women's Health Tunis, Tunisia	Eastern Mediterranean	Abortion, contraception, research	None
Guyo Jaldesa	University of Nairobi Nairobi, Kenya	Africa	Obstetrics and gynaecology	None
Dhammika Perera[a]	Marie Stopes International London, United Kingdom of Great Britain and Northern Ireland	Europe	Abortion, contraception	None
Alongkone Phengsavanh	University of Health Sciences Vientiane, Lao People's Democratic Republic	Western Pacific	Obstetrics and gynaecology, abortion care	None
Judiac Ranape[a]	Department of Health Cape Town, South Africa	Africa	Nursing, nurse training, abortion care	None
Kitihoun Serge	Reproductive Health Unit, Alfred Comlan Quenum Regional Institute of Public Health Ouidah, Benin	Africa	Abortion, contraception	None
Human rights adviser				
Christina Zampas	Center for Reproductive Rights Geneva, Switzerland	Europe	Law, human rights, sex work, forced sterilization	None

[a] These members also contributed to the scoping meeting for this domain, in advance of the ERRG meetings, along with the following additional contributing experts: Abigail Aiken (University of Texas, USA), Rodica Comendant (Reproductive Health Training Center, Republic of Moldova), Debora Diniz (Instituto de Bioética, Brazil), Angel Foster (University of Ottawa, Canada), Daniel Grossman (University of California, San Francisco, USA), Kinga Jelinksa (Women Help Women, Netherlands), Munir Kassa (Center for International Reproductive Health Training, Ethiopia), Rasha Khoury (Médecins Sans Frontières, Afghanistan), Alice Mark (National Abortion Federation, USA), Mariana Romero (Center for the Study of State and Society, Argentina), Marion Stevens (Sexual and Reproductive Justice Coalition, South Africa), Nadira Sultana (Global Fund – United Nations Office for Projects Services, Bangladesh).

Service delivery domain ERRG members

Name	Affiliation City, country	WHO region of residence	Expertise	Declarations/ conflicts of interest
Fauzia Akhter Huda[a]	Maternal and Child Health Division, International Centre for Diarrhoeal Disease Research Bangladesh (ICDDRB) Dhaka, Bangladesh	South-East Asia	Public health, health systems, abortion	None
Nana Yaa Appiah	Women's Voices Foundation Accra, Ghana	Africa	Pharmacy, social marketing, professional development	None
Karla Berdichevsky	Gender Equity and Reproductive Health, Mexico Federal Ministry of Health Mexico City, Mexico	Americas	Sexual and reproductive health programming, policy and research	None
Jemima Araba Dennis-Antwi	Ghana College of Nurses and Midwives Accra, Ghana	Africa	Health systems strengthening, maternal health, midwifery, nursing training	None
Surendra Dhital	Independent Pharmacist Kathmandu, Nepal	South-East Asia	Pharmacy, counselling, safe abortion	None
Caitlin Gerdts[a]	Ibis Reproductive Health Oakland, CA, USA	Americas	Qualitative research, use of technology, access to abortion	None
Daniel Maceira	Economics Department, University of Buenos Aires Buenos Aires, Argentina	Americas	Health systems research, health programming and policy development	None
Vinoj Manning[a]	Ipas Development Foundation New Delhi, India	South-East Asia	Health systems, abortion care	None
Sybil Nkeiru	Generation Initiative for Women and Youth Network (GIWYN) Lagos, Nigeria	Africa	Human rights activist	None
Hiromi Obara[a]	Department of Health Planning and Management, Bureau of International Health Cooperation, National Center for Global Health and Medicine Tokyo, Japan	Western Pacific	Health planning and management, Maternal health and abortion policy	None
Karan Parikh	International Youth Alliance for Family Planning (IYAFP) Mumbai, India	South-East Asia	Clinician, youth	None
Michelle Remme	United Nations University's International Institute for Global Health (UNU-IIGH) Kuala Lumpur, Malaysia	Western Pacific	Research, gender, health system financing	None
Karthik Srinivasan[b]	International Planned Parenthood Federation (IPPF) London, United Kingdom	Europe	Commodities, health system	None
Human rights adviser				
Christina Zampas	Center for Reproductive Rights Geneva, Switzerland	Europe	Law, human rights, sex work, forced sterilization	None

[a] These members also contributed to the scoping meeting(s) for this domain, in advance of the ERRG meetings, along with the following additional contributing experts: Patrick Aboagye (Ghana Health Services, Ghana), Laura Castleman (Ipas, Planned Parenthood and University of Michigan, USA), Amanda Cleeve (Karolinksa Institutet, Sweden), Saida Chowdhury (Independent consultant, USA), Rodica Comendant (Reproductive Health Training Center, Republic of Moldova), Joanna Erdman (Dalhousie University, Canada), Rebecca Gomperts (Women on Waves, Netherlands), Chisale Mhango (University of Malawi, Malawi), Monica Oguttu (Kisumu Medical and Education Trust, Kenya), Paul Mandira (United Nations Population Fund, USA), Mariana Romero (Center for the Study of State and Society, Argentina), Sarmad Soomar (International Youth Alliance for Family Planning, Pakistan).

[b] This member began working for a funding agency before the final ERRG meeting and therefore his involvement in guideline development ended at that point.

Law and policy domain ERRG members

Name	Affiliation City, country	WHO region of residence	Expertise	Declarations/ conflicts of interest
Marge Berer	International Campaign for Women's Right to Safe Abortion London, United Kingdom	Europe	Social science, abortion policy	None
Joanna Erdman[a]	Schulich School of Law, Dalhousie University Halifax, Canada	Americas	Human rights, health law and policy	None
Godfrey Kangaude	University of Pretoria and University of Toronto Blantyre, Malawi	Africa	Sexual and reproductive health and rights law	None
Akila Radhakrishnan	Global Justice Center New York, NY, USA	Americas	Law and policy	None
Ruben Avila Reyna	International Youth Alliance for Family Planning (IYAFP) Youth Taskforce Nuevo León, Mexico	Americas	Human rights, advocacy, youth	None
Chi-Chi Undie	Population Council Nairobi, Kenya	Africa	Abortion and contraception, policy	None
Human rights advisers				
Abhijit Das	Centre for Health and Social Justice New Delhi, India	South-East Asia	Human rights	None
Sara Hossain	Bar of the Supreme Court of Bangladesh Dhaka, Bangladesh	South-East Asia	Law and policy, human rights	None
Karima Khalil	Maternal and Child Health Consultant New Delhi, India	South-East Asia	Law and policy, human rights	None
Primah Kwagala	Director, Women's Probono Initiative Kampala, Uganda	Africa	Law and policy, human rights	None
Monica Arango Olaya	Faculty of Law, University of Oxford Oxford, United Kingdom	Europe	Law and policy, human rights	None
Xian Warner	Research and Program Coordinator, The Equality Institute Dili, Timor-Leste	Western Pacific	Law and policy, human rights	None
Christina Zampas[a]	Center for Reproductive Rights Geneva, Switzerland	Europe	Law, human rights, sex work, forced sterilization	None

[a] These members also contributed to the scoping meeting(s) for this domain, in advance of the ERRG meetings, along with the following additional contributing experts: Paola Bergallo (University of Torcuato Di Tella, Argentina), Lucia Berro Pizzarossa (University of Groningen, Netherlands), Scott Burris (Temple University, USA), Fiona de Londras (Birmingham University, United Kingdom), Silvia de Zordo (University of Barcelona, Spain), Debora Diniz (Instituto de Bioética, Brazil), Heather Douglas (University of Queensland, Australia), Daniel Grossman (University of California, San Francisco, USA), Selma Hajri (TAWHIDA Group for Research and Action on Women's Health, Tunisia), Jihan Jacob, Center for Reproductive Rights, Philippines), Minzee Kim (Ewha Womans University, Republic of Korea), Chisale Mhango (University of Malawi, Malawi), Mahesh Puri (Centre for Research on Environment, Health and Population Activities, Nepal), Patricia Schulz (Committee on the Elimination of Discrimination against Women, Switzerland), Patty Skuster (Ipas, USA), Marion Stevens (Sexual and Reproductive Justice Coalition, South Africa), Maya Unnithan (University of Sussex, United Kingdom).

Members of the Guideline Development Group (GDG), and declarations of interests

Name	Job title, affiliation City, country	WHO region of residence	Expertise	Declarations/ conflicts of interest
Fauzia Akhter Huda	Project Coordinator, Maternal and Child Health Division, International Centre for Diarrhoeal Disease Research Bangladesh (ICDDRB) Dhaka, Bangladesh	South-East Asia	Public health, health systems, abortion	None
Karla Berdichevsky	Director, Gender Equity and Reproductive Health, Mexico Federal Ministry of Health Mexico City, Mexico	Americas	Sexual and reproductive health programming, policy and research	None
Marge Berer	Coordinator, International Campaign for Women's Right to Safe Abortion London, United Kingdom	Europe	Law and policy	None
Laura Castleman (CHAIR)	Associate Medical Director, Planned Parenthood of Michigan and Adjunct Clinical Assistant Professor, University of Michigan Ann Arbor, MI, USA	Americas	Obstetrics and gynaecology	None
Michalina Drejza	Director on Research and Development, International Youth Alliance for Family Planning (IYAFP) Poznań, Poland	Europe	Obstetrics and gynaecology, youth	None
Joanna Erdman	Associate Professor, Health Law and Policy, Schulich School of Law, Dalhousie University Halifax, Nova Scotia, Canada	Americas	Law and policy	None
Kristina Gemzell Danielsson	Head, Department of Women's and Children's Health, Karolinska Institutet Stockholm, Sweden	Europe	Obstetrics and gynaecology, abortion research	None
Caitlin Gerdts	Vice President for Research, Ibis Reproductive Health Oakland, CA, USA	Americas	Qualitative research	None
Laura Gil	Clinician Bogotá, Colombia	Americas	Clinical	None
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Continued on the next page

Continued

Name	Job title, affiliation City, country	WHO region of residence	Expertise	Declarations/ conflicts of interest
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Rajat Khosla (during first stages of guideline planning)	SRH, Director's Office, WHO headquarters (formerly)	Human rights adviser
Caron Kim[a]	SRH, PUA, WHO headquarters	Abortion, contraception, sexual and reproductive health and rights in health emergencies
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Members of the WHO Secretariat

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Annex 2. Selected human rights treaties and their treaty monitoring bodies

For more detailed information on the how international human rights standards apply to abortion, refer to Web annex A: Key international human rights standards on abortion, available at https://apps.who.int/iris/handle/10665/349317.

Treaty (in chronological order)	Abbreviation	Year of adoption	Year entered into force	Treaty monitoring body (TMB)[a]	Abbreviation
International Convention on the Elimination of All Forms of Racial Discrimination	ICERD	1965	1969	Committee on the Elimination of Racial Discrimination	CERD
International Covenant on Civil and Political Rights	ICCPR	1966	1976	Human Rights Committee	HRC
International Covenant on Economic, Social and Cultural Rights	ICESCR	1966	1976	Committee on Economic, Social and Cultural Rights	CESCR
Convention on the Elimination of All Forms of Discrimination against Women	CEDAW	1979	1981	Committee on the Elimination of Discrimination against Women	CEDAW
Convention against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment	CAT	1984	1987	Committee against Torture	CAT
Convention on the Rights of the Child	CRC	1989	1990	Committee on the Rights of the Child	CRC
International Convention on the Protection of the Rights of All Migrant Workers and Members of Their Families	ICMW	1990	2003	Committee on Migrant Workers	CMW
Convention on the Rights of Persons with Disabilities	CRPD	2006	2008	Committee on the Rights of Persons with Disabilities	CRPD

[a] Also sometimes referred to as "treaty bodies".

Further information on the Core International Human Rights Instruments and their TMBs is available at: https://www.ohchr.org/EN/ProfessionalInterest/Pages/CoreInstruments.aspx

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Annex 4. Guideline development methods and process

A. Guideline development working groups

Please refer to Annex 1 for the names of members of each of the working groups (and declarations of interests). A summary of the key meetings held is provided at the end of this annex.

The WHO Guideline Steering Group

The WHO Guideline Steering Group led the guideline development process. Chaired by the WHO Department of Sexual and Reproductive Health and Research (SRH), it was composed of eight staff members from the Department, including seven from the Prevention of Unsafe Abortion (PUA) Unit and the Department's human rights adviser. Gender, ethics, social accountability and human rights expertise among the Steering Group members ensured that key underlying principles were adequately reflected. The Steering Group members drafted the initial scope of the guideline; identified and drafted the priority questions in "PICO" format (population, intervention, comparator, outcome); and identified individuals to be invited to participate as guideline methodologists and as members of the Evidence Synthesis Teams (ESTs), the Evidence and Recommendation Review Groups (ERRGs), the Guideline Development Group (GDG) and the External Review Group (ERG) (see below). The members of these groups and the participation of other external contributors were only confirmed after completion of a process of declaration and management of any conflicts of interest, which was managed by the Steering Group in consultation with the Office of Compliance, Risk Management and Ethics (see section B). The Steering Group identified the chair of the GDG, and this was confirmed by the other GDG members. The Steering Group oversaw the work of the ESTs, organized the ERRG and GDG meetings, and drafted the recommendations based on the decisions of the ERRGs and GDG. The Steering Group did not determine or agree on the final recommendations as this was the role of the GDG. The Steering Group was responsible for drafting, revising and finalizing the guideline in collaboration with the ERRG, GDG and ERG members and other contributors, and for overseeing the publication and dissemination of the guideline and the development of related implementation tools. Finally, the Steering Group is responsible for monitoring new information and user needs and for determining when the guideline may need to be updated. The WHO Steering Group was supported by the wider WHO Secretariat, which included 19 WHO staff members and consultants from the SRH Department and other departments at WHO headquarters and representatives from WHO regional offices.

Guideline methodologists

The guideline methodologists worked closely with the WHO Steering Group and members of the Evidence Synthesis Teams (ESTs) to appraise the evidence from systematic reviews using GRADE methodology (see section D). In addition, the guideline methodologists oversaw all methodological issues and were responsible for the GRADE assessments of the certainty of the evidence. One guideline methodologist was appointed for the Clinical services domain and one for the Law and policy domain, while a team from Cochrane Response served this role for the Service delivery domain.[1] Appreciating that the public health impact of laws and policies is complex, that evidence related to law and policy is not a research area that lends itself to randomized controlled trials or comparative observational studies, and that this evidence cannot be readily synthesized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, a pragmatic approach was applied (see details in section D).

Evidence Synthesis Teams (ESTs)

The ESTs planned and conducted the systematic reviews and prepared the GRADE Evidence-to-Decision (EtD) frameworks (which include evidence summaries, evidence profiles/tables and EtD tables). The ESTs comprised researchers from among WHO staff, consultants and fellows, as well as external collaborating research groups. For the **Clinical services domain**, the EST was formed of members of the Cochrane Fertility Regulation (CFR) Group, Family Planning fellows (WHO staff or interns), and the responsible technical officer from the Steering Group for this guideline. For the **Service delivery domain**, the EST comprised staff from Cochrane Response, Family Planning fellows (current and former WHO staff), and the responsible technical officer from the Steering Group. The CFR

1 Cochrane Response is an evidence consultancy business operated by the Cochrane Collaboration. It provides tailored and responsive evidence services, and accessible review formats.

Group and Cochrane Response have updated their systematic reviews to provide the evidence base for many of the recommendations in these two domains. For the **Law and policy domain**, the EST included WHO consultants as well as external teams based at two centres:

- The Policy Surveillance Program at the Center for Public Health Law Research (CPHLR), Temple University, Philadelphia, USA: Researchers within this programme created conceptual frameworks and legal mapping of the various interventions and the systems around them, and identified data for the empirical assessment of laws and policies.
- Birmingham Law School, University of Birmingham, United Kingdom: The team in Birmingham provided expertise in health law and policy, human rights, comparative law, and global legal studies. This team conducted systematic reviews to provide the evidence base for the law and policy recommendations.

The Evidence and Recommendation Review Groups (ERRGs) and the Guideline Development Group (GDG)

Rather than having one Guideline Development Group (GDG) from the start of the guideline development process, for the development of this wide-ranging consolidated guideline, three separate ERRGs were formed – one for each of the three domains: Clinical services, Service delivery and Law and policy. For the final stage of the process, one GDG was formed comprising 3–4 members from each of the three ERRGs. The three ERRGs had 6–13 members representing all regions and a range of expertise, including one youth representative from the International Youth Alliance for Family Planning (IYAFP). The ERRG members were identified and invited by the WHO Steering Group, as were the human rights advisers who also contributed to the meetings by ensuring consideration of relevant human rights during recommendation formulation. Each ERRG undertook a detailed review of the evidence, formulated and agreed on draft recommendations during a series of 4–5 online meetings between March 2020 and March 2021. Prior to each meeting, background documents – the EtD frameworks and draft recommendations – were shared with the ERRG members. Consultations via email, Skype, Microsoft Teams, GoToMeeting and Zoom were conducted as needed in between meetings to ensure input was received from each ERRG member for each area under review.

In early 2021, representatives from each ERRG were invited by the WHO Steering Group to join the GDG for the final meeting in late April 2021, during which the draft recommendations from all three ERRGs were presented for review and finalization. The confirmed members of the GDG in turn confirmed the WHO Steering Group's selection of a chair for the GDG. There were 18 GDG members (14 female, 4 male), representing all six WHO regions and a range of expertise, including a youth representative from IYAFP. A draft of the full guideline document, including the draft recommendations, was shared with all the GDG members to review in advance of the formal meeting, along with other relevant background documents (the EtD frameworks). During the meeting, the GDG reviewed and discussed the evidence and the draft recommendations, with the aim of reaching consensus on the certainty of the supporting evidence and the strength and direction of the new and updated recommendations (see Chapters 2 and 3). Subsequent to the GDG meeting, the members also had an opportunity to review the revised guideline document into which the decisions made during the GDG meeting had been integrated.

The External Review Group (ERG)

The WHO Steering Group, in consultation with the GDG, identified and confirmed nine technical experts and stakeholders with thematic area expertise relevant to the recommendations presented in this guideline to serve as members of the ERG. The ERG members were balanced in terms of geographic representation, and had no important conflicts of interest. Following the GDG meeting and the subsequent revisions to the draft guideline, the document was circulated to the ERG members. The role of the ERG members was to provide input regarding the accuracy, clarity of the language, implementation/adaptation considerations, and presentation of the guideline. The ERG also ensured that the GDG decision-making processes had considered and incorporated the contextual values and preferences of persons affected by the recommendations. Recommendations in the document, which had been finalized by the GDG, were not changed based on ERG input other than to improve clarity and readability, as needed. All comments from the ERG members were collated by the responsible technical officer and shared with the WHO Steering Group for review. No serious factual errors or concerns were identified that affected any of the recommendations or any major sections of the draft guideline.

Meeting observers and external partners

In accordance with guidance in the *WHO handbook for guideline development, second edition (2014),*[2] representatives from a range of relevant professional organizations and United Nations agencies were invited to attend the GDG meeting in April 2021 as observers with no role in determining the recommendations (see Annex 1). The invited observers included the United Nations Population Fund (UNFPA), the Royal College of Obstetricians and Gynaecologists (RCOG), the International Federation of Gynecology and Obstetrics (FIGO), the International Confederation of Midwives (ICM) and the International Council of Nurses (ICN), and representatives from all attended except for ICN. In addition, a range of WHO/HRP's implementing partner organizations were invited to review the draft guideline prior to submission to the GRC; these organizations included Ipas, the International Planned Parenthood Federation (IPPF), MSI Reproductive Choices, Pathfinder and Population Services International (PSI).

B. Management of declarations and conflicts of interests, and confidentiality

In accordance with the *WHO handbook for guideline development*, all invited members of the ERRGs, GDG, the ESTs, the ERG, and the GDG meeting observers, guideline reviewers representing implementing partner organizations, and other external contributors (e.g. consultants and collaborators) were asked to declare in writing any competing interests (academic, financial or other) at the time of invitation to participate in the guideline development or evidence review process. This was done by electronic submission of a signed WHO Declaration of Interests (DOI) form along with a copy of their curriculum vitae to the responsible technical officer prior to participation. In addition, internet searches were conducted on each invited member to assess any potential conflicts of interest that had not been disclosed. The management of conflicts of interest was explained to the invited participants, including the fact that no member would be allowed to participate in the meeting(s) if they failed to first complete and sign a DOI form.

The responsible technical officer assessed the DOI forms and CVs received with reference to the *WHO handbook for guideline development*, in consultation with the Director of the SRH Department and with the input of the WHO Steering Group, to determine the existence (and severity) of any conflict of interest, and agree upon a management plan. One conflict arose for one ERRG member during the course of guideline development, and this person thus did not attend any meetings thereafter. There were no other cases of any conflict of interest (this is also reported in the ERRG and GDG members lists in Annex 1).

Biographical information for all ERRG and GDG members deemed not to have significant conflicts of interest (i.e. conflicts that precluded their participation in the GDG) were posted on the WHO SRH Department's website for public comment for at least two weeks before the start of the respective meetings, with their consent (in 2020 for the ERRGs and in 2021 for the GDG). ERRG and GDG members were confirmed once this process was completed. On confirmation of their eligibility to participate, all ERRG, GDG and ERG experts were instructed to notify the responsible technical officer of any change in relevant interests during the course of their participation in the process. At the start of each meeting, all ERRG and GDG participants had the opportunity to verbally confirm, append or amend any declared interests so that all fellow GDG members and other attendees were made aware. They had a similar opportunity to do the same in writing before submitting comments on draft versions of the guideline.

Finally, it should be noted that each member of the ERRGs, GDG, ERG, ESTs and each guideline methodologist was asked to sign a confidentiality agreement relating to the guideline development process and outcomes. In addition, the responsible technical officer securely stored all received electronic and printed hard copies of the signed DOI forms and curriculum vitae to ensure that confidentiality was maintained.

C. Scope of the guidance: defining topic areas and outcomes of interest

In September 2018, an online survey was undertaken to initiate the process of updating WHO guidance on safe abortion. The objectives of this survey were (i) to identify relevant areas that require an update or new areas that need to be added to the guidance and (ii) to generate suggestions for making the guidelines more user-friendly. The survey was distributed within various networks in the sexual and reproductive health field and resulted in 122 responses.

2 WHO handbook for guideline development, second edition. Geneva: World Health Organization; 2014 (https://apps.who.int/iris/handle/10665/145714).

Thereafter, scoping meetings for each of the three domains (Clinical services, Service delivery, and Law and policy) were conducted with a range of experts, between November 2018 and June 2019. The purpose of these meetings was to determine the key topic areas that required formulation of key questions in the "PICO" format (population, intervention, comparator, outcomes) and to formulate and discuss these questions. The PICO questions were further reviewed, modified and finalized in the follow-up email exchanges between the WHO Steering Group and the ERRG members for each domain. The topic areas for the final PICOs of each domain, as determined during the scoping meetings, are provided in Box A below. The PICO questions for each domain are provided in Annexes 8, 9 and 10.

In addition to the scoping meetings, three technical meetings also focused on issues relating to abortion care in humanitarian settings (June 2019), values and preferences relating to abortion care (September 2019), and youth concerns relating to abortion care (April 2021) (further details on these meetings and issues are presented in Box B at the end of this annex and in the Web annex B: Technical meetings during guideline development).

BOX A: Topic areas per domain for development of PICOs for new and updated recommendations

Law and policy	Criminalization Grounds-based approaches Gestational age limits Mandatory waiting periods Third-party authorization Restrictions on abortion providers Conscientious objection by a health worker
Clinical services	Rh isoimmunization Pain management for medical and surgical abortion and for cervical priming Cervical priming prior to surgical abortion Self-management of medical abortion (all subtasks) Medical abortion using new methods (regimens including letrozole) Medical management of missed abortion Follow-up care or additional services after abortion
Service delivery	**Health workers providing services:** self, community health workers, pharmacy workers, pharmacists, traditional and complementary medicine professionals, auxiliary nurses, auxiliary nurse midwives, nurses, midwives, associate/advanced associate clinicians, generalist medical practitioners **Services:** • Provision of information on safe abortion • Counselling across the continuum of care • Cervical priming with medication and osmotic dilators prior to surgical abortion • Surgical abortion (vacuum aspiration [VA] and dilatation and evacuation [D&E]) • Medical management of induced abortion (all subtasks; including self-management) • Medical management of intrauterine fetal demise (IUFD) • Medical and surgical management of incomplete abortion • Initial management of non-life-threatening complications • Initiation and continuation of injectable contraceptives (including self-injection) **Service-delivery methods:** • Community-based outreach models for provision of abortion care • Medical abortion care provided through telemedicine • Harm-reduction counselling on abortion care • Social marketing methods for abortion services • Self-sourcing of abortion medications online

D. Review of the evidence and formulation of recommendations

Defining and reviewing priority questions

The full list of PICO questions was confirmed during follow-up communications among the WHO Steering Group and the ERRG members after the scoping meetings for each domain, which were described in the previous section. All the PICO questions and related details are provided in Annexes 8, 9 and 10.

Systematic review methods (evidence retrieval)

A list of all reviews conducted for the development of this guideline is presented in Annex 7. Refer to the published systematic reviews and to the packages of supplementary materials online for information about the specific methods used, including search strategies. Refer to beginning of this annex for information about the Evidence Synthesis Teams (ESTs).

Sources for evidence relating to the PICOs of interest for the Clinical services and Service delivery domains included randomized controlled trials (RCTs) as well as non-randomized controlled trials, controlled before-and-after studies, interrupted time series and cohort studies. The following databases were searched from inception to December 2020, without language filters:

- Global databases: ClinicalTrials.gov, Cochrane database, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica database (Embase), POPLINE, PubMed.
- Regional databases: African Index Medicus (AIM), Chinese Biomedical Literature Database, Global Index Medicus, Index Medicus for South-East Asia (IMSEAR), Index Medicus for WHO Eastern Mediterranean, Latin American and Caribbean Health Sciences Literature (LILACS), Western Pacific Regional Index Medicus.

In addition, a search of trial registry sites and organizational websites was conducted, and information from experts in the field was also used to identify any major ongoing or completed but unpublished trials that could be relevant to the guideline recommendations. Data from studies meeting the inclusion criteria were extracted using a standardized form and organized into Summary of Findings tables within the GRADE evidence summaries, using the online GRADE (Grading of Recommendations Assessment, Development and Evaluation) application.[3]

For the Law and policy domain, the primary databases searched included Google Scholar, JSTOR, Hein Online and PubMed, from 2010 to 2021. For this domain, in addition to RCTs and other types of studies, the reviews also included legal and policy analyses, regulatory documents, and legal and policy reviews.[4]

Assessment of the quality and certainty of the evidence for recommendations

In accordance with the WHO guideline development process, the GDG formulated the recommendations guided by the quality/certainty of the available evidence.[5] WHO has adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to recommendation development, which defines the quality/certainty of evidence as the extent to which one can be confident that the reported estimates of effect (desirable or undesirable) available from the evidence are close to the actual effects of interest.[6] The GRADE approach specifies four levels of certainty of evidence, which should be interpreted as follows:

- High – We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate – We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low – Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low – We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

3 GRADEpro GDT. GRADEpro Guideline Development Tool [Software] (developed by Evidence Prime, Inc.). McMaster University; 2020 (https://gradepro.org/).
4 de Londras F, Cleeve A, Rodriguez M, Lavelanet A. Integrating rights and evidence: a technical advance in abortion guideline development. BMJ Glob Health. 2021;6(2):e004141.
5 WHO handbook for guideline development, 2014.
6 Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading the quality of evidence and the strength of recommendations. The GRADE Working Group; 2013 (https://gdt.gradepro.org/app/handbook/handbook.html).

As a baseline, RCTs provide "high-quality" evidence, while non-randomized trials and observational studies provide "low-quality" evidence. This baseline quality rating may be downgraded based on consideration of study design limitations (risk of bias – assessed using the criteria outlined in the *Cochrane handbook for systematic reviews of interventions* along six domains)[7], inconsistency, imprecision, indirectness and publication bias. For observational studies, other considerations, such as magnitude of effect, could lead to upgrading of the rating if there are no limitations that indicated a need for downgrading. The EST members and guideline methodologists, in accordance with standard operating procedures approved by the WHO Steering Group, performed the grading of review evidence.

The GRADE approach to appraising the quality of quantitative evidence was used for all the critical outcomes identified in the PICO questions,[8] and a GRADE evidence profile (GRADE table) was prepared for each quantitative outcome within each PICO; these are presented in the supplementary materials available online.

With regard to the Law and policy domain, there was an existing composite recommendation in the 2012 *Safe abortion* guidance, which spoke to these issues and related interventions; the topics identified during the scoping process for this updated guideline (see Box A) stemmed from there. However, there was no existing standardized approach for assessing the quality or certainty of the evidence relating to laws and policies on abortion using a rights-based analysis.[9] Therefore, an innovative approach was developed to evaluate the evidence that effectively integrated human rights protection and enjoyment as part of health outcomes and analysis, while considering several important factors and their potential interactions.[10] This is in line with WHO's norms and values, and thus underpins integrated evidence for application within an Evidence-to-Decision (EtD) framework.

The outcomes of interest for the Law and policy domain were informed by the conceptual frameworks and legal mapping initially performed by the EST team at Temple University (see section A), which mapped the various interventions and the systems around them and identified empirical research assessing the health effects of laws and policies. This mapping emphasized policy surveillance, advancing technology and methods for legal evaluation, teaching policy surveillance methods, and sharing credible scientific data with researchers, policy-makers and the public to make the case for laws that improve health. Next, the team developed causal logic models for the legal interventions on abortion to display plausible pathways from the implementation of the restriction to health and socioeconomic outcomes. The third step involved using the models as a guide to conduct a second rapid scan, in order to identify non-legal studies investigating whether the processes and outcomes posited in the models do, in fact, occur, and with what frequency and severity, and with what consequences. This evidence, in turn, supported plausible inferences of causality for practical policy and guideline development purposes. The Identifying Data for the Empirical Assessment of Law (IDEAL) method attempts to create an objective framework for crystallizing the various influences and consequences attributable to the impact of specific abortion restrictions, leading to the identification of untapped scientific evidence on plausible effects of the law.[11]

The quantitative evidence retrieved from all types of studies and documents was assessed for precision, directness and magnitude of effect, while the qualitative evidence was assessed for adequacy, and compiled in an EtD table. An overarching Rights Analysis Table, which identified human rights standards relevant to the specific interventions, was applied to the evidence table, leading to the development of a Human Rights to Evidence Table, organized by outcome of interest. The full methods are described in de Londras et al. (2021).[12]

Formulation of recommendations and determining the strength of recommendations

The WHO Steering Group supervised and finalized the preparation of evidence summaries, including GRADE tables and Summary of Findings tables, for each PICO question. For the Clinical services and Service delivery domains, the evidence summaries followed the new Evidence-to-Decision (EtD) framework, known as the WHO-INTEGRATE

7 Each included study is assessed and rated to be at low, high or unclear risk of bias for sequence generation, allocation concealment, blinding of study personnel and participants, attrition, selective reporting and other sources of bias (Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, Welch V, editors. Cochrane handbook for systematic reviews of interventions, Version 6.2. The Cochrane Collaboration; 2021 [https://training.cochrane.org/handbook/current]).

8 Schünemann et al., editors, GRADE Handbook, 2013.

9 Rehfuess E, Stratil JM, Portela A, Baltussen R, Scheel IB, Norris SL. The WHO-INTEGRATE evidence to decision framework version 1.0: integrating WHO norms and values and a complexity perspective. BMJ Glob Health. 2019;4:e000844.

10 de Londras et al., 2021.

11 Burris S, Ghorashi AR, Cloud LF, Rebouché R, Skuster P, Lavelanet A. Identifying data for the empirical assessment of law (IDEAL): a realist approach to research gaps on the health effects of abortion law. BMJ Glob Health. 2021;6:e005120.

12 de Londras et al., 2021.

framework. This new framework is broader and better suited to system-level interventions. The six substantive criteria of the WHO-INTEGRATE framework are the following: balance of health benefits and harms; human rights and sociocultural acceptability; health equity, non-discrimination and equality; societal implications; financial and economic considerations; and feasibility and health system considerations. The additional meta-criterion is quality of evidence (i.e. type, size and limitations of the available studies used as evidence). The WHO-INTEGRATE framework allows for the fact that some interventions are complex and have multiple components interacting synergistically or dissynergistically, may be non-linear in their effects, or may be context dependent. This framework is better able to accommodate recommendation formulation for the Law and policy domain, as well as the Clinical services and Service delivery domains, thus allowing guideline users to make informed decisions on all interventions. Also integral to the recommendation formulation process across all domains is the values placed on the outcomes and the preferences of the women affected by the recommendations. Taking this into account along with all the criteria of the WHO-INTEGRATE framework, as applied to each intervention for the specified population, new and updated recommendations were formulated by the ERRG and GDG members and qualified as either strong ("recommend") or weak ("suggest"; with specified conditions for application) recommendations in favour of the intervention, or as strong recommendations against the intervention/in favour of the comparator.

Recommendations were considered "new" (as labelled in the table at the end of the Executive Summary and in Chapter 3) if no recommendation existed in a previous WHO guideline on the specific topic or intervention in question for the specified population. In particular it should be noted that the 2012 *Safe abortion* guidance provided a composite recommendation related to law and policy; in this guideline, this was developed this into seven separate recommendations, but they are not considered to be "new" (i.e. Recommendations 1,2,3,6,7,21,22).

E. Decision-making by the GDG during guideline development

The GDG meeting took place in April 2021 to review, revise and finalize the draft recommendations from all three domains that had been prepared by the ERRGs, as described above. Decision-making was based on discussion of the synthesized evidence and the use of the DECIDE Framework[13] The final adoption of each recommendation was made by consensus, defined as full agreement among all GDG participants when at all possible – this is the preferred method. In one instance, voting was used since consensus could not be reached. The decision on how to present the medical abortion regimens was made based on the large majority voting in support of upholding the way it is described and presented in the previous guidelines. WHO staff attending the meeting, EST members, methodologists and meeting observers were not allowed to vote.

F. Compilation, review and presentation of the guideline content

The WHO responsible technical officer led the writing of the guideline with external/consultant writers, with significant input from the ESTs, the guideline methodologists and other members of the WHO Steering Group. In advance of the GDG meeting, an early draft of the full guideline document was prepared. The guideline methodologists drafted the GRADE evidence summaries and the WHO Steering Group members drafted corresponding Evidence-to-Decision (EtD) frameworks. The full draft and these supplementary materials were shared electronically with all GDG members (see Annex 1) two weeks before the GDG meeting, which was held during the last week of April 2021.

Following the GDG meeting, revisions were made to accurately reflect the deliberations and decisions of the GDG members on the recommendations and to incorporate their feedback on the draft. Subsequently, the revised draft guideline was shared electronically with all GDG members for two weeks for further comment. It was simultaneously shared for comment with all members of the External Review Group (ERG), the GDG meeting observers, and the representatives of implementing partner organizations (see section A and Annex 1), who were unconnected with the process of guideline development.

Next, the Steering Group carefully evaluated the written input of all the reviewers (via email and direct comments/edits on the draft document) for inclusion in the final guideline document and the revised version was reviewed by the director of the WHO SRH Department and edited for clarity. The final draft was submitted for review at a meeting of the WHO Guidelines Review Committee (GRC) and was fully approved by the GRC in August 2021 after some requested revisions had been completed.

13 Evidence to Decision frameworks (EtDs) for policy makers [website]. Cochrane Norway; 2021 (https://www.cochrane.no/decide-frameworks-policy-makers).

Evidence derived from the systematic reviews in support of the new and updated recommendations was summarized in EtD frameworks to provide the evidence base on effectiveness that informed the new recommendations in this guideline. These EtD frameworks are presented separately in the three packets of supplementary materials available online at https://www.who.int/publications/i/item/9789240039483:

- Supplementary material 1: Evidence-to-Decision frameworks for the law and policy recommendations
- Supplementary material 2: Evidence-to-Decision frameworks for the clinical service recommendations
- Supplementary material 3: Evidence-to-Decision frameworks for the service delivery recommendations and best practice statements

Scoping meetings: November 2018 – June 2019

BOX B: Key meetings during guideline development (in Geneva, Switzerland, or online)

Two-day scoping meetings were held for each of the three domains of this guideline, during which external experts on the subject areas and methodology (see Annex 1) identified the priority topics and the specific areas requiring new or updated recommendations or good practice statements.

- **Law and policy domain:** Geneva, November 2018. This meeting facilitated discussion and the development of new approaches to guideline development for (i) abortion law and policy, and (ii) integration of human rights.
- **Clinical services domain**: Virtual meeting, December 2018.
- **Service delivery domain**: Geneva, June 2019.

Technical meetings:

(i) Implementation considerations for abortion care in humanitarian settings: A two-day technical meeting was held in Geneva in June 2019. This meeting convened approximately 20 experts in the fields of humanitarian aid, conflict settings, abortion care and human rights (including three youth representatives) together with 20 representatives from the WHO Secretariat. The expert participants came from nine countries in the regions of Africa, the Eastern Mediterranean, Europe and North America. During the meeting participants identified specific barriers and facilitating factors for implementation of safe abortion in humanitarian/emergency settings. Common barriers that were identified included: stigma, the role of social norms and values, the lack of clinical skills and knowledge, and perceived legal barriers. Practices that facilitate implementation of quality abortion care in these settings are: engagement with key stakeholders (in particular with community and religious leaders), developing a concrete implementation strategy with identification of potential entry points, and ensuring data collection and monitoring. For further details, see Web annex B: Technical meetings during guideline development.

(ii) Global abortion values and preferences: An online survey was prepared and disseminated in October and November 2018. In September 2019, a two-day technical meeting was convened in Geneva with a diverse range of stakeholders, including 19 participants from 15 different organizations/countries (including three youth representatives) and 8 members of the WHO Secretariat. For the first time, this was a meeting focused solely on unpacking the meaning of "values and preferences" in relation to abortion. By the end of the meeting, the information generated from the rich discussions formed a basis for the guideline development discussions on the values and preferences of women, which was one of the key criteria in the recommendation formulation process. For further details, including a summary of the literature review findings, see Web annex B: Technical meetings during guideline development.

BOX B: *Continued*

(iii) Youth concerns relating to abortion care: For each of the scoping and technical meetings for this guideline, mentioned in this box, there were representatives from the International Youth Alliance for Family Planning (IYAFP) to provide a youth perspective, and one representative from IYAFP also served on each ERRG and one on the final GDG. In addition, a dedicated two-day technical meeting was held online in April 2021, bringing together 16 members of the IYAFP Youth for Abortion Taskforce which IYAFP had formed to support and inform the guideline development process, and 4 WHO staff members from the Preventing Unsafe Abortion (PUA) Unit of WHO's Department of Sexual and Reproductive Health and Research. Participants included youths (up to age 30) with demonstrated leadership skills in the field of adolescent sexual and reproductive health and rights, representing 13 countries across the WHO regions. The meeting discussions centred around three key themes: youth's values and preferences related to abortion services, addressing barriers and abortion stigma, and scaling up promising practices and interventions. Key issues discussed included the elements of an enabling environment and meaningful youth engagement. IYAFP members are developing a position paper as the main output of the meeting. For further details, see Web annex B: Technical meetings during guideline development.

Evidence and Recommendations Review Group (ERRG) meetings: March 2020 – March 2021

The ERRG meetings (4–5 meetings for each of the three domains) all occurred online, each one taking place across two days, facilitated by the WHO responsible technical officer and other members of the WHO Steering Group. At these meetings, members of the Evidence Synthesis Teams presented their systematic reviews of the evidence, and the ERRG members (see section A and Annex 1) discussed and reviewed the evidence and formulated draft recommendations, implementation considerations and good practice statements to be presented for further review, revision and finalization by the GDG.

- Clinical services domain: March 2020, May 2020, June 2020, September 2020, February 2021
- Service delivery domain: Pre-ERRG June 2020, October 2020, January 2021, early March 2021, late March 2021
- Law and policy domain: March-April 2020, June 2020, August–September 2020, March 2021.

Guideline Development Group (GDG) meeting

Online, 27–30 April 2021. During the GDG meeting, the GDG members reviewed, discussed, revised and finalized the draft recommendations, implementation considerations and good practice statements from all three domains.

WHO Guidelines Review Committee (GRC) meeting

7 July 2021.

Annex 5. Health worker categories and roles

The health worker types considered in the guideline are described in the table below. Descriptions have been adapted for the purpose of this guideline to be generic enough to apply across settings. They are indicative and illustrative and are not intended as a substitute for the formal definitions of professional bodies or titles used in specific countries.

Broad category	Description of qualifications and tasks, for the purpose of this guideline	Illustrative examples of other terms for these types of health workers (some examples may be specific to a country or regional context)
Community health worker (CHW)	A person who performs functions related to health-care delivery/information provision and has been trained in some way in the context of the task but has received no formal professional or paraprofessional certificate or tertiary education degree.	Lay health worker, village health worker, female community health volunteer, trained birth attendant, trained helpline worker, abortion accompanier, hotline counsellor
Pharmacy worker	Technicians and assistants who perform a variety of tasks associated with dispensing medicinal products under the guidance of a pharmacist. They inventory, prepare and store medications and other pharmaceutical compounds and supplies, and may dispense medicines and drugs to clients and instruct on their use as prescribed by health professionals. Technicians typically receive two or three years of training in a pharmaceutical school, with an award not equivalent to a university degree. Assistants have usually also been through two or three years of secondary school with a subsequent period of on-the-job training or apprenticeship.	Pharmacy assistant, pharmacy technician dispenser, pharmacist aide, dispensary assistant
Pharmacist	A health-care practitioner who dispenses medicinal products. A pharmacist can counsel on the proper use and adverse effects of drugs and medicines following prescriptions issued by medical doctors/health-care professionals. Education includes university-level training in theoretical and practical pharmacy, pharmaceutical chemistry or a related field.	Chemist, clinical pharmacist, community pharmacist
Traditional and complementary medicine professionals	A professional of traditional and complementary systems of medicine (non-allopathic physician) whose training includes a four- or five-year university degree that teaches human anatomy, physiology, management of normal labour and the pharmacology of modern medicines used in obstetrics and gynaecology, in addition to their systems of medicine. For the purpose of this guideline, these doctors are included with reference to the provision of elements of abortion-related care as per conventional medical practice.	Ayush doctor, Ayurvedic physician, doctor of complementary systems of medicine, non-allopathic physician
Auxiliary nurse midwife (ANM) and auxiliary nurse	An auxiliary nurse is someone trained in basic nursing skills but not in nursing decision-making. An ANM has basic nursing skills and some midwifery competencies but is not fully qualified as a midwife. The duration of training may vary from a few months up to three years. A period of on-the-job training may be included, and this is sometimes formalized in apprenticeships.	Auxiliary midwife, family welfare visitor
Nurse	A person who has been legally authorized (registered) to practise after examination by a state board of nurse examiners or similar regulatory authority. Education includes three or more years in nursing school, and leads to a university or postgraduate university degree or the equivalent.	Registered nurse, clinical nurse specialist, licensed nurse, BSc nurse
Midwife	A person who has been registered by a state midwifery or similar regulatory authority and has been trained in the essential competencies for midwifery practice. Training typically lasts three or more years in nursing or midwifery school and leads to a university degree or the equivalent. A registered midwife has the full range of midwifery skills, which include abortion.	Registered midwife, community midwife, nurse-midwife
Advanced associate clinician and associate clinician	A professional clinician with basic competencies to diagnose and manage common medical and surgical conditions and also to perform some types of surgery. Training generally requires three or four years post-secondary education in an established higher education institution. The clinician is registered and their practice is regulated by a national or subnational regulatory authority.	Assistant medical officer, clinical officer, medical licentiate practitioner, health officer, physician assistant, surgical technician, non-physician clinician, medical assistant, nurse practitioner
Generalist medical practitioner	A medical doctor who holds a university-level degree in basic medical education but does not have a specialization in obstetrics and gynaecology.	Family doctor, general practitioner, medical doctor, physician
Specialist medical practitioner	A medical doctor with postgraduate clinical training and specialization in obstetrics and gynaecology.	Gynaecologist, obstetrician

Source: adapted with minor revisions from WHO (2015) *(18)*, including updating some of the names of health worker categories to use current preferred WHO terminology, as presented in the International Standard Classification of Occupations (ISCO), Part III: Definitions of major groups, sub-major groups, minor groups and unit groups, updated 21 June 2016 (available at: https://www.ilo.org/public/english/bureau/stat/isco/isco08/index.htm).

Annex 6. Monitoring and evaluation of quality abortion care: identification of indicators

Methods and preliminary results

To achieve consensus on indicators that can be used to effectively document progress in quality abortion care at programmatic and country levels, a scoping review and multiple expert consultation processes have been conducted by scientists from the London School of Hygiene and Tropical Medicine (LSHTM) and WHO.

Scoping review: The scoping review yielded a summary of abortion measures and indicators reported over the 10-year period 2008–2018 in scientific literature and materials identified on major non-governmental organization websites. In total, 1999 abstracts and 7 additional relevant documents were screened for indicators, yielding 792 indicators identified from 142 documents. The findings of the scoping review were recently published in *BMJ Global Health* and the 792 indicators are available on a searchable spreadsheet among the supplementary materials for the publication.[1]

Consultation meeting: At an initial (virtual) consultation meeting in June 2020, multiple sets of indicators that could be used for global- and programme-level monitoring were presented. These included a sub-set of 17 core indicators that had been selected from among the indicators identified in the scoping review and from among indicators for monitoring abortion care based on measurement initiatives implemented variously by the UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), the WHO Regional Office for Africa, the Maternal Mortality Initiative (of the WHO Department for Sexual and Reproductive Health and Research) and Ibis Reproductive Health. In total, 52 unique indicators were proposed during the consultation meeting. The WHO health systems strengthening monitoring and evaluation framework was also presented as a potential structure for quality abortion monitoring and evaluation (M&E).

Consolidation: During a consolidation phase, a team of LSHTM and WHO scientists eliminated 29 out of the 52 indicators, removing indicators with duplication of information, using as main review criteria (i) relevance within the health systems strengthening monitoring and evaluation framework, and (ii) feasibility for M&E. Six indicators were added to represent categories in the health system strengthening monitoring and evaluation framework which previously had no associated proposed indicators (such as social protection and infrastructure) and in an effort to align with the Sustainable Development Goals (SDG) targets related to sexual and reproductive health and rights. These six additional indicators were sourced from the original scoping review list of indicators,[2] the Ibis Reproductive Health quality of care indicators,[3] and the WHO Department of maternal, newborn, child and adolescent health (MCA) indicators on respectful care.[4]

Online consultation: In an online consultation in March 2021, measurement and M&E experts in abortion care were invited to comment on (i) the relevance to abortion programmes of the WHO health systems strengthening monitoring and evaluation framework, (ii) the validity, feasibility, importance and sensitivity to change of each proposed indicator, and (iii) suggestions for alternative indicators. Twenty-two (out of 27) invited experts reviewed a total of 29 consolidated indicators during the online consultation. The 29 indicators were categorized in the health systems strengthening monitoring and evaluation framework areas of governance (5), financing (1), infrastructure (1), information system (1), health workforce (1), intervention access and services readiness (5), intervention quality and safety (5), coverage of interventions (1), prevalence of risk behaviours and risk factors (1), improved health outcomes and equity (4), responsiveness (2) and social protection (2).

Next steps

The core team from LSHTM and WHO is currently finalizing the indicator list following review of input gathered during the online consultation, recognizing that the indicator list will require periodic assessment for strengthening and maintaining utility and relevance. A report will be published in due course.

1 Filippi V, Dennis M, Calvert C, Tunçalp Ö, Ganatra B, Kim CR, Ronsmans C. Abortion metrics: a scoping review of abortion measures and indicators. BMJ Global Health. 2021;6(1):e003813.
2 Ibid.
3 Dennis A, Blanchard K, Bessenaar T. Identifying indicators for quality abortion care: a systematic literature review. J Fam Plann Reprod Health Care. 2017;43(1):7-15.
4 Quality of care for maternal and newborn health: a monitoring framework for network countries, updated February 2019. Geneva: World Health Organization; 2019 (https://www.who.int/docs/default-source/mca-documents/qed-quality-of-care-for-maternal-and-newborn-health-a-monitoring-framework-for-network-countries.pdf, accessed 3 September 2021).

Annex 7. Systematic reviews and links to PICOs and recommendations

Topic area	Title and authors of review (and reference details, if published)	Related PICO numbers(s), as listed in annexes	Related recommendation number(s) as presented in the main document
Topics scoped for development of new or updated recommendations			
Law and policy topics **For the Evidence-to-Decision (EtD) frameworks, refer to Supplementary material 1[1]**	**All reviews conducted by the Law and Policy Evidence Synthesis Team for development of this guideline[2]**	**Refer to Annex 8**	
Criminalization[3]	Impact of criminalization on abortion-related outcomes	1	1
Grounds-based approaches	Impact of grounds on abortion-related outcomes	2	2
Gestational age limits	Impact of gestational limits on abortion-related outcomes	3	3
Mandatory waiting periods	Impact of mandatory waiting periods on abortion-related outcomes	4	6
Third-party authorization	Impact of third-party authorization on abortion-related outcomes	5,6,7,8,9	7
Abortion provider restrictions	Impact of provider restrictions on abortion-related outcomes	10	21
Conscientious objection	Impact of conscientious objection on abortion-related outcomes	11	22
Clinical service topics **For the Evidence-to-Decision (EtD) frameworks, refer to Supplementary material 2[4]**	**All reviews conducted by the Clinical services Evidence Synthesis Team for development of this guideline**	**Refer to Annex 9**	
Rh isoimmunization	New systematic review: Chan M, Gill R, Kim C. The effect of routine anti-D administration among unsensitized Rh negative individuals who have an abortion. BMJ Sex Reprod Health. 2021 (in press).	1	8
Pain management for surgical abortion	Updated review by Cochrane Fertility Regulation (CFR) Group: Renner R-M, Edelman A, McKercher AE, Jensen JTJ, Nichols MDN. Pain control in first trimester surgical abortion. 2020 *(forthcoming)* New systematic review: DePiñeres T. Pain management regimens for surgical abortion > 14 weeks gestation. 2020 *(unpublished)*	2, 3	11 & 12 13 & 14
Pain management for medical abortion	New review by CFR Group: Reynolds-Wright JJ, Woldetsadik MA, Morroni C, Cameron S. Pain management for medical abortion before 14 weeks' gestation. 2020 *(forthcoming)* New systematic review: Korotkaya Y, Kim C. Pain control in second-trimester medical termination of pregnancy: a systematic review. 2019 *(unpublished)*	4, 5	15 16
Cervical priming prior to surgical abortion < 12 weeks	Updated review by CFR Group: Kapp N, Nguyen A, Atrio J, Lohr P. Cervical preparation for surgical abortion less than 14 weeks. 2020 *(forthcoming)*	6a	17
Cervical priming prior to surgical abortion ≥ 12 weeks	Updated review by CFR Group: Newmann SJ, Tufa T, Drey E, Meckstroth K, Diedrich JT. Cervical preparation for second trimester dilation and evacuation. 2019 *(forthcoming)*	6b,7,8,9	18
Other medical methods to induce abortion	New systematic review: Tolu L, Kim C. The efficacy, safety, and acceptability of alternative methods of medication abortion to the routine mifepristone and/or misoprostol. 2020 *(manuscript in progress)*	10,11,12	27c
Missed abortion < 14 weeks	New systematic review: DePiñeres T. Management options for pregnant individuals with missed abortion < 14 weeks. 2020 *(unpublished)*	13,14,15	31

1 Supplementary material 1, available at: https://www.who.int/publications/i/item/9789240039483
2 Authors of all seven reviews include: Amanda Cleeve, Fiona de Londras, Alana Farrell, Magdalena Furgalska, Antonella Lavelanet, Maria Isabel Rodriguez.
3 These first three recommendations are presented in Chapter 2. The remainder are presented in Chapter 3.
4 Supplementary material 2, available at: https://www.who.int/publications/i/item/9789240039483

Topic area	Title and authors of review (and reference details, if published)	Related PICO numbers(s), as listed in annexes	Related recommendation number(s) as presented in the main document
Self-management of medical abortion (eligibility, administration of medications, assessment of outcome)	New systematic review: Clark E, Tolu L, Gill R, Kim C. Eligibility and outcome assessment. 2020 *(unpublished)* New review by CFR Group: Gambir K, Kim C, Necastro KA, Ganatra B, Ngo TD. Self-administered versus provider-administered medical abortion. Cochrane Database Syst Rev. 2020;(3):CD013181.	16	50 (Self-management)
Service delivery topics **For the Evidence-to-Decision (EtD) frameworks, refer to Supplementary material 3[5]**	**All reviews conducted by the Service delivery Evidence Synthesis Team for development of this guideline**	**Refer to Annex 10**	
Provision of information	Updated review by Cochrane Response (on pharmacy workers): Villanueva G, Probyn K, Bergman H, Petkovic J, Cogo E, Buckley B, et al. Health worker roles in providing safe abortion care and post-abortion contraception: information provision by pharmacy workers. 2021 *(unpublished)*	1	4
Counselling	Updated review by Cochrane Response (on traditional and complementary medicine professionals, pharmacists, pharmacy workers and community health workers): Villanueva G, Probyn K, Bergman H, Petkovic J, Cogo E, Buckley B, et al. Health worker roles in providing safe abortion care and post-abortion contraception: pre- and post-abortion counselling. 2021 *(unpublished)*	2	5
Cervical priming using osmotic dilators or medication prior to induced surgical abortion	Updated review by Cochrane Response (on traditional and complementary medicine professionals, associate/advanced associate clinicians, midwives, nurses or auxiliary nurses/auxiliary nurse midwives): Villanueva G, Probyn K, Bergman H, Petkovic J, Cogo E, Buckley B, et al. Cervical priming using osmotic dilators or medications. 2021 *(unpublished)*	3	19 & 20
Vacuum aspiration for all indications at < 14 weeks Vacuum aspiration for management of incomplete abortion	Updated Cochrane Review (on traditional and complementary medicine professionals, auxiliary nurse midwives, auxiliary nurses, nurses, midwives, associate/advanced associate clinicians): Kim C, Barnard S, Park MH, Ngo TD. Doctors or mid-level providers for abortion. Cochrane Database Syst Rev. 2021 *(forthcoming)*	4 & 10	24 & 38
Dilatation and evacuation (D&E) for surgical abortion at ≥ 14 weeks	New systematic review (on traditional and complementary medicine professionals, associate/advanced associate clinicians, midwives): Feyssa M, Kim C. Systematic review on effectiveness, safety and acceptability of second trimester abortion by midlevel providers. 2021 *(unpublished)*	5	26
Medical abortion at < 12 weeks (eligibility, administration of medications, assessment of outcome)	Updated Cochrane Review (on traditional and complementary medicine professionals, auxiliary nurse midwives, auxiliary nurses, midwives, nurses, associate/advanced associate clinicians): Kim C, Barnard S, Park MH, Ngo TD. Doctors or mid-level providers for abortion. Cochrane Database Syst Rev. 2021 *(forthcoming)* New review by Cochrane Response (on pharmacists, pharmacy workers and community health workers): Villanueva G, Cogo E, Petkovic J, Bergman H, Probyn K, Buckley B, et al. Medical abortion facilitation. 2021 *(unpublished)*	6	28
Medical abortion at ≥ 12 weeks	New systematic review (on traditional and complementary medicine professionals, associate/advanced associate clinicians, midwives, nurses, auxiliary nurses): Feyssa M, Kim C. Systematic review on effectiveness, safety and acceptability of second trimester abortion by midlevel providers. 2021 *(unpublished)*	7	30
Medical management of intrauterine fetal demise (IUFD)	New review by Cochrane Response: Villanueva G, Probyn K, Bergman H, Petkovic J, Cogo E, Buckley B, et al. Health worker roles in providing safe abortion care and post-abortion contraception: medical management of intrauterine fetal demise (IUFD). 2020 *(unpublished)*	8	33
Medical management of incomplete abortion	Updated review by Cochrane Response: Villanueva G, Probyn K, Bergman H, Petkovic J, Cogo E, Buckley B, et al. Health worker roles in providing safe abortion care and post-abortion contraception: medical management of incomplete abortion. 2020 *(unpublished)*	9	37

5 Supplementary material 3, available at: https://www.who.int/publications/i/item/9789240039483

Topic area	Title and authors of review (and reference details, if published)	Related PICO numbers(s), as listed in annexes	Related recommendation number(s) as presented in the main document
Diagnosis and management of abortion-related complications	Updated review by Cochrane Response (on traditional and complementary medicine professionals, associate/advanced associate clinicians, midwives, nurses, auxiliary nurses/auxiliary nurse midwives): Villanueva G, Probyn K, Bergman H, Petkovic J, Cogo E, Buckley B, et al. Health worker roles in providing safe abortion care and post-abortion contraception: diagnosis and management of abortion related complications. 2021 *(unpublished)*	11	39 & 40
Delivery of injectable contraceptives	Updated review by Cochrane Response (on traditional and complementary medicine professionals medicine, pharmacists, pharmacy workers) Villanueva G, Probyn K, Bergman H, Petkovic J, Cogo E, Buckley B, et al. Health worker roles in providing safe abortion care and post-abortion contraception: injectable contraception. 2020 *(unpublished)*	12	46
Telemedicine for provision of medical abortion care (comprehensive abortion care or individual components)	Updated review by Cochrane Response: Villanueva G, Probyn K, Bergman H, Petkovic J, Cogo E, Buckley B, et al. Health worker roles in providing safe abortion care and post-abortion contraception: telemedicine. 2020 *(unpublished)*	13	48
Community-based outreach models for provision of abortion care	New systematic review by Cochrane Response: Villanueva G, Probyn K, Bergman H, Petkovic J, Cogo E, Buckley B, et al. Health worker roles in providing safe abortion care and post-abortion contraception: Community outreach models. 2021 *(unpublished)*	14	49 (Best practice statement [BPS])
Harm-reduction counselling for persons seeking induced abortion	New systematic review: Stifani B, Gill R, Kim C. Harm-reduction counselling to reduce the harms of unsafe abortion: a systematic review. 2021 *(manuscript under review)*	15	49 (BPS)
Social marketing outreach for pregnant women seeking induced abortion	New systematic review: Abubeker F, Tufa T, Kim C. Impact of social marketing interventions on safe abortion services. 2021 *(unpublished)*	16	49 (BPS)
Self-sourcing of medications through online services for pregnant women seeking induced abortion	New systematic review: Abubeker F, Tufa T, Kim C. Safety, effectiveness, and acceptability of self-sourcing of medications for induced abortion. 2021 *(unpublished)*	17	49 (BPS)
Self-administration of injectable contraceptives in the post-abortion period	Updated review by Cochrane Response: Villanueva G, Bergman H, Cogo E, Petkovic J, Buckley B, Probyn K, et al. Health worker roles in providing safe abortion care and post-abortion contraception: self-administration of injectable contraceptives. 2020 *(unpublished)*	18	51 (Self-management)
II. Topics not scoped, but an updated evidence review was conducted			
Prophylactic antibiotics	Existing review: Low N, Mueller M, Van Vliet HAAM, Kapp N. Perioperative antibiotics to prevent infection after first-trimester abortion. Cochrane Database Syst Rev. 2012;(3):CD005217. *(Updated evidence review conducted in 2021)*	N/A	9
Pre-abortion ultrasound	Existing review: Kulier R, Kapp N. Comprehensive analysis of the use of pre-procedure ultrasound for first-and second-trimester abortion. Contraception, 2011;83(1):30-3. *(Updated evidence review conducted by Cochrane Response in April 2021)*	N/A	10
Surgical methods for first trimester abortion	Existing review: Kulier R, Cheng L, Fekih A, Hofmeyr GJ, Campana A. Surgical methods for first trimester termination of pregnancy. Cochrane Database Syst Rev. 2001;(4):CD002900. *(Updated evidence review conducted in April 2021)*	N/A	23
Medical management of induced abortion	Existing review: Abubeker FA, Lavelanet A, Rodriguez MI, Kim C. Medical termination for pregnancy in early first trimester (≤ 63 days) using combination of mifepristone and misoprostol or misoprostol alone: a systematic review. BMC Womens Health. 2020;20(1):142. Updated review: Whitehouse K, Brant A, Sporstol Fonhus M, Lavelanet A, Ganatra B, et al. Medical regimens for abortion at 12 weeks and above: a systematic review and meta-analysis. Contracept X. 2020;2:100037.	N/A	27 29

Topic area	Title and authors of review (and reference details, if published)	Related PICO numbers(s), as listed in annexes	Related recommendation number(s) as presented in the main document
Medical management of IUFD	Existing review: Cleeve A, Fønhus MS, Lavelanet A. A systematic review of the effectiveness, safety, and acceptability of medical management of intrauterine fetal death at 14–28 weeks of gestation. Int J Gynaecol Obstet. 2019;147(3):301-12.	N/A	32
Post-abortion follow-up	Existing reviews: Grossman D, Ellertson C, Grimes DA, Walker D. Routine follow-up visits after first-trimester induced abortion. Obstet Gynecol. 2004:103(4):738-45. Grossman D, Grindlay K. Alternatives to ultrasound for follow-up after medication abortion: a systematic review. Contraception. 2011:83(6):504-10. *(Updated evidence review conducted by Cochrane Response in April 2021)*	N/A	34
III. Topics for recommendations that were carried forward or brought into this guideline without further review			
Methods of surgical abortion at gestational ages ≥ 14 weeks	Carried forward: Lohr PA, Hayes JL, Gemzell-Danielsson K. Surgical versus medical methods for second trimester induced abortion. Cochrane Database Syst Rev. 2008;(1):CD006714.	N/A	25 (Recommendation 5 from WHO, 2012)
Medical management of incomplete abortion	Carried forward: Kim C, Barnard S, Neilson JP, Hickey M, Vazquez JC, Dou L. Medical treatments for incomplete miscarriage. Cochrane Database Syst Rev. 2017(1);CD007223.	N/A	35 36a & 36b (Recommendations 1a and 1b from WHO, 2018)
Post-abortion contraception	Brought in: Refer to *Medical eligibility criteria for contraceptive use* (WHO, 2015)	N/A	41 (Recommendation from the MEC, WHO, 2015)
Timing of contraception and surgical abortion	Carried forward: N/A	N/A	42 (Recommendation 13 from WHO, 2012)
Timing of contraception and medical abortion	Carried forward: Kim C, Nguyen AT, Berry-Bibee E, Ermias Y, Gaffield ME, Kapp N. Systemic hormonal contraception initiation after abortion: a systematic review and meta-analysis. Contraception. 2021;103(5):291-304. Ermias Y, Berry-Bibee E, Nguyen AT, Curtis K. Post-abortion IUD insertion: a systematic review. 2017 *(unpublished)*	N/A	43 (Recommendations 4a and 4b from WHO, 2018) 44 (Recommendation from WHO, 2015)
Insertion and removal of implants Tubal ligation	Carried forward: Refer to *OptimizeMNH* guideline (WHO, 2012)	N/A	45 47 (Recommendations from WHO, 2015)
Over-the-counter oral contraceptive pills Over-the-counter emergency contraceptive pills Condom use	Brought in: Refer to *Self-care interventions for health and well-being* (WHO, 2021)	N/A	52 (Self-management) 53 (Self-management) 54 (Self-management)

Annex 8. Law and policy domain PICO questions

PICO: P = population; **I** = intervention; **C** = comparator (where applicable*); **O** = outcome(s)[1]

* Where a comparator is available, these data have been included, but very few studies that report on abortion-related policy interventions include a comparator of any kind.

Abortion regulation

Criminalization

PICO 1: The impact of criminalization (see Recommendation 1)

PICO question: For pregnant people seeking abortion and also for medical professionals providing abortion services, what is the impact of criminalization on delayed abortion, continuation of pregnancy, opportunity costs (including psychological opportunity costs), unlawful abortion, self-managed abortion, referral to another provider, workload implications (including reassignment, issues with organization of work, as well as increases or decreases in workload), system costs (includes direct system costs, and "diversions" from public health systems to paid-for services/private fees), perceived impact on provider–client relationship, stigmatization of health-care providers (considering the application of the intervention), criminal justice procedures, harassment, anti-abortion sting operations, availability of trained providers, reporting of suspected unlawful abortion?

P: Pregnant people seeking abortion; medical professionals providing abortion services

I: Criminalization

C: None (studies do not need to specify comparator)

O:[2]

- Delayed abortion
- Continuation of pregnancy
- Opportunity costs (includes psychological opportunity costs)
- Unlawful abortion
- Self-managed abortion
- Referral to another provider
- Workload implications (including reassignment issues with organization of work, as well as increases or decreases in workload)
- System costs (includes direct system costs, and "diversions" from public health systems to paid-for services/private fees)
- Perceived impact on provider–client relationship
- Stigmatization of health-care providers (considering the application of the intervention)
- Criminal justice procedures
- Harassment
- Anti-abortion sting operations
- Availability of trained providers
- Reporting of suspected unlawful abortion.

1 For further information on the findings of the reviews based on the PICOs presented in this annex, refer to the EtD frameworks in Supplementary material 1.

2 For each of the PICOs in this annex, the outcomes for both populations (pregnant people seeking abortion and medical professionals providing abortion services) have been combined in one list; for more specific information about the outcomes of interest for each review, refer to the EtD frameworks in Supplementary material 1.

Grounds-based approaches

PICO 2: The impact of grounds-based approaches (see Recommendation 2)

PICO question: For pregnant people seeking abortion and also for medical professionals providing abortion services, what is the impact of grounds-based approaches (that limit access to and/or provision of abortion on "grounds" or that prohibit access to abortion) on delayed abortion, continuation of pregnancy, opportunity costs (including psychological opportunity costs), unlawful abortion, self-managed abortion, anticipated or experienced family disharmony, anticipated or experienced exposure to interpersonal violence or exploitation, anticipated or experienced reproductive coercion, disproportionate impact, referral to another provider, workload implications (including reassignment, issues with organization of work, as well as increases or decreases in workload), perceived imposition on personal conscience or ethics, perceived impact on provider–client relationship, system costs (includes direct system costs, and "diversions" from public health systems to paid-for services/private fees), stigmatization of health-care providers (considering the application of the intervention)?

P: Pregnant people seeking abortion; medical professionals providing abortion services

I: Grounds-based approaches (that limit access to and/or provision of abortion on "grounds" or that prohibit access to abortion)

C: None (studies do not need to specify comparator)

O:

- Delayed abortion
- Continuation of pregnancy
- Opportunity costs (includes psychological opportunity costs)
- Unlawful abortion
- Self-managed abortion
- Anticipated or experienced family disharmony
- Anticipated or experienced exposure to interpersonal violence or exploitation
- Anticipated or experienced reproductive coercion
- Disproportionate impact
- Referral to another provider
- Workload implications (including reassignment issues with organization of work, as well as increases or decreases in workload)
- Perceived imposition on personal conscience or ethics
- Perceived impact on provider–client relationship
- System costs (includes direct system costs, and "diversions" from public health systems to paid-for services/private fees)
- Stigmatization of health-care providers (considering the application of the intervention).

Gestational age limits

PICO 3: The impact of gestational age limits (see Recommendation 3)

PICO question: For pregnant people seeking abortion and also for medical professionals providing abortion services, what is the impact of gestational age limits on delayed abortion, continuation of pregnancy, opportunity costs (including psychological opportunity costs), unlawful abortion, self-managed abortion, disqualification from unlawful abortion, disproportionate impact, referral to another provider, workload implications (including reassignment, issues with organization of work, as well as increases or decreases in workload), system costs (includes direct system costs, and "diversions" from public health systems to paid-for services/private fees), perceived impact on provider–client relationship, stigmatization of health-care providers (considering the application of the intervention)?

P: Pregnant people seeking abortion; medical professionals providing abortion services

I: Gestational age limits

C: None (studies do not need to specify comparator)

O:

- Delayed abortion
- Continuation of pregnancy
- Opportunity costs (including psychological opportunity costs)
- Unlawful abortion
- Self-managed abortion
- Disqualification from unlawful abortion
- Disproportionate impact
- Referral to another provider
- Workload implications (including reassignment issues with organization of work, as well as increases or decreases in workload)
- System costs (includes direct system costs, and "diversions" from public health systems to paid-for services/private fees)
- Perceived impact on provider–client relationship
- Stigmatization of health-care providers (considering the application of the intervention).

Pre-abortion

Mandatory waiting periods

PICO 4: The impact of mandatory waiting periods (see Recommendation 6)

PICO question: For pregnant people seeking abortion and also medical professional providing abortion services, what is the impact of mandatory waiting periods on delayed abortion, continuation of pregnancy, opportunity costs (including psychological opportunity costs), disproportionate impact, unlawful abortion, self-managed abortion, disqualification from lawful abortion, referral to another provider, workload implications (including reassignment, issues with organization of work, as well as increases or decreases in workload), system costs (includes direct system costs, and "diversions" from public health systems to paid-for services/private fees), perceived impact on provider–client relationship, stigmatization of health-care providers (considering the application of the intervention)?

P: People seeking abortion services; medical professionals providing abortion services

I: Mandatory waiting periods

C: None (studies do not need to specify comparator)

O:

- Delayed abortion
- Continuation of pregnancy

- Opportunity costs (including abortion travel and psychological opportunity costs))
- Disproportionate impact
- Unlawful abortion
- Self-managed abortion
- Disqualification from lawful abortion
- Referral to another provider
- Workload implications (including reassignment, issues with organization of work, as well as increases or decreases in workload)
- System costs (includes direct system costs, and "diversions" from public health systems to paid-for services/private fees)
- Perceived impact on provider–client relationship
- Stigmatization of health-care providers (considering the application of the intervention).

Third-party authorization for abortion (see Recommendation 7)

PICO 5: Impact of judicial bypass

PICO question: For pregnant people seeking abortion, what is the impact of judicial bypass on delayed abortion, continuation of pregnancy, opportunity costs (including psychological opportunity costs), unlawful abortion, self-managed abortion, anticipated or experienced family disharmony, anticipated or experienced exposure to interpersonal violence or exploitation, anticipated or experienced reproductive coercion, system costs (includes direct system costs, and "diversions" from public health systems to paid-for services/private fees)?

P: Pregnant people seeking abortion

I: Judicial bypass

C: None (studies do not need to specify comparator)

O:

- Delayed abortion
- Continuation of pregnancy
- Opportunity costs (including abortion travel and psychological opportunity costs)
- Unlawful abortion
- Self-managed abortion
- Anticipated or experienced family disharmony
- Anticipated or experienced exposure to interpersonal violence or exploitation
- Anticipated or experienced reproductive coercion
- System costs (includes direct system costs, and "diversions" from public health systems to paid-for services/private fees).

PICO 6: Impact of judicial bypass versus parental consent

PICO question: For pregnant people seeking abortion, what is the impact of judicial bypass versus parental consent on delayed abortion, continuation of pregnancy, opportunity costs (including psychological opportunity costs), unlawful abortion, self-managed abortion, anticipated or experienced family disharmony, anticipated or experienced exposure to interpersonal violence or exploitation, anticipated or experienced reproductive coercion, system costs (includes direct system costs, and "diversions" from public health systems to paid-for services/private fees)?

[P-I-O same as PICO 5 but with a comparator (C) added: parental consent]

PICO 7: Impact of parental consent versus parental notification laws/requirements

PICO question: For pregnant people seeking abortion, what is the impact of parental consent versus parental notification laws/requirements on delayed abortion, continuation of pregnancy, opportunity costs (including psychological opportunity costs), unlawful abortion, self-managed abortion, anticipated or experienced family disharmony, anticipated or experienced exposure to interpersonal violence or exploitation, anticipated or experienced reproductive coercion, system costs (includes direct system costs, and "diversions" from public health systems to paid-for services/private fees)?

[P and O same as PICO 5; I = parental consent and C = parental notification laws/requirements]

PICO 8: Impact of authorization by parent through consent or notification

PICO question: For pregnant people seeking abortion, what is the impact of authorization by parent through consent or notification on delayed abortion, continuation of pregnancy, opportunity costs (including psychological opportunity costs), unlawful abortion, self-managed abortion, anticipated or experienced family disharmony, anticipated or experienced exposure to interpersonal violence or exploitation, anticipated or experienced reproductive coercion, system costs (includes direct system costs, and "diversions" from public health systems to paid-for services/private fees)?

[P-C-O same as PICO 5 but I = authorization by parent through consent or notification]

PICO 9: Impact of authorization by spousal consent

PICO question: For pregnant people seeking abortion, what is the impact of authorization by spousal consent on delayed abortion, continuation of pregnancy, opportunity costs (including psychological opportunity costs), unlawful abortion, self-managed abortion, anticipated or experienced family disharmony, anticipated or experienced exposure to interpersonal violence or exploitation, anticipated or experienced reproductive coercion, system costs (includes direct system costs, and "diversions" from public health systems to paid-for services/private fees)?

[P-C-O same as PICO 5 but I = authorization by spousal consent]

Abortion provider restrictions

PICO 10: Impact of provider restrictions (see Recommendation 21)

PICO question: For pregnant people seeking abortion and also for medical professionals providing abortion services, what is the impact of provider restrictions on delayed abortion, continuation of pregnancy, opportunity costs (including psychological opportunity costs), disproportionate impact, unlawful abortion, self-managed abortion, referral to another provider, workload implications (including reassignment, issues with organization of work, as well as increases or decreases in workload), system costs (including direct system costs, and "diversions" from public health systems to paid-for services/private fees), perceived imposition on personal conscience or ethics, perceived impact on provider–client relationship, stigmatization of health-care providers (considering the application of the intervention)?

P: Pregnant people seeking abortion; medical professionals providing abortion services

I: Provider restrictions

C: None (studies do not need to specify comparator)

O:

- Delayed abortion
- Continuation of pregnancy
- Opportunity costs (including abortion travel and stigmatization, and psychological opportunity costs)
- Disproportionate impact
- Unlawful abortion
- Self-managed abortion

- Referral to another provider
- Workload implications (including reassignment, issues with organization of work, as well as increases or decreases in workload)
- System costs (including direct system costs, and "diversions" from public health systems to paid-for services/private fees)
- Perceived imposition on personal conscience or ethics
- Perceived impact on provider–client relationship
- Stigmatization of health-care providers (considering the application of the intervention).

Conscientious objection

PICO 11: Impact of conscientious objection (see Recommendation 22)

PICO question: For pregnant people seeking abortion and also medical professionals providing abortion services, what is the impact of conscientious objection on delayed abortion, continuation of pregnancy, opportunity costs (including psychological opportunity costs), unlawful abortion, self-managed abortion, referral to another provider, workload implications (including reassignment, issues with organization of work, as well as increases or decreases in workload), system costs (includes direct system costs, and "diversions" from public health systems to paid-for services/private fees), perceived imposition on personal conscience or ethics, perceived impact on provider–client relationship, stigmatization of health-care providers (considering the application of the intervention)?

P: Pregnant people seeking abortion; medical professionals providing abortion services

I: Conscientious objection/refusal

C: None (studies do not need to specify comparator)

O:

- Delayed abortion
- Continuation of pregnancy
- Opportunity costs (including abortion travel and stigmatization, and psychological opportunity costs)
- Unlawful abortion
- Self-managed abortion)
- Referral to another provider
- Workload implications (including reassignment, issues with organization of work, as well as increases or decreases in workload)
- System costs (includes direct system costs, and "diversions" from public health systems to paid-for services/private fees)
- Perceived imposition on personal conscience or ethics
- Perceived impact on provider–client relationship
- Stigmatization of health-care providers (considering the application of the intervention).

Annex 9. Clinical services domain PICO questions

PICO: P = population; **I** = intervention; **C** = comparator; **O** = outcome(s)[1]

Pre-abortion

Rh isoimmunization

PICO 1: No anti-D administration in unsensitized Rh-negative individuals seeking abortion (see Recommendation 8 [NEW])

PICO question: For an unsensitized Rh-negative individual seeking abortion at < 12 weeks of gestation, is no administration of anti-D a safe and effective alternative to routine anti-D administration?

P: Unsensitized Rh-negative individuals seeking abortion at < 12 weeks (undergoing either medical or surgical abortion)

I: No anti-D administration

C: Routine anti-D administration

O:

- Rate of isoimmunization in subsequent pregnancy
- Rate of antibody formation after initial pregnancy.

Pain management for surgical abortion

PICO 2: Pain control for surgical abortion at < 14 weeks of gestation (see Recommendations 11 and 12 [NEW])

PICO question: For a pregnant person seeking surgical abortion at < 14 weeks of gestation, is pain control with any particular method (I) safer, more effective and/or more satisfactory/acceptable compared with pain control with a different method or no pain control (C)?

P: Pregnant persons seeking surgical abortion at less than 14 weeks of gestation.

I:

i. Paracervical block (PCB) (this includes the different concentrations, type [lidocaine], carbonated vs not, depth of injection)

ii. PCB with premedication

iii. Intravenous (IV) conscious sedation plus PCB

iv. General anaesthesia

v. Topical anaesthesia (e.g. lidocaine)

vi. Non-pharmacological intervention (music, acupuncture, “verbicaine”, etc.)

C:

i. No PCB

ii. PCB alone

iii. PCB with premedication

iv. IV conscious sedation plus PCB

O:

- Effectiveness (maximum pain as measured by visual analogue scale; VAS)
- Anxiety scores using VAS
- Safety (complications related to pain control methods, use of supplemental narcotic, use of any additional analgesic medication, duration of recovery time, hospital admission), side-effects
- Satisfaction/acceptability.

1 For further information on the findings of the reviews based on the PICOs presented in this annex, refer to the EtD frameworks in Supplementary material 2.

PICO 3: Pain control for surgical abortion at ≥ 14 weeks of gestation (see Recommendations 11, 13 and 14 [NEW])

PICO question: For a pregnant person seeking surgical abortion at ≥ 14 weeks of gestation (including cervical priming prior to the procedure), is pain control with any particular method (I) safer, more effective and/or more satisfactory/acceptable compared with pain control with a different method or no pain control (C)?

P: Pregnant persons seeking surgical abortion at 14 weeks of gestation or above

I:

i. PCB (this includes the different concentrations, type [lidocaine], carbonated vs not, depth of injection)

ii. PCB with premedication

iii. IV conscious sedation plus PCB

iv. General anaesthesia

v. Topical anaesthesia (e.g. lidocaine)

vi. Non-pharmacological intervention (music, acupuncture, "verbicaine", etc.)

C:

i. No PCB

ii. PCB alone

iii. PCB with premedication

iv. IV conscious sedation plus PCB

O:

- Effectiveness (maximum pain as measured by VAS)
- Anxiety scores using VAS
- Safety (complications related to pain-control methods, use of supplemental narcotic, use of any additional analgesic medication, duration of recovery time, hospital admission), side-effects
- Satisfaction/acceptability.

Pain management for medical abortion

PICO 4: Pain control for medical abortion at < 14 weeks of gestation (see Recommendation 15)

PICO question: For a pregnant person seeking medical abortion at < 14 weeks of gestation, is pain control with any particular (i) pharmacological method (given prophylactically or after onset of pain) or (ii) non-pharmacological method safer, more effective and/or more satisfactory/acceptable compared with any other such method or no treatment/placebo?

P: Pregnant persons seeking medical abortion at < 14 weeks of gestation

I:

i. Pharmacological methods (Timing: prophylactic or after onset of pain)

- Ibuprofen
- Acetaminophen plus codeine
- Anti-emetics
- Loperamide
- Tramadol

ii. Non-pharmacological methods (music, acupuncture, "verbicaine", etc.)

C:

i. Pharmacological methods (Timing: prophylactic or after onset of pain)

- Ibuprofen
- Acetaminophen plus codeine
- Anti-emetics
- Loperamide
- Tramadol

ii. Non-pharmacological methods (music, acupuncture, "verbicaine", etc.)

iii. No treatment/placebo

O:

- Effectiveness (maximum pain as measured by VAS)
- Safety (complications related to pain-control methods, use of any supplemental narcotic, use of any additional analgesic medication), side-effects
- Effectiveness of medical abortion regimen, defined as successful completion without additional surgical intervention
- Time to expulsion
- Satisfaction/acceptability.

PICO 5: Pain control for medical abortion at ≥ 14 weeks of gestation (see Recommendation 16 [NEW])

PICO question: For a pregnant person seeking medical abortion at ≥ 14 weeks of gestation, is pain control with any particular (i) pharmacological method (given prophylactically or after onset of pain) or (ii) non-pharmacological method safer, more effective and/or more satisfactory/acceptable compared with any other such methods or no treatment/placebo?

P: Pregnant persons seeking medical abortion at 14 weeks of gestation or above

I:

i. Pharmacological methods (Timing: prophylactic or after onset of pain)

- Pretreatment (ibuprofen, acetaminophen plus codeine, antiemetics, loperamide, tramadol)
- IV opiates
- PCB

ii. Non-pharmacological methods (music, acupuncture, "verbicaine", etc.)

C:

i. Pharmacological methods (Timing: prophylactic or after onset of pain)

- Pretreatment (ibuprofen, acetaminophen plus codeine, antiemetics, loperamide, tramadol)
- IV opiates
- PCB

ii. Non-pharmacological methods (music, acupuncture, "verbicaine", etc.)

iii. No treatment/placebo

O:

- Effectiveness (maximum pain as measured by VAS)
- Safety (complications, use of any supplemental narcotic, use of any additional analgesic medication), side-effects
- Effectiveness of medical abortion regimen, defined as successful completion without additional surgical intervention
- Time to expulsion
- Satisfaction/acceptability.

Cervical priming

PICO 6a: Cervical priming at < 12 weeks of gestation (see Recommendation 17)

PICO question: For a pregnant person seeking surgical abortion at < 12 weeks of gestation, is cervical priming effective, safe and acceptable?

P: Pregnant persons seeking surgical abortion < 12 weeks

I: Cervical priming with medication or mechanical methods

C: Cervical priming with placebo, with medication (using different routes, doses or treatment intervals) or with different mechanical methods

O:

- Effectiveness
- Satisfaction/acceptability
- Safety.

PICO 6b: Cervical priming at ≥ 12 weeks with medications (comparing different regimens) (see Recommendations 18b–d [NEW])

PICO question: For a pregnant person seeking surgical abortion at ≥ 12 weeks of gestation, is cervical priming with mifepristone plus misoprostol or with mifepristone alone a safe, effective and satisfactory/acceptable alternative to cervical preparation with misoprostol alone?

P: Pregnant persons seeking surgical abortion at ≥ 12 weeks

I: Cervical priming with

i. Mifepristone plus misoprostol [various routes, doses, intervals]

ii. Mifepristone alone [various routes, doses, intervals]

C: Cervical priming with misoprostol alone [various routes, doses, intervals]

O:

- Effectiveness (pre-procedure cervical dilatation, need for further dilatation, ease of procedure, time to complete procedure)
- Safety (complications, need for additional interventions, pre- and post-procedure pain), side-effects
- Satisfaction (client and provider)/acceptability
- Cost (comparative cost and cost to the client).

PICO 7: Cervical priming at ≥ 12 weeks with medications compared with mechanical methods (see Recommendation 18b [NEW])

PICO question: For a pregnant person seeking surgical abortion at ≥ 12 weeks of gestation, is cervical priming with medical methods (mifepristone, misoprostol, or both) a safe, effective and satisfactory/acceptable alternative to mechanical methods (laminaria, Foley bulb, Dilapan)?

P: Pregnant persons seeking surgical abortion at ≥ 12 weeks

I: Cervical priming with medical methods

i. Mifepristone alone

ii. Misoprostol plus mifepristone

iii. Misoprostol alone

C: Cervical priming with mechanical methods (i.e. laminaria, Foley bulb, Dilapan)

O:

- Effectiveness (pre-procedure cervical dilatation, need for further dilatation, ease of procedure, time to complete procedure)
- Safety (complications, need for additional interventions, pre- and post-procedure pain), side-effects

- Satisfaction (client and provider)/acceptability
- Cost (comparative cost and cost to the client).

PICO 8: Cervical priming at ≥ 12 weeks with medication(s) plus laminaria compared with laminaria alone (see Recommendation 18d [NEW])

PICO question: For a pregnant person seeking surgical abortion at ≥ 12 weeks of gestation, is cervical priming with medication(s) plus laminaria a safe, effective and satisfactory/acceptable alternative to cervical preparation with laminaria alone?

P: Pregnant persons seeking surgical abortion at ≥ 12 weeks

I: Cervical priming with medication(s) plus laminaria

i. Mifepristone plus misoprostol plus laminaria

ii. Misoprostol plus laminaria

iii. Mifepristone plus laminaria

C: Cervical priming with laminaria alone

O:

- Effectiveness (pre-procedure cervical dilatation, need for further dilatation, ease of procedure, time to complete procedure)
- Safety (complications, need for additional interventions, pre- and post-procedure pain), side-effects
- Satisfaction (client and provider)/acceptability
- Cost (comparative cost and cost to the client).

PICO 9: Cervical priming at ≥ 12 weeks by mechanical method(s) before dilatation and evacuation (D&E) (see Recommendation 18 [NEW])

PICO question: For a pregnant person seeking surgical abortion (D&E) at ≥ 12 weeks of gestation, is cervical priming with one mechanical method a safe, effective and satisfactory/acceptable alternative to cervical priming with a different mechanical method?

P: Pregnant person seeking surgical abortion at ≥ 12 weeks

I: Cervical priming with one mechanical method before D&E

C: Cervical priming with a different mechanical method before D&E

O:

- Effectiveness (pre-procedure cervical dilatation, need for further dilatation, ease of procedure, time to complete procedure)
- Safety (complications, need for additional interventions, pre- and post-procedure pain), side-effects
- Satisfaction (client and provider)/acceptability
- Cost (comparative cost and cost to the client).

Abortion

New medical methods for abortion

PICO 10: Medical abortion with letrozole plus misoprostol, compared with misoprostol alone (see Recommendation 27c [NEW])

PICO question: For a pregnant person seeking medical abortion, is medical abortion with letrozole plus misoprostol a safe, effective and satisfactory/acceptable alternative to medical abortion with misoprostol alone?

P: Pregnant persons seeking medical abortion (all gestational ages)

I: Medical abortion with letrozole plus misoprostol [various routes, doses, intervals]

C: Medical abortion with misoprostol alone [various routes, doses, intervals]

O:

- Effectiveness (ongoing pregnancy rate, procedure completed without surgical intervention)
- Safety (serious adverse events and complications), side-effects
- Expulsion time from initiation of treatment
- Satisfaction/acceptability
- Cost (comparative and cost to the client).

PICO 11: Medical abortion with letrozole plus misoprostol, compared with mifepristone plus misoprostol

PICO question: For a pregnant person seeking medical abortion, is medical abortion with letrozole plus misoprostol a safe, effective and satisfactory alternative to medical abortion with mifepristone plus misoprostol?

P: Pregnant persons seeking medical abortion (all gestational ages)

I: Medical abortion with letrozole plus misoprostol [various routes, doses, intervals]

C: Medical abortion with mifepristone plus misoprostol [various routes, doses, intervals]

O:

- Effectiveness (ongoing pregnancy rate, completed without surgical intervention)
- Safety (serious adverse events and complications), side-effects
- Expulsion time from initiation of treatment
- Satisfaction/acceptability
- Cost (comparative and cost to the client).

PICO 12: Medical abortion with mifepristone plus letrozole, compared with misoprostol alone

PICO question: For a pregnant person seeking medical abortion, is medical abortion with mifepristone plus letrozole a safe, effective and satisfactory alternative to medical abortion with misoprostol alone?

P: Pregnant person seeking medical abortion

I: Medical abortion with mifepristone plus letrozole [various routes, doses, intervals]

C: Medical abortion with misoprostol alone [various routes, doses, intervals]

O:

- Effectiveness (ongoing pregnancy rate, completed without surgical intervention)
- Safety (serious adverse events and complications), side-effects
- Expulsion time from initiation of treatment
- Satisfaction/acceptability
- Cost (comparative and cost to the client).

Missed abortion at < 14 weeks of gestation

PICO 13: Medical management of missed abortion with mifepristone plus misoprostol (see Recommendation 31 [NEW])

PICO question: For a pregnant person with missed abortion at < 14 weeks of gestation, is medical management with mifepristone plus misoprostol a safe, effective and satisfactory/acceptable alternative to medical management with misoprostol alone?

P: Pregnant persons with missed abortion < 14 weeks

I: Medical management with mifepristone plus misoprostol [various routes, doses, intervals]

C: Medical management with misoprostol alone [routes, doses, intervals]

O:

- Effectiveness (failed expulsion/ongoing retained products, completed without surgical intervention)
- Safety (serious adverse events and complications), side-effects
- Expulsion time from initiation of treatment
- Satisfaction/acceptability
- Cost of treatment.

PICO 14: Medical management of missed abortion with all regimens (see Recommendation 31 [NEW])

PICO question: For a pregnant person with missed abortion at < 14 weeks of gestation, is medical management (all regimens) a safe, effective and satisfactory/acceptable alternative to expectant management?

P: Pregnant persons with missed abortion < 14 weeks

I: Medical management (all regimens)

C: Expectant management

O:

- Effectiveness (failed expulsion/ongoing retained products, completed without surgical intervention)
- Safety (serious adverse events and complications), side-effects
- Expulsion time from initiation of treatment
- Satisfaction/acceptability
- Cost of treatment.

PICO 15: Surgical management of missed abortion (see Recommendation 31 [NEW])

PICO question: For a pregnant person with missed abortion at < 14 weeks of gestation, is surgical management a safe, effective and satisfactory/acceptable alternative to medical or expectant management?

P: Pregnant persons with missed abortion < 14 weeks

I: Surgical management

C:

- Medical management
- Expectant management

O:

- Effectiveness (failed expulsion/ongoing retained products, completed without surgical intervention
- Safety (serious adverse events and complications), side-effects
- Expulsion time from initiation of treatment
- Satisfaction/acceptability
- Cost of treatment.

Self-management approaches

Self-management of medical abortion (see Recommendation 49)

PICO 16: Self-management of medical abortion

PICO question: For a pregnant person seeking medical abortion, is self-management of the process of medical abortion (assessing eligibility, administration of mifepristone and/or misoprostol, self-assessing outcome/success), without direct supervision of a trained health worker, a safe, effective and satisfactory/acceptable alternative to medical abortion managed by a trained health worker?

P: Pregnant persons seeking medical abortion at any gestational age

I: Pregnant persons self-managing the process of medical abortion (in whole) without direct supervision of a trained health worker

C: Medical abortion managed by a trained health worker (all medication abortion regimens)

O:

- Effectiveness (success of abortion without need for surgical intervention following the procedure)
- Safety (serious adverse events and complications)
- Satisfaction/acceptability
- Physical and emotional experience (side-effects, positive and negative emotions, internalized stigma), knowing when to seek medical care (unscheduled visits, phone calls to the clinic, emergency visits)
- Cost.

PICO 16a: Self-assessment of eligibility for MA

PICO question: For a pregnant person seeking medical abortion, is self-assessment of eligibility[2] for medical abortion a safe, effective and satisfactory/acceptable alternative to eligibility assessment by a physician or other trained health worker?

P: Pregnant persons seeking medical abortion at any gestational age

I: Pregnant persons self-managing the first part of the medical abortion process by self-assessing their eligibility for medical abortion without direct supervision of a health worker

C: Eligibility assessment performed by a trained health worker

O:

- Proportion of pregnant persons deemed eligible for medical abortion
  - Proportion of pregnant persons who were deemed ineligible due to gestational age
  - Proportion of pregnant persons who were deemed ineligible due to contraindications
- Accuracy of these assessments when measured against an independent verifier and/or diagnostic standard
- Ongoing pregnancy
- Completed without surgical intervention
- Safety (serious adverse events and complications)
- Satisfaction/acceptability
- Cost.

2 Eligibility criteria defined as: < 12 weeks; no contraindications; no signs or symptoms of ectopic pregnancy.

PICO 16b: Self-administering medications for medical abortion

PICO question: For a person seeking medical abortion, is self-administration of medications for medical abortion, when provided with instructions for their use from a reliable source, a safe, effective and satisfactory/acceptable alternative to administration of medications by a trained health worker?

P: Pregnant persons seeking medical abortion at any gestational ages

I: Pregnant persons self-administering the medications for medical abortion (as part of the medical abortion process) without direct supervision by a health worker (but with instructions from a reliable source of health care)

C: Administration of medications for medical abortion by a trained health worker

O:

- Pregnant persons' adherence to the recommended medical abortion regimen following instructions
- Effectiveness (ongoing pregnancy rate, completed without surgical intervention)
- Safety (serious adverse events and complications), side-effects
- Expulsion time from initiation of treatment
- Physical and emotional experience (side-effects, positive and negative emotions, internalized stigma), knowing when to seek medical care (unscheduled visits, phone calls to the clinics, emergency visits)
- Satisfaction/acceptability
- Cost (comparative and cost to the client).

PICO 16C: Self-assessment of the outcome of the medical abortion process

PICO question: For an individual who has undergone medical abortion, is self-assessment of the outcome/success of medical abortion a safe, effective and satisfactory/acceptable alternative to assessment of the outcome/success by a trained health worker?

P: Individuals who have undergone medical abortion

I: Pregnant persons self-managing the last part of the medical abortion process by self-assessing the outcome/success of the abortion without direct supervision by a trained health worker

C: Assessment of outcome/success of abortion by a trained health worker

O:

- Effectiveness (proportion of pregnant persons assessed to have successful abortion, accuracy of these assessments when measured against an independent verifier and/or diagnostic standard)
- Ongoing pregnancy rate
- Completed without surgical intervention
- Safety (serious adverse events and complications), side-effects
- Expulsion time from initiation of treatment;
- Physical and emotional experience (side-effects, positive and negative emotions, internalized stigma), knowing when to seek medical care (unscheduled visits; phone calls to the clinics, emergency visits)
- Satisfaction/acceptability
- Cost (comparative and cost to the client).

Annex 10. Service delivery domain PICO questions

PICO: P = population; **I** = intervention; **C** = comparator; **O** = outcome(s)[1]

Note: For a description of all the health worker categories mentioned in this annex, please refer to Annex 5.

Services applicable across the continuum of care

Provision of information

PICO 1: Pharmacy workers to provide accurate information (see Recommendation 4)

PICO question: For a person seeking information about abortion care (before or after treatment/abortion), is information on the availability of safe providers for abortion care (abortion provision, care for complications of abortion, care for incomplete abortion) provided by a pharmacy worker a safe, effective and satisfactory/acceptable alternative to no provision of information (usual practice)?

P: Person seeking information about abortion care before their treatment, or following an incomplete abortion or complications of abortion (including medical or surgical, at any gestational age)

I: Information and linkage to abortion services, in the community or in other locations, by pharmacy workers

C: No information (usual practice)

O:

- Effectiveness (pharmacy workers' correct knowledge of safe abortion and possible complications, of safe post-abortion care, and of indications for referral)
- Privacy and confidentiality in provision of information
- Accessibility of the services for the person who requires them
- Satisfaction with/acceptability of the information and services provided.

Counselling

PICO 2: Pre- and post-abortion counselling (see Recommendation 5)

PICO question: For a pregnant person having an abortion, is pre- and post-abortion counselling provided by a traditional and complementary medicine professional, pharmacist, pharmacy worker or community health worker a safe, effective and satisfactory/acceptable alternative to counselling provided by in-clinic staff?

P: Pregnant persons having an abortion

I: Pre- and post-abortion counselling by traditional and complementary medicine professionals, pharmacists, pharmacy workers or community health workers

C: Counselling provided by in-clinic staff (i.e. generalist or specialist medical practitioners, nurses or midwives)

O:

- Effectiveness (health workers' and clients' correct knowledge of contraceptive options, of safe and appropriate abortion services, and of safe post-abortion care)
- Satisfaction with/acceptability of the contraception advice provided, and the counselling and services provided
- Availability of contraceptive counselling and services
- Accessibility of information and method of choice
- Privacy and confidentiality of client respected during provision of counselling and services
- Participation in provision of counselling and services
- Quality of counselling and services
- Informed decision-making after provision of counselling and services
- Accountability in the provision of counselling and services
- Mix in types of contraception offered in the counselling.

1 For further information on the findings of the reviews based on the PICOs presented in this annex, refer to the EtD frameworks in Supplementary material 3.

Pre-abortion

Cervical priming prior to surgical abortion

PICO 3: Cervical priming using osmotic dilators or medication (see Recommendations 19 and 20)

PICO question: For a pregnant person having an induced surgical abortion, is provision of cervical priming using osmotic dilators or medication by a traditional and complementary medicine professional, associate/advanced associate clinician, midwife, nurse or auxiliary nurse/auxiliary nurse midwife a safe, effective and satisfactory/acceptable alternative to provision of cervical priming by a physician?

P: Pregnant persons having an induced abortion with vacuum aspiration or D&E

I: Cervical priming with

i. osmotic dilators provided by traditional and complementary medicine professionals, associate/advanced associated clinicians, midwives, nurses or auxiliary nurse/auxiliary nurse midwives

ii. medications provided by traditional and complementary medicine professionals, associate/advanced associate clinicians, midwives, nurses, auxiliary nurse/auxiliary nurse midwives, pharmacists or pharmacy workers

C: Cervical priming performed by physicians with (i) osmotic dilators or (ii) medications

O:

- Safety (serious adverse events and complications)
- Effectiveness (degree of dilatation and provider's perception of ease of procedure)
- Satisfaction/acceptability.

Abortion

Surgical abortion at gestational ages < 14 weeks

PICO 4: Vacuum aspiration for all indications at gestational ages < 14 weeks (see Recommendation 24)

PICO question: For a pregnant person seeking induced abortion or treatment for incomplete abortion or miscarriage (i.e. all indications for vacuum aspiration), is provision of vacuum aspiration by a traditional and complementary medicine professional, auxiliary nurse midwife or auxiliary nurse a safe, effective and satisfactory/acceptable alternative to provision of vacuum aspiration by a physician?

P: Pregnant persons seeking an induced abortion or treatment for incomplete abortion or miscarriage

I: Vacuum aspiration provided by traditional and complementary medicine professional, auxiliary nurse midwives or auxiliary nurses

C: Vacuum aspiration provided by generalist or specialist medical practitioners (obstetricians/gynaecologists)

O:

- Safety (serious adverse events and complications)
- Effectiveness (success of abortion following the procedure
- Satisfaction/acceptability.

Surgical abortion at later gestational ages

PICO 5: Dilatation and evacuation (D&E) for surgical abortion at ≥ 14 weeks (see Recommendation 26)

PICO question: For a pregnant person having a surgical abortion (D&E), is provision by a traditional and complementary medicine professional, associate/advanced associate clinician, midwife a safe, effective or satisfactory/acceptable alternative to provision of care by a doctor?

P: Pregnant women seeking surgical abortion at ≥ 14 weeks of gestation

I: D&E provided by traditional and complementary medicine professionals, associate/advanced associate

clinicians, midwives

C: Surgical abortion provided by generalist and specialist medical practitioners

O:

- Effectiveness (success of abortion following the procedure)
- Safety (serious adverse events and complications)
- Satisfaction/acceptability.

Medical abortion for gestational ages < 12 weeks and its component tasks (see Recommendation 28)

PICO 6: Provision of medical abortion care at < 12 weeks

PICO question: For a pregnant person seeking medical abortion at < 12 weeks, is provision of medical abortion (i.e. assessment of eligibility, administering quality assured medications, assessment of outcome/success) by a traditional and complementary medicine professional, pharmacist, pharmacy worker or community health worker, a safe, effective and satisfactory/acceptable alternative to provision of medical abortion by a physician?

P: Pregnant persons seeking medical abortion

I: Medical abortion provided by traditional and complementary medicine professionals, pharmacists, pharmacy workers or community health workers

C: Medical abortion provided by generalist or specialist medical practitioners (obstetrician/gynaecologists)

O:

- Safety (serious adverse events and complications)
- Effectiveness (success of abortion without need for surgical intervention following the treatment)
- Satisfaction/acceptability.

PICO 6a: Assessment of eligibility for MA

PICO question: For a pregnant person seeking medical abortion, is assessment of eligibility for medical abortion by a traditional and complementary medicine professional, pharmacist, pharmacy worker or community health worker a safe, effective and satisfactory/acceptable alternative to – and as accurate as – assessment by a physician?

P: Pregnant persons seeking medical abortion

I: Eligibility assessment by traditional and complementary medicine professionals, pharmacists, pharmacy workers or community health workers

C: Eligibility assessment by generalist or specialist medical practitioners (obstetrician/gynaecologists)

O:

- Effectiveness (proportion of pregnant persons deemed eligible for medical abortion by provider type and accuracy of these assessments when measured against an independent verifier and/or diagnostic standard)
- Safety (serious adverse events, excluding treatment for incomplete abortion or ongoing pregnancy)
- Effectiveness (success of abortion following the procedure)
- Satisfaction.

PICO 6b: Administration of medications for MA

PICO question: For a pregnant person seeking medical abortion, is administration of medications for medical abortion (i.e. information provision, dispensing of quality assured medications, referral to a reputable source for medications) with instructions for their use by a traditional and complementary medicine professional, pharmacist, pharmacy worker or community health worker a safe, effective and satisfactory/acceptable alternative to administration by a physician?

P: Pregnant persons seeking medical abortion

I: Administration of medications (i.e. information provision, dispensing of quality assured medications, referral to a reputable source for medications) with instructions for their use by traditional and complementary medicine professionals, pharmacists, pharmacy workers or community health workers

C: Administration of medications (i.e. information provision, dispensing of quality assured medications, referral to a reputable source for medications) by generalist or specialist medical practitioners

O:

- Participants understanding of the protocol, as shown by taking the correct regimen
- Safety (serious adverse events, excluding treatment for incomplete abortion or ongoing pregnancy)
- Effectiveness (success of abortion following the procedure)
- Satisfaction.

PICO 6C: Accurate assessment of success of the MA process

PICO question: For a pregnant person seeking medical abortion, is assessment of the success of the medical abortion process by a traditional and complementary medicine professional, pharmacist, pharmacy worker or community health worker a safe, effective and satisfactory/acceptable alternative to – and as accurate as – assessment by a physician?

P: Pregnant persons seeking medical abortion

I: Assessment of success of abortion by traditional and complementary medicine professionals, pharmacists, pharmacy workers or community health workers

C: Assessment of success of abortion by generalist or specialist medical practitioners

O:

- Effectiveness of the assessment of the outcome (proportion of pregnant persons assessed for success of abortion by provider type and accuracy of these assessments when measured against an independent verifier and/or diagnostic standard)
- Effectiveness (success of abortion following the procedure)
- Safety (serious adverse events, excluding treatment for incomplete abortion or ongoing pregnancy, ectopic pregnancy)
- Satisfaction.

Management of induced abortion at gestational ages ≥ 12 weeks

PICO 7: Provision of abortion care at ≥ 12 weeks (see Recommendation 30)

PICO question: For a pregnant person seeking induced abortion, is medical or surgical abortion by a traditional and complementary medicine professional, associate clinician, midwife, nurse, auxiliary nurse, pharmacist, pharmacy worker or community health worker a safe, effective or satisfactory alternative to provision of abortion care by doctors?

P: Pregnant women seeking medical or surgical abortion after 12 weeks of gestation

I: Medical abortion or surgical abortion provided by traditional and complementary medicine professionals, associate clinicians, midwives, nurses, auxiliary nurses, pharmacists, pharmacy workers or community health workers

C: Medical abortion or surgical abortion provided by generalist and specialist medical practitioners

O:

- Effectiveness (success of abortion without need for further medical or surgical intervention)
- Safety (serious adverse events and complications)
- Satisfaction.

Intrauterine fetal demise (IUFD)

PICO 8: Medical management of intrauterine fetal demise (IUFD) (see Recommendation 33 [NEW])

PICO question: For a pregnant person diagnosed with intrauterine fetal demise (IUFD), is medical management of IUFD (with mifepristone and misoprostol, or misoprostol alone) provided by a traditional and complementary medicine professional, associate/advanced associate clinician, midwife, nurse, auxiliary nurse/auxiliary nurse midwife, pharmacist, pharmacy worker or community health worker a safe, effective and satisfactory alternative to medical management by a physician?

P: Pregnant persons diagnosed with IUFD

I: Medical management with mifepristone and misoprostol or misoprostol alone provided by traditional and complementary medicine professionals, associate/advanced associate clinicians, midwives, nurses, auxiliary nurses/auxiliary nurse midwives, pharmacists, pharmacy workers or community health workers

C: Medical management with mifepristone and misoprostol or misoprostol alone provided by generalist or specialist medical practitioners

O:

- Safety (serious adverse events and complications)
- Effectiveness (success of abortion without need for surgical intervention following the procedure)
- Satisfaction/acceptability.

Post-abortion

Incomplete abortion at gestational ages < 14 weeks

PICO 9: Management of incomplete abortion with misoprostol (see Recommendation 37)

PICO question: For a pregnant person with incomplete abortion, is management of incomplete abortion with misoprostol provided by a traditional and complementary medicine professional, pharmacist, pharmacy worker or community health worker a safe, effective and satisfactory/acceptable alternative to management with misoprostol provided by a physician?

P: Pregnant persons with incomplete abortion

I: Medical management with misoprostol provided by traditional and complementary medicine professionals, pharmacists, pharmacy workers or community health workers

C: Medical management with misoprostol provided by generalist or specialist medical practitioners

O:

- Safety (serious adverse events and complications)
- Effectiveness (success of abortion without need for surgical intervention following the procedure)
- Satisfaction/acceptability.

PICO 10: Vacuum aspiration for management of uncomplicated incomplete abortion (see Recommendation 38)

PICO question: For a pregnant person seeking an induced abortion, is provision of vacuum aspiration for induced abortion/incomplete abortion/miscarriage (all indications) by traditional and complementary medicine professionals, auxiliary nurses or auxiliary nurse midwives a safe, effective or satisfactory option to provision of vacuum aspiration by physicians?

P: Pregnant persons seeking induced abortion

I: Vacuum aspiration provided by traditional and complementary medicine professionals, auxiliary nurses or auxiliary nurse midwives

C: Vacuum aspiration provided by generalist or specialist medical practitioners (obstetrician/gynaecologists)

O:

- Effectiveness (success of abortion following the procedure)
- Safety (serious adverse events and complications)
- Satisfaction/acceptability.

Recognizing and managing complications (see Recommendations 39 and 40)

PICO 11: Diagnosis and management of abortion-related complications

PICO question: For a person presenting with complication(s) of an induced abortion and in a stable condition, is diagnosis and management of abortion-related complications by a traditional and complementary medicine professional, pharmacist, pharmacy worker or community health worker a safe, effective and satisfactory/acceptable alternative to – and as accurate as – diagnosis and management by a physician?

P: Women presenting with complication(s) of an induced abortion and in a stable condition

I: Diagnosis and management of complications by traditional and complementary medicine professional, pharmacists, pharmacy workers or community health workers

i. Diagnosis and management of infection by traditional and complementary medicine professionals, pharmacists, pharmacy workers, community health workers

ii. Diagnosis and management of haemorrhage by traditional and complementary medicine professionals, pharmacists, pharmacy workers, community health workers

C: Diagnosis and management of infection and heavy bleeding by generalist and specialist medical practitioners

O:

- Effectiveness (accurate determination of a complication followed by an offer of correct treatment or referral depending on professional capacity and clinical setting)
- Safety (serious adverse events)
- Satisfaction/acceptability.

Post-abortion contraception

PICO 12: Post-abortion provision of injectable contraceptives (see Recommendation 46)

PICO question: For a person in the post-abortion period needing contraception, is provision of injectable contraceptives (initiation or continuation) by a traditional and complementary medicine professional, pharmacy worker or community health worker, a safe, effective and satisfactory/acceptable alternative to provision by a trained health worker?

P: Women in the post-abortion period needing contraception

I: Delivery of injectable contraceptives, by traditional and complementary medicine professionals, pharmacy workers or community health workers

C: Delivery of injectable contraceptives by trained health workers

O:

- Contraceptive uptake and continuation

- Safety (serious adverse events and complications related to provision of the method)
- Effectiveness (method failure)
- Satisfaction/acceptability.

Service delivery considerations

Non-facility-based/outpatient/home-based care

PICO 13: Telemedicine (see Recommendation 48)

PICO question: For a pregnant person seeking medical abortion, is medical abortion care provided through telemedicine (comprehensive care or individual components) a safe, effective and satisfactory/acceptable alternative to in-person medical abortion care?

P: Pregnant persons seeking medical abortion

I: Medical abortion care provided through telemedicine, including comprehensive medical abortion care, or any number of the following individual components:

- Eligibility assessment for medical abortion through telemedicine
- Counselling and/or instructions for medical abortion through telemedicine
- Instructions for and active facilitation of medical abortion through telemedicine
- Follow-up of medical abortion through telemedicine

C: In-person medical abortion care

O:

- Effectiveness (rates of ongoing pregnancy, success of abortion without need for surgical intervention following the procedure, and of surgical evacuation post abortion)
- Safety (serious adverse events and complications)
- Satisfaction/acceptability
- Rate of adherence to recommended dose regimen (self-reported)
- Reported cost of services.

PICO 14: Community-based outreach (see Best Practice Statement 49)

PICO question: For a pregnant person seeking induced abortion, are community-based outreach models for provision of abortion care safe, effective and satisfactory/acceptable alternatives to provision of abortion care in a health-care facility by a trained health worker?

P: Pregnant persons seeking induced abortion

I: Outreach involving health workers

C: Provision of care in a health-care facility by trained health workers

O:

- Safety (serious adverse events and complications)
- Effectiveness (success of abortion without need for surgical intervention following the procedure)
- Cost-effectiveness
- Increased health seeking behaviours
- Satisfaction/acceptability.

Setting:

- Weak infrastructure
- Legally restrictive.

PICO 15: Harm-reduction counselling (see Best Practice Statement 49)

PICO question: For a pregnant person seeking an induced abortion, is harm-reduction counselling on abortion care a safe, effective and satisfactory/acceptable alternative to routine in-clinic service delivery?

P: Pregnant persons seeking an induced abortion

I: Harm-reduction counselling

C: Routine in-clinic service delivery

O:

- Safety (serious adverse events and complications)
- Effectiveness (success of abortion without need for surgical intervention following the procedure)
- Satisfaction/acceptability.

Setting:

- Humanitarian settings
- Non-humanitarian settings.

PICO 16: Social marketing outreach/communicating safe abortion (see Best Practice Statement 49)

PICO question: For a pregnant person seeking an induced abortion, can social marketing outreach provide improved access to safe, effective and satisfactory/acceptable induced abortion services compared with provision of abortion care in a health-care facility by a trained health worker?

P: Pregnant persons seeking an induced abortion

I: Social marketing methods for induced abortion services

C: In-clinic abortion service provision

O:

- Safety (serious adverse events and complications)
- Effectiveness (success of abortion without need for surgical intervention following the procedure)
- Access (affordability, utilization, client volume, attendance and coverage per population)
- Quality of care (abortion methods of choice, quality of information given to pregnant person, provider competence, pregnant person/provider relationship)
- Adverse effects (undesirable impacts on existing public or private services, inappropriate use of services)
- Equitable access or utilization (distribution of access across sociodemographic characteristics)
- Cost/service (from a societal perspective or perspective of marketer/franchiser, franchisee or pregnant person/client)
- Satisfaction/acceptability.

PICO 17: Self-sourcing medications for induced abortion (see Best Practice Statement 49)

PICO question: For a pregnant person seeking induced abortion, is self-sourcing of medications through online sources a safe, effective and satisfactory/acceptable alternative to obtaining a prescription and/or medications from a trained health worker?

P: Pregnant persons seeking induced abortion

I: Pregnant persons self-sourcing medications for an abortion through an online source without a prescription

C: Pregnant persons obtain a prescription and/or medications from a health worker (specialist or generalist medical practitioner, traditional and complementary medicine professional, midwife, nurse, auxiliary nurse, auxiliary nurse midwife, pharmacist, pharmacy workers, community health worker)

O:

- Safety (serious adverse events and complications)
- Effectiveness (success of abortion without need for surgical intervention following the procedure)

- Quality of medications
- Satisfaction/acceptability.

Self-management approaches

Self-management approaches for post-abortion contraception

PICO 18: Post-abortion self-administration of injectable contraceptives (see Recommendation 50)

PICO question: For a person in the post-abortion period needing contraception, is self-administration of injectable contraceptives (initiation or continuation) a safe, effective and satisfactory/acceptable alternative to provision by a trained health worker?

P: Women in the post-abortion period needing contraception

I: Self-administration of injectable contraceptives (initiation or continuation)

C: Delivery of injectable contraceptives by trained health workers

O:

- Contraceptive uptake and continuation
- Safety (serious adverse events and complications related to provision of the method)
- Effectiveness (method failure)
- Satisfaction/acceptability.

Annex 11. Details about guideline dissemination and updating

Dissemination

The full guideline will be published digitally (both an interactive web-based version and a PDF document available online for download) and in print. The recommendations from this guideline will also feature in the annually updated compendium of recommendations approved by the WHO Guidelines Review Committee (GRC), which will be produced by the WHO Department of Sexual and Reproductive Health and Research (SRH) across all thematic areas. The digital versions of the guideline will be available via the WHO website.[1] The links to the digital versions will be disseminated through nongovernmental organization (NGO) partners, the websites of professional associations, and social media platforms. Supplementary materials including the corresponding GRADE Evidence-to-Decision (EtD) frameworks for each of the recommendations are also available online.[2] Print versions of the guideline will be distributed to WHO regional and country offices, NGO partners and professional associations.

Translation of the guideline into Spanish (in collaboration with the Pan American Health Organization [PAHO]), French and Portuguese is planned. Translations into other United Nations languages will be developed as needed. Third-party translations into additional languages will be encouraged, provided they comply with WHO guidance on such translations.

The guideline will be launched through dissemination meetings in each WHO region, and specific knowledge transfer and adaptation activities and implementation research will take place in select countries based on need and expressed interest to move ahead with implementation of the recommendations. Additional products will support the launch of the guideline to allow for regional colleagues to disseminate the key information widely. Such products include:

- a PowerPoint presentation that summarizes the key messages and new elements to the guideline;
- a PowerPoint presentation on the evidence behind selected recommendations;
- social media tiles.

WHO regional offices and a number of interested agencies and NGO partners are expected to be active partners in the regional, national and local dissemination and adaptation of this guideline and in developing derivative informational materials.

Updating

This guideline will be presented online in an interactive web-based format soon after publication of the standard format version, which will be available for download. The web-based format will allow the guideline to be a "living guideline", facilitating review of new research evidence to ensure that it can be brought to the GDG for review and then updated as appropriate in the guideline on an ongoing basis. This consolidated guideline currently combines and updates recommendations from three former WHO guidelines on abortion care,[3] and future updates will also cover new related topics, as needed.

The rapidly evolving nature of the interventions and approaches for quality abortion care, especially those for self-management of abortion, calls for a continuous review of the literature. The WHO Guideline Steering Group (see Annex 1) is in the process of developing a database system that will allow for continuous search and review of the evidence. This in turn will help with future updates of the recommendations and will inform any areas that may potentially require a new recommendation. There are many areas for which no evidence was found or which are only supported by low-certainty evidence (see Chapter 4, section 4.3), and in these cases new recommendations or a change in the published recommendation, respectively, may be warranted. Any concern about the validity of an existing recommendation can be communicated promptly to the Prevention of Unsafe Abortion (PUA) Unit at WHO's Department of Sexual and Reproductive Health and Research (email: srhpua@who.int), after which the PUA

1 Available at: https://www.who.int/publications/i/item/9789240039483
2 Available at: https://www.who.int/publications/i/item/9789240039483
3 Safe abortion: technical and policy guidance for health systems, second edition. Geneva: World Health Organization; 2012 (https://www.who.int/publications/i/item/9789241548434).
Health worker roles in providing safe abortion care and post-abortion contraception. Geneva: World Health Organization; 2015 (https://www.who.int/reproductivehealth/publications/unsafe_abortion/abortion-task-shifting/en/).
Medical management of abortion. Geneva: World Health Organization; 2018 (https://www.who.int/reproductivehealth/publications/medical-management-abortion/en/).

Unit will seek approval from the WHO GRC to undergo the process for a "rapid guidance", and plans will be made to update the recommendation as needed.

All technical products developed during the process of developing this guideline – including full reports of systematic reviews, corresponding search strategies and dates of searches – will be archived for future reference and use. Where there are concerns about the validity of a recommendation based on new evidence, the systematic review addressing the primary question will be updated. To update the review, the search strategy used for the initial review will be re-applied. Any new questions identified following the original scoping exercise for the guideline will undergo a similar process of evidence retrieval, synthesis and application of the GRADE approach in accordance with the standards in the *WHO handbook for guideline development*.[4] For further information on the "living guidelines" process, refer to recent publications by Vergara-Merino et al. (2020)[5] and Vogel et al. (2019).[6]

4 WHO handbook for guideline development, second edition. Geneva: World Health Organization; 2014 (https://apps.who.int/iris/handle/10665/145714).

5 Vergara-Merino L, Verdejo C, Carrasco C, Vargas-Peirano M. Living systematic review: new inputs and challenges. Medwave. 2020;20(11):e8092.

6 Vogel J, Dowswell T, Lewin S, Bonet M, Hampson L, Kellie F, et al. Developing and applying a "living guidelines" approach to WHO recommendations on maternal and perinatal health. BMJ Glob Health. 2019;4(4):e001683.

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EXHIBIT C



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January 16, 2026

Re: Docket No. FDA-2025-P-3288

Dear Drs. Francis, Artigues, Chupp, and Stanford:

This letter responds to the citizen petition received by the Food and Drug Administration (FDA or Agency) on August 20, 2025 (Petition). The Petition requests that FDA: (1) deny approval of an application for mifepristone[1] for miscarriage management "due to lack of sufficiently rigorous safety studies under conditions of real-world use"; [2] (2) "deny approval for any use of mifepristone for miscarriage management or for other new drug indications"; (3) quantify "the risk of hemorrhage, sepsis, retained tissue and need for surgical completion" before approving any new indication; (4) require "that additional safety studies be conducted, under conditions of anticipated use, prior to consideration of approval of mifepristone for use in miscarriage management," (5) prohibit dispensing of mifepristone for any use via "telehealth visit" or by "interactive computer service, mail, or common carrier," and (6) "acknowledge the political

[1] Korlym and a generic version of Korlym (Mifepristone Tablets, 300 mg) contain the active ingredient mifepristone and are approved for the control of hyperglycemia (high blood sugar levels) due to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance and have failed surgery or are not candidates for surgery. We interpret your Petition as not making any requests related to those products and, accordingly, references in this response to "mifepristone" do not apply to them.

[2] Your August 2025 Petition states that you are resubmitting your January 7, 2025, citizen petition in which you "request[ed] that [FDA] deny the currently supplemental application for . . . use of mifepristone in miscarriage management due to lack of sufficiently rigorous safety studies under conditions of real-world use." We therefore interpret your August 2025 Petition to make the same request (Petition at 1).

pretext that has steered [FDA's] mifepristone regulations."[3]

The Petition also requests that: "[f]or any use of mifepristone, FDA should (a) at a minimum retain the current REMS [(risk evaluation and mitigation strategy)], (b) better yet strengthen the REMS, as described below or by "restoring the REMS in place before 2016, and (c) ideally revoke FDA's approval of mifepristone for abortion."[4]

With respect to the REMS, the Petition states that such "strengthened REMS" would require, at minimum, the following:

1. Ultrasound confirmation of fetal or embryonic demise (if being used for treatment of miscarriage) according to the criteria published by the Society of Radiologists in Ultrasound Multispecialty Panel on Early First Trimester Miscarriage and Exclusion of a Viable Intrauterine Pregnancy, which includes:

    - Crown-rump length of 7 mm (millimeters) or greater and no heartbeat;
    - Mean sac diameter of 25 mm or greater and no embryo;
    - Absence of embryo with heartbeat 2 weeks or more after a scan that showed a gestational sac without a yolk sac; or
    - Absence of an embryo with a heartbeat 11 days or more after a scan that showed a gestational sac with a yolk sac.

2. That all patients have an in-person follow-up to confirm that no tissue remains after the use of mifepristone.

3. That all adverse events which occur after the use of mifepristone are reported to FDA by any prescriber or health care professional treating any subsequent adverse event via a user- friendly FDA-maintained online adverse event reporting portal.

4. That all [licensed] health care professionals receive information from FDA about the need for a high index of suspicion for *Clostridium sordellii (aka Paraclostridium sordellii)* sepsis when a woman presents after mifepristone use with malaise and/or nausea and vomiting, along with a high white blood count. This information, which is currently contained in the black box warning, must be distributed by letter to all licensed health care professionals.

5. That all women who are given mifepristone must receive a copy of the currently existing black box warnings. Further, prescribing information must include at least the boxed warning that is currently included in the prescribing information for mifepristone for pregnancy termination.

6. That all women who are given mifepristone be made aware that it is critically important for the treating healthcare professional to be aware of her use of mifepristone in order to appropriately treat any adverse event she experiences after mifepristone use.[5]

[3] Petition at 1-5.
[4] Petition at 5.
[5] Petition at 2–4.

The Petition also requests that dispensing of mifepristone via telehealth visit, "let alone by interactive computer service, mail, or common carrier," be prohibited.[6]

We have carefully considered the information submitted in the Petition. For the reasons set forth below, we deny without comment your specific requests in the Petition regarding the approvability of any potential pending application for a drug product containing mifepristone that would fall within the scope of your Petition. In addition, we deny your Petition insofar as the Agency continues to consider the complex scientific and legal issues you raise and is unable to resolve them within the 150-day time frame set forth in section 505(q) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(q)).

I. BACKGROUND

A. Summary of Drug Product History

On September 28, 2000, FDA approved Mifeprex (mifepristone) Tablets, 200 milligrams (mg) for the "medical termination of intrauterine pregnancy through 49 days' pregnancy" (new drug application (NDA) 020687).[7] The application was approved under title 21, part 314, subpart H of the Code of Federal Regulations (CFR); specifically, 21 CFR 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with 21 CFR 314.520, FDA restricted the distribution of Mifeprex as specified in the September 2000 approval letter.[8] Those restrictions included, among other things, a requirement that mifepristone be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals (commonly referred to as the in-person dispensing requirement).

Subsequently, Mifeprex was identified as one of the products that was deemed to have in effect an approved REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) because on the effective date of Title IX, subtitle A of FDAAA (March 28, 2008), Mifeprex had in effect elements to assure safe use.[9] On June 8, 2011, FDA approved a REMS for Mifeprex, consisting of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

On March 29, 2016, FDA approved an efficacy supplement (S-020) to NDA 020687 for Mifeprex. The supplement included, among other things, expanding the gestational age up to which Mifeprex has been shown to be safe and effective (through 70 days gestation).[10]

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[6] Petition at 4.
[7] Mifeprex labeling (NDA 020687) approved Sep. 28, 2000, "Indication and Usage," available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.pdf.
[8] See FDA approval letter for Mifeprex (NDA 020687), dated Sep. 28, 2000, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.pdf.
[9] 73 FR 16313 (Mar. 27, 2008).
[10] Mifeprex labeling (NDA 020687) approved Mar. 29, 2016, section 1, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.

On April 11, 2019, FDA approved a generic version of Mifeprex, Mifepristone Tablets, 200 mg (abbreviated new drug application (ANDA) 091178). At the same time that FDA approved the generic version of Mifeprex in 2019, FDA approved a modification to the REMS for Mifeprex to establish a single, shared system REMS for mifepristone products for the medical termination of intrauterine pregnancy through 70 days gestation (referred to as the Mifepristone REMS Program). On January 3, 2023, FDA approved a modification to the Mifepristone REMS Program to remove the in-person dispensing requirement and to add a pharmacy certification requirement. On September 30, 2025, FDA approved a second generic version of Mifeprex, Mifepristone Tablets, 200 mg (ANDA 216616).

B. Section 505(q) of the FD&C Act

Section 505(q) of the FD&C Act (21 U.S.C. 355(q)) was added by section 914 of FDAAA (Public Law 110-85, 121 Stat. 823) and was amended by the Food and Drug Administration Safety and Innovation Act (Public Law 112-144, 126 Stat. 993). Section 505(q), as originally added by FDAAA, applies to certain citizen petitions and petitions for stay of agency action that request that FDA take any form of action relating to a pending application submitted under section 505(b)(2) or (j) of the FD&C Act and governs the manner in which these petitions are treated. Among other things, section 505(q)(1)(F) of the FD&C Act governs the time frame for final agency action on a petition subject to section 505(q). Under this provision, FDA must take final agency action on such a petition no later than 150 days after the date on which the petition is submitted.

II. DISCUSSION

The contentions in your Petition, described below, focus on three areas: (1) safety studies of mifepristone for termination of pregnancy or miscarriage management,[11] (2) "proper safeguards"[12] for the use of drug products containing mifepristone, and (3) "evidence-based medical standards"[13] for FDA's regulation of drug products containing mifepristone. Your Petition makes requests regarding the approvability of any potential pending application for a drug product containing mifepristone. We do not interpret section 505(q) of the FD&C Act to require that the Agency render a final Agency decision within the 150-day statutory deadline on the approvability of a potential pending application when a final decision on the approvability of any such application has not yet been made. Your Petition also requests FDA change the approved conditions of use, including by "strengthen[ing] the REMS," for the currently approved applications for drug products containing mifepristone. Accordingly, as explained below, we deny your Petition without comment on whether we would take the specific actions you request.

A. Petition's Contentions

1. Safety Data Associated with the Use of Mifepristone for Termination of Pregnancy, Miscarriage Management, or Any Other New Indication

[11] Petition at 1-2.
[12] Petition at 2.
[13] Petition at 5.

In your Petition, you refer to "new information about increasing risks of real-world mifepristone use" that, you assert, "call[s] into question the safety data which FDA previously reported for mifepristone use for termination of pregnancy."[14] You contend that post marketing surveillance is needed "because the clinical trials which supported the initial approval of mifepristone were neither blinded, controlled nor randomized."[15] You assert that "Danco [the application holder for Mifeprex (NDA 020687)] did not fulfill the requirements for post marketing surveillance required by FDA at approval."[16] You contend that changes to adverse event reporting requirements under the Mifepristone REMS Program have rendered this requirement "inadequate for tracking mifepristone related complications and deaths," and accordingly, "[FDA's Adverse Event Reporting System (FAERS)] data cannot be relied upon."[17] You also assert that "current real-world data indicates that mifepristone use in induced abortion is associated with significantly more adverse events than FDA was aware of." [18]

Regarding clinical trials, you assert that "the clinical trials which supported the initial approval of mifepristone were neither blinded, controlled nor randomized."[19] You contend that "during clinical trials it is impossible for sponsors to ascertain every possible adverse event that patients may experience when taking a new drug or an existing drug for a new indication."[20] You assert that "[g]iven the paucity of information gathered in studies to date on the safety of mifepristone for miscarriage management, " before any approval for this indication, "it is necessary that further robust studies of the safety of mifepristone for miscarriage management be conducted focusing on the rates of hemorrhage, serious and fatal infections and deaths which are known to occur during the use of mifepristone for termination of pregnancies."[21] You assert that it is "critically important that the conditions under which the drug is administered during these safety studies mirror the conditions of use expected in the real world."[22]

Regarding adverse event reporting, you contend that the "current REMS for mifepristone when prescribed for induced abortion is completely inadequate to track or prevent serious complications."[23] You state that "FAERS data cannot be relied upon to demonstrate that [mifepristone] is safe for miscarriage management" because FDA does not obtain "comprehensive information about adverse events following mifepristone use for induced abortion."[24] You assert that the absence of a "requirement or mechanism for abortion provider tracking of complications and deaths, or any requirement that the treating physician report those deaths and complications to FDA, guarantees that these deaths and complications will be vastly underreported" in FAERS.[25] You state that the "system" for reporting adverse events for mifepristone "need[s] to be overhaul[ed]" because of the "reliance solely on interested parties to

[14] Petition at 1.
[15] Petition at 6-7.
[16] Petition at 6.
[17] Petition at 9 and 24.
[18] Petition at 24.
[19] Petition at 7.
[20] Petition at 7.
[21] Petition at 17–18.
[22] Petition at 18.
[23] Petition at 7–8.
[24] Petition at 24.
[25] Petition at 9–10.

report, the large percentage of uncodable events, the redaction of critical clinical information unrelated to personally identifiable information, and the inadequacy of the reports."[26]

You contend that the 2016 REMS modification that removed the REMS requirement for "mandatory reporting of serious adverse events by certified prescribers of mifepristone for induced abortion, except for death," which occurred at the same time as "removal of other patient protections from the mifepristone REMS," "decreased the already limited effectiveness of FAERS."[27] You assert that the Prescriber Agreement Form "only requires that a prescriber 'provide [or refer] for surgical intervention' if necessary, and…report any deaths following mifepristone use," and that this requirement is "currently grossly inadequate for tracking mifepristone-related complications and deaths."[28] You assert that because FAERS reports reveal that in over half of the cases, someone other than the abortion provider managed the patient's complications," this "means that complications and deaths will often be missed by the abortion provider."[29] You assert that States cannot "fill in missing information on adverse events following the use of mifepristone" because although "some states collect adverse event data following abortion and share that information with the Centers for Disease Control and Prevention (CDC)," there is "extremely limited" value in the CDC's Abortion Surveillance Findings and Reports. You further note that there are "four nonreporting states . . . that account for a quarter of all abortions."[30]

You assert that "[w]ithout knowing the actual number of deaths and complications resulting from the real-world use of mifepristone for induced abortion, it is impossible for FDA to assess the current safety of mifepristone for use to induce abortion."[31] You contend that any "new indication for mifepristone will rely heavily on the perception of safety of mifepristone in induced abortion" and that such a "perception . . . lacks scientific support in real world use."[32] You state that there are "[n]o high-quality studies [that] clearly delineate the risks of mifepristone use under current real-world conditions," and that therefore no new indication "for extending the use of mifepristone should be considered, nor should mifepristone be approved for a new indication for use in miscarriage management."[33] To support your contention, you assert that "no meaningful safety information can be gleaned" from a 2021 meta-analysis by Jay Ghosh, et al, (2021 meta-analysis) of "all randomized controlled trials assessing the effectiveness or safety of methods for miscarriage management" that "would sufficiently support" the "current" new indication for miscarriage management.[34] You state that 2021 meta-analysis calls into question the utility of the available data due to limitations in that data, including "low" or

[26] Petition at 28.
[27] Petition at 24.
[28] Petition at 9.
[29] Petition at 9.
[30] Petition at 29–30.
[31] Petition at 10.
[32] Petition at 10.
[33] Petition at 13.
[34] Petition at 13–17 (quoting Ghosh J, Papadopoulou A, Devall AJ, Jeffery HC, Beeson LE, Do V, Price MJ, Tobias A, Tunçalp Ö, Lavelanet A, Gülmezoglu AM, Coomarasamy A, Gallos ID. Methods for managing miscarriage: a network meta-analysis. Cochrane Database Syst Rev. 2021 Jun 1;6(6):CD012602. doi: 10.1002/14651858.CD012602.pub2..

"very low" certainty in the findings.[35]

You also assert that the "efficacy numbers . . . may be inaccurate." You refer to Chu et al., Schreiber et al, and Trinder et al to support your position that there "may be little to no benefit to adding mifepristone in cases of incomplete miscarriage," which you state can be "effectively managed using misoprostol alone."[36] You characterize the 2021 meta-analysis as finding that medical management of miscarriage, including with mifepristone, was more effective than expectant management or placebo, but less effective than surgical methods, and that expectant management or placebo had higher chance of serious complications. However, you refer to limitations in the data, including "inconsistency and heterogeneity" with respect to "type of miscarriage (missed and incomplete)."[37]

2. "Proper Safeguards" for Drug Products Containing Mifepristone

In your Petition, you contend that FDA should deny approval of drug products containing mifepristone for any new indication because of "the need to ensure that proper safeguards are on these drugs."[38] Specifically, you state that "[p]rior to even considering any [new indication] for additional uses of mifepristone, FDA must significantly strengthen the [REMS] with [ETASU] for the current uses of mifepristone and demonstrate that the proposed strengthened REMS is able to account for and mitigate the known safety risks of hemorrhage, sepsis, retained tissue and need for surgical completion which exist for the current use of mifepristone for pregnancy termination."[39]

You contend that "[f]or any use of mifepristone, FDA should (a) at a minimum retain the current REMS, (b) better yet strengthen the REMS, as described [in the Petition] or by restoring the REMS in place before 2016, and (c) ideally revoke FDA's approval of mifepristone for abortion."[40]

As noted above, you assert that "the current REMS for mifepristone when prescribed for induced abortion is completely inadequate to track or prevent serious complications."[41] You also assert that without your requested "safeguards in place for all uses of mifepristone for abortion and for miscarriage management, no use of mifepristone can possibly be safe and no true informed consent for the use of mifepristone can be possible."[42] In support of these assertions, you state that there are serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, which necessitate a REMS.[43] You state that "the risks of hemorrhage, retained tissue, and ongoing

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[35] Petition at 17.
[36] Petition at 14–15.
[37] *See id*. You quote the authors as suggesting that this inconsistency and heterogeneity is important because, according to a subgroup analysis, "surgical and medical methods may be more beneficial in women with missed miscarriage compared to women with incomplete miscarriage." *Id*.
[38] Petition at 2.
[39] Petition at 2.
[40] Petition at 5.
[41] Petition at 7–8.
[42] Petition at 4.
[43] Petition at 7.

pregnancy increase with increasing gestational age" when mifepristone is used for medical abortion and "appears to be true for mifepristone use in missed miscarriage as well."[44] You also state that the "alternative [to medical abortion], surgical evacuation, is associated with less complications."[45]

You raise concerns with the Prescriber Agreement Form required by the approved REMS. You assert that the Prescriber Agreement Form requires that prescribers can accurately assess duration of pregnancy and diagnose ectopic pregnancies, but that there is no requirement for the prescriber to actually do either.[46] You also assert that the requirement in the Prescriber Agreement Form for the prescriber to agree to provide or refer a patient for surgical intervention if needed and report any deaths following use of mifepristone "is currently grossly inadequate" due to the limitations in FAERS discussed above.[47]

In addition, you assert that FDA should not approve any drug product containing mifepristone for any indication without a "significantly strengthen[ed] REMS," with at least seven elements.[48] In support of this assertion, you say that "[w]ithout these safeguards in place for all uses of mifepristone for abortion and for miscarriage management, no use of mifepristone can possibly be safe and no "true informed consent for the use of mifepristone can be possible."[49]

First, you contend that a REMS for mifepristone use for any indication should require "[u]ltrasound confirmation of fetal or embryonic demise (if being used for the treatment of miscarriage) according to the criteria published by the Society of Radiologists in Ultrasound Multispecialty Panel on Early First Trimester Miscarriage and Exclusion of a Viable Intrauterine Pregnancy."[50] In support of this assertion, you assert that an ultrasound "is the standard of care for dating first trimester pregnancies" and the American College of Obstetricians and Gynecologists (ACOG) "recognizes that a pregnancy which does not have an early ultrasound is inadequately dated."[51] You also assert that the "standard of care for diagnosis of ectopic pregnancy is . . . an ultrasound" and, "[w]ithout an ultrasound, it is not possible to ensure than an early pregnancy is located within the uterine cavity."[52] You state that the "risks for mifepristone use in abortion are gestational age dependent and require an ultrasound for accurate gestational age determination and determination if a pregnancy is ectopic."[53] You also state that "[w]ithout [a] precise diagnosis of gestational age, it is not possible to give an accurate picture of the risks of the [abortion] procedure, since the risks of hemorrhage, retained tissue, and ongoing pregnancy increase with increasing gestational age."[54] You state that this "appears to be true for mifepristone use in missed miscarriage as well."[55]

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[44] Petition at 8.
[45] Petition at 12.
[46] Petition at 8, 9.
[47] Petition at 9.
[48] Petition 2-5.
[49] Petition at 4.
[50] Petition at 2–3.
[51] Petition at 8.
[52] Petition at 9.
[53] Petition at 4.
[54] Petition at 8.
[55] Petition at 8.

Second, you contend that a REMS for mifepristone use for any indication should require that "all patients have an in-person follow-up to confirm that no tissue remains after the use of mifepristone."[56] In support of this assertion, you state that the studies included in the 2021 meta-analysis "scheduled follow-up appointments for participants that usually included ultrasonography."[57,58] Citing Chu et al, you state that "[w]omen who have not completed their miscarriages may need further medical or surgical treatment," and you cite ACOG to support your contention that patients should have an in-person follow-up appointment, to include an ultrasound, within one to two weeks after the procedure.[59]

Third, you contend that a REMS for mifepristone use for any indication should require "all adverse events which occur after the use of mifepristone [to be] reported to FDA by any prescriber or health care professional treating any subsequent adverse event via a user-friendly FDA-maintained online adverse event reporting portal.[60] In support of this assertion, you state that the reports from the current sponsors of mifepristone for medical abortion "provide a very limited picture of the dangers posed by mifepristone."[61] You state that the "already limited effectiveness of FAERS" decreased in 2016 when the REMS requirement for certified prescribers to report serious adverse events to the sponsors was narrowed to only require reporting deaths to the sponsors.[62] You also state that the REMS requirement for certified prescribers to report certain adverse events to the drug sponsor and the drug sponsor to report to FDA leaves the drug sponsors to act as "the screening agents as to which complications are reported to FDA."[63] You state that the adverse event reporting requirement for certified prescribers under the REMS is insufficient because emergency care providers, who "are more likely than prescribers to treat the adverse events," are not required to report adverse events.[64] You state that there have been discrepancies in the number of adverse events, referencing a paper by Cirucci et al "comparing adverse events claimed to have been reported by Planned Parenthood, but never appearing in the FAER[S] database."[65]

Fourth, you assert that a REMS for mifepristone use for any indication must require that all licensed health care professionals receive information from FDA, in the form of a letter, containing information from the boxed warning about the need for a high index of suspicion for *Clostridium sordellii* (aka *Paraclostridium sordellii*) sepsis when a woman presents after mifepristone use with malaise and/or nausea and vomiting, along with a high white blood count."[66] In support of this assertion, you state that there have been deaths associated with

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[56] Petition at 3.
[57] Petition at 3, 21.
[58] Ghosh J, Papadopoulou A, Devall AJ, Jeffery HC, Beeson LE, Do V, Price MJ, Tobias A, Tunçalp Ö, Lavelanet A, Gülmezoglu AM, Coomarasamy A, Gallos ID. Methods for managing miscarriage: a network meta-analysis. Cochrane Database Syst Rev. 2021 Jun 1;6(6):CD012602. doi: 10.1002/14651858.CD012602.pub2.
[59] Petition at 21.
[60] Petition at 3.
[61] Petition at 22.
[62] Petition at 24.
[63] Petition at 22–23, citing Aultman K, Cirucci CA, Harrison DJ, Beran BD, Lockwood MD, Seiler S. Deaths and Severe Adverse Events after the use of Mifepristone as an Abortifacient from September 2000 to February 2019. Issues Law Med. 2021 Spring;36(1):3-26.
[64] Petition at 23–24.
[65] Petition at 23.
[66] Petition at 3.

Clostridium sordelli sepsis following use of mifepristone for the medical termination of intrauterine pregnancy.[67] You also state that the Centers for Disease Control and Prevention and FDA convened "an emergency meeting in Atlanta in 2006 during which mifepristone was clearly demonstrated to affect innate immunity."[68] You state that one presenter recommended "that the use of mifepristone be reduced or eliminated."[69]

Fifth, you assert that a REMS for mifepristone use for any indication should require "that all women who are given mifepristone . . . receive a copy of the currently existing black box warnings" and that prescribing information for any newly approved mifepristone product "must include at least the boxed warning that is currently included in the prescribing information for mifepristone for pregnancy termination."[70]

Sixth, you assert that a REMS for mifepristone use for any indication should require that "all women who are given mifepristone be made aware that it is critically important for the treating healthcare professional to be aware of her use of mifepristone in order to appropriately treat any adverse event she experiences after mifepristone use."[71] In support of this assertion, you state that if patients do not make treating healthcare professionals aware of mifepristone use, healthcare professionals are less likely to recognize adverse events following mifepristone use and this would "hinder[ ] patient care and FDA's post marketing surveillance of the drug."[72]

Seventh, you assert that mifepristone for any indication should "never be provided in a [telehealth] visit" or "dispensed via interactive computer service, mail, or common carrier."[73] In support of this assertion, you state that it is "not possible to provide the necessary safety screening nor to make a definitive diagnosis of miscarriage or the viability or duration of the pregnancy via telehealth visit."[74] You state that "Federal law prohibits dispensing abortion drugs by interactive computer service, mail, or common carrier."[75] You state that "[a]nytime an abortion drug is approved for any indication, a strong likelihood exists that, whether on-label or off-label, the drug will be used in practice for abortion," and thus, FDA should "ensure that any approval of mifepristone comes with a REMS that ensures that it not be dispensed by interactive computer service, mail, or common carrier."[76]

3. Evidence-Based Medical Standards for FDA's Regulation of Drug Products Containing Mifepristone

In your Petition, you contend that FDA should "acknowledge the political pretext that has steered [FDA's] mifepristone regulations since the beginning" and FDA should "commit to

[67] Petition at 10–12.
[68] Petition at 10.
[69] Petition at 10.
[70] Petition at 3–4.
[71] Petition at 4.
[72] Petition at 26.
[73] Petition at 4 (emphasis omitted). Your Petition states that mifepristone "should never be provided via health visit." We understand "health" in this statement to refer to "telehealth."
[74] Petition at 4 and 30.
[75] Petition at 31.
[76] Petition at 31.

evidence-based medical standards in the future."[77] You contend that "FDA never had evidence that mifepristone was safe and effective" because "FDA's action rested on pretext from the start."[78] You state that "FDA's actions approving and deregulating mifepristone have always been an unlawful pretext for expanding abortion access and undermining state pro-life laws."[79]

In support of these assertions, you provide quoted language from 2021 through 2024 from a variety of Federal government sources including the White House, U.S. Department of Health and Human Services, and U.S. Department of Justice, which include statements by the then-President and then-Vice President, press briefings, press releases, and fact sheets.[80] You also provide quoted language from a vacated court opinion and an FDA oral history interview from 2019.[81,82] You contend that "[e]ven FDA's label admits that these drugs are not safe."[83] You point to the approved drug product's labeling that contains a warning that serious and sometimes fatal infections and bleeding can occur, direction to exclude ectopic pregnancies, and notation of possible need for treatment at an emergency room or surgical intervention.[84]

You further assert that "FDA's removal of safeguards on mifepristone in 2016 lacked sufficient evidence to support the changes."[85] In support of this assertion, you state that "FDA did not rely on any study that evaluated the changes as a whole" and that FDA "relied on studies that included safety measures omitted under the labeled conditions of use."[86] You also assert that "FDA lacked appropriate evidence" for the removal of the in-person dispensing requirement from the REMS.[87] In support of this assertion, you state that "FDA based its decision . . . on (1) adverse event reports and (2) published literature that the agency conceded was not adequate."[88]

B. FDA's Response

As described above, section 505(q)(1)(F) of the FD&C Act requires FDA to take final agency action on the Petition within 150 days of submission. Therefore, we must take action on the Petition at this time. For the reasons explained below, we deny without comment the specific requests in the Petition regarding the approvability of any potential pending application for a drug product containing mifepristone or change to the approved conditions of use for any currently approved application for a drug product containing mifepristone that would fall within the scope of your Petition.

Any FDA decision to approve or not approve a specific application is based on the particular

[77] Petition at 1–5.
[78] Petition at 37.
[79] Petition at 31.
[80] Petition at 32–37.
[81] Petition at 39 quoting *All. for Hippocratic Med. v. U.S. Food & Drug Admin.*, 668 F. Supp. 3d 507, 544 (N.D. Tex.), rev'd and remanded sub nom. *Food & Drug Admin. v. All. for Hippocratic Med.*, 602 U.S. 367, 144 S. Ct. 1540, 219 L. Ed. 2d 121 (2024), and vacated and remanded, 117 F.4th 336 (5th Cir. 2024).
[82] Petition at 32.
[83] Petition at 38.
[84] Petition at 38.
[85] Petition at 39.
[86] Petition at 39.
[87] Petition at 40.
[88] Petition at 40.

facts that are applicable to that application at the time of the decision, including whether the data and information submitted in the application are sufficient to support approval. To the extent that there is any pending application for a drug product containing mifepristone that would fall within the scope of your Petition, FDA has not made a final determination to approve it.[89] Further, if there were such a pending application, addressing the issues raised in the Petition could necessitate taking final agency action regarding the approvability of certain aspects of that pending application before taking final agency action on the approvability of the application as a whole. In light of this, we believe it is appropriate to evaluate the statutory and regulatory provisions governing the content and review of NDAs and ANDAs in connection with the statutory provision of section 505(q) of the FD&C Act governing the time frame for action on the Petition.

The FD&C Act and FDA regulations establish procedural protections for applicants in the context of application review. Section 505 of the FD&C Act and FDA regulations 21 CFR part 314 describe certain procedures by which the Agency reviews an NDA or ANDA and notifies an applicant if it determines that an application is approved or may not be approved, or identifies the deficiencies in the application and the steps an applicant may take to respond to the deficiencies.[90] In addition, the statute and regulations describe a specific process through which an applicant whose application the Agency has found does not meet the requirements for approval may challenge the Agency's determination.[91] Under this process, the Agency will give the applicant notice of an opportunity for a hearing on whether the application is approvable in its present form, with a specific time frame and process should the applicant request such a hearing.[92] These procedures ensure that applicants have an adequate opportunity to challenge a finding by the Agency that a product does not meet the requirements for approval.

There is no evidence that in enacting section 505(q) of the FD&C Act, Congress intended to bypass the application review process or to lessen an applicant's procedural rights by requiring that the Agency make decisions that constitute final agency action regarding the approvability of certain aspects of pending applications on a piecemeal basis outside of the process established under the FD&C Act and FDA regulations.[93] Therefore, we do not interpret section 505(q) of

[89] Under 21 CFR 314.430, we are generally prohibited from disclosing the existence of an application unless the applicant has publicly disclosed or acknowledged the existence; further, even if an applicant has publicly disclosed or acknowledged the existence of an application, no information regarding that application is generally publicly available prior to its approval.

[90] See section 505(c) and (j) of the FD&C Act; and 21 CFR 314.105(a) and (d) (FDA will approve an NDA or ANDA and send the applicant an approval letter if none of the reasons in 21 CFR 314.125 or 314.127 for refusing to approve the NDA or ANDA applies). See also section 505(c), (d), and (j) of the FD&C Act; 21 CFR 314.125 and 314.127 (listing reasons that FDA may refuse to approve an NDA or ANDA); and 21 CFR 314.110 (setting forth the requirements for a complete response letter).

[91] See section 505(c)(1)(B) and (d) of the FD&C Act; and 21 CFR 314.200.

[92] Id.

[93] In other citizen petition responses, we have responded to requests related to general standards for approval (e.g., bioequivalence criteria for generic drug products) that may pertain to one or more pending drug product applications without commenting on the approvability of any particular aspect of a specific pending application. We believe that this approach of describing our general policies or standards for approval of a drug application (beyond that described in this response) would not be appropriate in this case because, as stated, FDA's review of a given application would inform our decisions regarding the sufficiency of the specific data and information needed for

the FD&C Act to require that the Agency render a final Agency decision within the 150-day statutory deadline on the approvability of a specific aspect of an application when a final decision on the approvability of any such application has not yet been made.

Accordingly, we deny without comment the specific requests in the Petition regarding the approvability of any potential pending application for a drug product containing mifepristone that would fall within the scope of your Petition. Your Petition also requests FDA modify currently approved applications for drug products containing mifepristone to ensure (1) "proper safeguards"[94] for these products and (2) "evidence-based medical standards"[95] underpin FDA's regulations of these products as with any other drug product regulated by FDA. Your requests raise complex scientific and policy issues that FDA cannot resolve within the 150-day time frame set forth in section 505(q) of the FD&C Act, and we deny your Petition without comment on whether we would take the specific actions you request. FDA will consider the issues raised by your Petition, as appropriate, when making determinations regarding currently marketed drug products containing mifepristone as part of FDA's ongoing regulation of these products. We will continue to evaluate data and information to ensure appropriate regulatory decisions are made using the same standards that are applied to all drug product applications under section 505 of the FD&C Act.

III. CONCLUSION

For the reasons discussed in this response, your Petition is denied.

Sincerely,

TRACY B. HOEG -S

Digitally signed by TRACY B. HOEG -S
Date: 2026.01.15 20:36:18 -05'00'

Tracy Beth Høeg, M.D., Ph.D.
Acting Director
Center for Drug Evaluation and Research
Food and Drug Administration

approval. We will continue to evaluate the appropriateness of responding to citizen petitions requesting actions related to any pending application (if one should exist) on a case-by-case basis.

[94] Petition at 2.

[95] Petition at 5, 32.

EXHIBIT D

U.S. FOOD & DRUG ADMINISTRATION

Evan Masingill
Chief Executive Officer
GenBioPro, Inc.
3651 Lindell Road, STE D1041
Las Vegas, NV 89103

December 17, 2025

Re: Docket No. FDA-2025-P-2162

Dear Mr. Masingill:

I am writing to inform you that the Food and Drug Administration (FDA or Agency) has not yet resolved the issues raised in the citizen petition submitted by GenBioPro, Inc. on July 3, 2025. The petition requests that the Agency: "(1) refrain from taking any action that would reduce patient access to the drug mifepristone and/or increase the burdens associated with prescribing or dispensing mifepristone, absent new robust scientific or clinical evidence that meets applicable statutory standards warranting such a change; and (2) confirm that any steps that may be taken to modify, suspend, or withdraw FDA approval for mifepristone, including in response to any court order, will follow all applicable rules and procedures for any withdrawal or suspension required under the Administrative Procedure Act ("APA"), the FDCA, and implementing regulations, and that Petitioner will be permitted to continue to market and sell mifepristone in the United States until all such procedures have been completed."

FDA has been unable to reach a decision on your petition because it raises complex issues requiring extensive review and analysis by Agency officials. This interim response is provided in accordance with FDA regulations on citizen petitions (21 CFR 10.30(e)(2)). We will respond to your petition as soon as we have reached a decision on your requests.

Sincerely,

Carol Bennett -S

Digitally signed by Carol Bennett -S
Date: 2025.12.17 12:15:15 -05'00'

Carol J. Bennett
Deputy Director
Office of Regulatory Policy
Center for Drug Evaluation and Research

U.S. Food & Drug Administration
10903 New Hampshire Avenue
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EXHIBIT E

JAMA | Special Communication | WOMEN'S HEALTH

The US Food and Drug Administration's Regulation of Mifepristone

Sophie Dilek, MPH; Joanne Rosen, JD, MA; Anna Levashkevich, MSPH; Joshua M. Sharfstein, MD; G. Caleb Alexander, MD, MS

IMPORTANCE Mifepristone, used with misoprostol, is the most common abortion regimen in the US. It is also a focal point of reproductive health policy and politics, with controversy over its legal status and regulation by the US Food and Drug Administration (FDA).

OBJECTIVE To characterize the FDA's decision-making with respect to the regulation of mifepristone, with a particular interest in the agency's rationale for establishing, maintaining, or modifying key components of its regulatory approach over time.

EVIDENCE REVIEW Qualitative analysis of 5239 pages of FDA documents obtained through a Freedom of Information Act request, including sponsors' Risk Evaluation and Mitigation Strategy (REMS) assessment reports, FDA review of these reports, internal memos, and regulatory correspondence (2011-2023), supplemented by a review of publicly available information. Review focused on FDA justifications for implementing, maintaining, or modifying postapproval safety measures and the supporting evidence cited.

FINDINGS Five key moments in the FDA's regulation of mifepristone that have led to the current state of oversight were identified: (1) conversion to the REMS framework in June 2011; (2) reevaluation of REMS necessity in October 2013; (3) a sponsor-requested label change in May 2015; (4) the response to the COVID-19 pandemic in 2020 and 2021; and (5) a comprehensive reassessment of the REMS in November 2021. Key themes across this period were consistent findings on safety, lack of ideological bias in staff scientists' recommendations, and the limited impact of political interference—to date—on the agency's oversight. Even as litigation, the COVID-19 public health emergency, and evolving practice standards changed the context of mifepristone regulation, the agency generally followed the policy approach favored by scientists at the agency.

CONCLUSIONS AND RELEVANCE FDA oversight of mifepristone, developed during key moments from 2011 to 2023, has been shaped by scientific evidence and a cautious regulatory approach led by scientists at the agency.

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Mifepristone is a progesterone receptor antagonist with antiglucocorticoid activity. In combination with misoprostol, it is the most widely used abortion regimen in the US.[1] Mifepristone is also approved by the US Food and Drug Administration (FDA) for the control of hyperglycemia in adults with endogenous Cushing syndrome who are not candidates for curative surgery. First approved by the FDA in 2000 for pregnancy termination through 49 days' gestation, mifepristone had already been subject to controversy for more than a decade and has remained under intense scrutiny by parties across the spectrum of the abortion debate. There is consensus among leading US and international professional associations and regulatory authorities that mifepristone is effective for pregnancy termination and that serious complications, such as heavy bleeding or sepsis, are very rare.[2,3]

The FDA has imposed special restrictions on mifepristone to support its safe use. Initially, these conditions were part of 21 CFR Part 314 Subpart H, a regulatory pathway that permitted the FDA to require specific safety-related measures for drugs with serious safety concerns or potential for significant risk.[4] The final plan accompanying the 2000 FDA approval of mifepristone included prescriber qualifications, dispensation limited to certain settings, signed patient agreement forms, provision of a patient medication guide, and mandatory reporting of adverse events.[5]

With the passage of the Food and Drug Administration Amendments Act (FDAAA) in 2007, oversight transitioned to a new statutory framework. Under the FDAAA, the agency was authorized to require a formal program known as a Risk Evaluation and Mitigation Strategy (REMS) for both newly approved drugs and previously approved drugs with known serious risks. REMS could include specific measures, known as Elements to Assure Safe Use (ETASU), for products whose safety varies markedly depending on the context of their use. Per the FDAAA, ETASUs must be commensurate with specific serious risks listed in the labeling of the drug and

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should not be unduly burdensome on patient access. Additionally, the FDA is required to periodically review and reassess whether regulatory elements continue to be necessary to assure safe use. Mifepristone was among the drugs the FDA deemed to require a REMS based on existing restrictions governing its use. The official REMS for mifepristone was formally approved in 2011.

Substantial debate has surrounded the mifepristone REMS program. Some organizations and politicians, including those opposed to abortion, have argued that availability of the drug should be restricted fully or substantially to avoid adverse events.[6] Others, including researchers and professional associations, have argued that the continuation of additional safety precautions is unnecessary.[7] This debate surfaced again on October 1, 2025, when the FDA approved a new generic version of mifepristone.[8]

These competing perspectives are also reflected in litigation. In cases such as *US Food and Drug Administration v Alliance for Hippocratic Medicine*, parties have argued that the FDA improperly applied the US Food, Drug, and Cosmetic Act in its initial approval of and subsequent decisions regarding mifepristone.[9] Conversely, in cases such as *Purcell v Kennedy* (formerly *Chelius v Becerra*), parties have argued that the continuation of the mifepristone REMS program is unnecessary.[10] These cases, together with the *Dobbs v Jackson Women's Health Organization* decision overturning *Roe v Wade*, have set the stage for renewed federal review of mifepristone, as well as state-level efforts to limit, ban, or protect access to mifepristone.

Despite extensive public discussion and litigation, to date, there has been no review of FDA documents to shed light on how regulatory decisions about mifepristone have been made.

Document Review and Analysis

Study Design and FOIA History

In May 2019, we submitted a Freedom of Information Act (FOIA) request to the FDA regarding the design, conduct, and evaluation of FDA postapproval safety programs for 6 products, including mifepristone.[11] Based on similar prior work examining postapproval opioid regulation,[12,13] we requested a variety of documents relevant to each program, including the sponsors' REMS assessment reports, FDA reviews of these reports, internal memos, and regulatory correspondence.

Over 4 productions between March and September 2023, the FDA provided 1977 pages of documents regarding mifepristone. We reviewed and indexed these documents and then used the peer-reviewed literature on mifepristone safety and effectiveness, publicly available policy briefs, FDA-published archives, and the initially provided documents to identify additional documents of interest. We requested these documents from the FDA, yielding an additional 3262 pages of materials. The FDA redacted some documents based on exceptions for "confidential commercial information" (5 USC §552 [b][4]) and/or "personal privacy" (5 USC §552 [b][6]).[14] We appealed some redactions, resulting in the deredaction of 1 document. Our final analysis included 264 documents representing 5239 pages covering the FDA's safety program for mifepristone from June 2011 to January 2023 (eTable in the Supplement).

Document Coding and Analysis

Two authors (A.L., S.D.) performed primary document review, with oversight from a third (G.C.A.), followed by primary analysis and discussion among all authors. Each source document was reviewed and indexed to track the document subject, document type, creation date, length, and the presence of redacted material. Our primary focus was the FDA's rationale for the initial establishment of the mifepristone safety program and the agency's subsequent decisions to maintain, modify, or remove specific regulatory elements over time. We sought to identify key moments in this regulatory history, as well as key themes of the FDA's actions. Our analytic approach centered on a close reading of internal FDA review documents and other materials relevant to the agency's oversight of the mifepristone REMS program. Within each REMS review document, we extracted content related to the agency's stated rationale for maintaining or modifying specific ETASUs and evidence cited in support of regulatory decisions.

History of the FDA's Mifepristone REMS Program

Our review of documents identified 5 key moments related to the regulation of mifepristone over time: (1) conversion to the REMS framework in June 2011; (2) reevaluation of REMS necessity in October 2013; (3) a sponsor-requested label change in May 2015; (4) response to the COVID-19 pandemic in 2020 and 2021; and (5) a comprehensive reassessment of the REMS in November 2021 (**Table**).

Key Moment 1: Conversion to REMS Framework (June 2011)

The sunsetting of Subpart H following the passage of the FDAAA presented the FDA with a key opportunity to consider whether to require a formal REMS for mifepristone and to make substantive changes to its postapproval regulation.

Documents suggest there was substantial communication between the FDA and sponsor Danco over the initial use of the REMS authority for mifepristone. However, the FDA extensively redacted documents describing the agency's internal deliberations regarding specific regulatory requirements under the REMS, and the details of this exchange are not available.

The final approved REMS closely mirrored the Subpart H requirements. Under the REMS, these restrictions were formalized as ETASUs: certification of prescribers with specialized training or experience; restricted distribution to clinics, medical offices, and hospitals under the supervision of a certified prescriber; and documentation of safe-use conditions (FDA Review of Risk Evaluation and Mitigation Strategy for Mifepristone, June 2011 [Reference ID FDACDER006118-FDACDER006144]).

The FDA adopted an implementation system to monitor adherence and required the manufacturer to submit assessment reports to the FDA 1 year following approval and every 3 years thereafter, as well as in response to specific regulatory events, such as safety-related label changes (FDA Review of Risk Evaluation and Mitigation Strategy for Mifepristone, June 2011 [Reference ID FDACDER006118-FDACDER006144]).

Key Moment 2: Reevaluation of the Need for the REMS (October 2013)

In October 2012, the director of the Center for Drug Evaluation and Research (CDER), Janet Woodcock, requested a reevaluation

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Table. Evolution of Mifepristone Regulatory Elements Over Time

Requirement	Pre-REMS, Sept 2000-June 2011	Key moment 1: Conversion to REMS Framework, June 2011	2: Reevaluation of REMS necessity, October 2013	3: Sponsor-requested label change, March 2016	4: COVID-19 pandemic, July 2020-April 2021	5: Comprehensive reassessment of REMS, November 2021
Certification of prescribers: Prescribers required to have specific training or experience	Prescribers required to meet specific qualifications as part of approval under 21 CFR Part 314 Subpart H	Requirement maintained under the REMS framework as ETASU	No change	No change	No change	No change
Certification of dispensing setting: Dispensing health care settings, such as pharmacies, must be specially certified	No requirement for pharmacy certification as part of approval under 21 CFR Part 314 Subpart H	No change	No change	No change	No change	Pharmacy certification was recommended for approval in November 2021 as ETASU B but change not formally implemented until January 2023 following approval of regulatory materials reflecting updated REMS elements
Restricted distribution: Dispensing restricted to certain health care settings	Distribution limited to clinics, medical offices, and hospitals under supervision of a certified prescriber as part of approval under 21 CFR Part 314 Subpart H	Requirement maintained under REMS framework as ETASU	No change	No change	In response to litigation, enforcement discretion exercised with respect to this requirement between July 2020 and January 2021 In April 2021, agency announced formal policy of enforcement discretion	In-person dispensation requirement recommended for removal in November 2021 but change not formally implemented until January 2023 following approval of regulatory materials reflecting updated REMS elements
Documentation of safe use conditions: Drug can only be dispensed to patients with documentation of safe-use conditions	Prescribers required to provide the patient agreement form and Medication guide, obtain patient signature on agreement form, and place in medical record as part of approval under 21 CFR Part 314 Subpart H	Requirement maintained under REMS framework as ETASU	No change	Patient agreement form recommended for removal by staff scientists, though maintained per commissioner's request Medication guide was removed from the REMS but maintained under labeling requirements	No change	No change

Abbreviations: CFR, Code of Federal Regulations; ETASU, Elements to Assure Safe Use; REMS, Risk Evaluation and Mitigation Strategies.

of mifepristone to determine whether the REMS continued to be necessary, prompting a review that was completed the following year (Key Document 1 in the Supplement). As part of this assessment, FDA staff scientists reviewed safety data and reported that the "overall safety profile of Mifeprex has not changed over the last 6-7 years and is consistent with current product labeling."

The scientists reviewed each ETASU in turn. After assessing the impact of removing or retaining each element, the scientists explicitly outlined the pros and cons of maintaining the REMS. In support of REMS elimination, they cited the stable safety profile and data indicating that safe-use practices were already embedded in most sites. In support of REMS maintenance, they argued that there was a relative lack of familiarity with medical abortion among clinicians given limited training opportunities. Scientists also noted controversies over the medication in considering changes to restricted distribution, writing "Concerns regarding protests or targeting may deter retail pharmacies from stocking Mifeprex." Ultimately, they concluded that the REMS should be maintained.

Key Moment 3: Sponsor-Requested Label Change (May 2015)

In May 2015, mifepristone's sponsor submitted an efficacy supplement proposing substantial changes to the drug's labeling, including extending the approved gestational age from 49 days to 70 days; reducing the dose of mifepristone; modifying the dosing regimen and the interval between mifepristone and misoprostol; changing the route of misoprostol administration; and broadening the qualifications for certified prescribers. Because these labeling changes affected the conditions for safe use, they triggered the need for a formal REMS modification. Consequently, the FDA reviewed the efficacy supplement and the REMS in parallel, issuing coordinated decisions on March 29, 2016 (Key Document 2 in the Supplement).[15]

In undertaking this review, the FDA conducted a comprehensive assessment of available evidence, including published studies reflecting clinical practice, 16 years of accumulated postmarketing safety data, and the most recent sponsor-submitted

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REMS assessment report. Collectively, these sources demonstrated that the revised dosing regimen, route of administration, and expanded clinician qualifications were appropriate.[15] Consistent with these findings, the FDA concluded that "Overall, the rate of deaths and SARs [Serious Adverse Reactions] is acceptably low and data for the proposed regimen do not suggest a safety profile that deviates from that of the originally approved regimen."[15] The agency also revised the assessment plan by eliminating certain adverse event metrics from the sponsor's required reports because this information was already being provided to the FDA through other pathways, including spontaneous adverse event reporting (Key Document 2 in the Supplement).

Two additional considerations arose during this regulatory review that do not appear to have been raised by the company. The first related to the medication guide, a handout given to all patients with information about mifepristone. Because of a broader shift in REMS regulation, the FDA removed the medication guide from the REMS program but still required its distribution to patients under patient labeling provisions.

The second consideration was the patient agreement form, which patients were required to sign under the existing REMS. In the review document, FDA scientists argued that this form was "duplicative of the informed consent and counseling processes that take place in the US, consistent with medical standard of care and current clinical practice guidelines for abortion providers," as well as the medication guide (Key Document 2 in the Supplement).

The FDA commissioner at the time, Dr Robert Califf, overrode this decision. In a memo, CDER director Janet Woodcock wrote, "After being briefed on the planned changes to the [New Drug Application] that the Center was considering, the Commissioner concluded that continuing the REMS requirement for a signed patient agreement form would not interfere with access and would provide additional assurance that the patient is aware of the nature of the procedure, its risks, and the need for appropriate follow-up care" (Key Document 3 in the Supplement).

Key Moment 4: The COVID-19 Pandemic (2020-2021)

The COVID-19 pandemic created a challenging moment for mifepristone regulation. The FDA faced the key question of whether to modify REMS provisions governing the medication, as the FDA had done with 2 other drugs that were under an in-person dispensation requirement.[16]

In May 2020, the American College of Obstetricians and Gynecologists (ACOG) sued the FDA to challenge the enforcement of the in-person dispensation and signature requirements for mifepristone during the pandemic. The FDA opposed this action, arguing that these requirements were necessary to mitigate serious risks associated with the medication.[16] The court found that ACOG's action was likely to succeed and issued a preliminary injunction in July 2020 enjoining the FDA from enforcing these requirements while the litigation continued.

Our review of documents found that the FDA's position in the ACOG litigation was contrary to the views of scientists in the FDA's review division. On June 10, 2020—the same day that the FDA filed its brief in the litigation—an office within CDER wrote a memo to the center director reviewing the various mifepristone REMS requirements (Key Document 4 in the Supplement). The staff scientists acknowledged that "the public, including patients seeking medical abortion, have been advised to practice social distancing and avoidance of public places, to minimize their risk of exposure to the novel coronavirus." They highlighted the intended purpose of the in-person dispensing requirement—to ensure that patients receive counseling at the time of dispensation and to facilitate completion of the patient agreement form—before stating that these benefits could be achieved through telemedicine. The scientists concluded that if other REMS requirements were met, then "the in-person dispensing of mifepristone for medical termination of early pregnancy may present additional COVID-related risks to patients and healthcare personnel…Accordingly, it would be appropriate to exercise enforcement discretion with respect to this element of the Mifepristone REMS Program during the COVID-19 [public health emergency]." This internal memo, however, did not change the FDA's position in the litigation.

In January 2021, the Supreme Court reinstated the in-person requirements. Soon after, the FDA initiated a new review of these requirements. In an April 2021 memo from FDA staff to the CDER director, scientists cited 4 published studies finding no evidence of an increase in serious safety concerns occurring with medical abortion as a result of modifying the in-person dispensation requirement between June 2020 and January 2021 (Key Document 5 in the Supplement). The CDER director endorsed this conclusion (Memorandum to Acting Commissioner Regarding In-Person Dispensing Requirement in Mifepristone REMS Program During the COVID-19 Public Health Emergency, April 2021 [Reference ID FDACDER006897-FDACDER006898]). Later that month, the FDA adopted a formal policy of enforcement discretion, meaning it would not enforce the in-person dispensation requirement.

Key Moment 5: Comprehensive Reassessment of the REMS (November 2021)

In November 2021, the FDA undertook a comprehensive reassessment of the REMS program, creating another opportunity for significant changes to mifepristone's postapproval regulation. The agency considered a range of options, from resuming enforcement of the in-person dispensation requirement to eliminating the REMS program altogether.

The comprehensive reassessment was conducted by an internal FDA team. Findings were shared at a meeting in November 2021 (Key Document 6 in the Supplement). The team relied primarily on a scoping literature review spanning 2016-2021 and safety data collected since the initiation of the COVID-19 public health emergency. Evidence was evaluated in relation to the necessity of each ETASU. FDA scientists once again affirmed the safety of the medication, writing that the agency "routinely monitors adverse events reported to FAERS [FDA Adverse Event Reporting System] and published in the medical literature with mifepristone for medical termination of pregnancy…to date, no new safety concerns have been identified."

On prescriber certification, agency scientists identified no new data demonstrating a continued need for certification; however, in the view of agency scientists, the literature also did not support removing the certification. On the patient agreement form, the team referenced 2 studies indicating a potential increase in the number of new prescribers, which they argued warranted a greater need for standardized patient education (Key Document 6 in the Supplement).

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On the in-person dispensation requirement, the FDA team cited results from 16 publications documenting the absence of significant concerns associated with various mifepristone delivery models. They also referenced as supporting evidence the absence of new safety concerns during the public health emergency when enforcement discretion was exercised and mifepristone was available without in-person dispensation (Key Document 6 in the Supplement).

To meet the agency's obligation to ensure REMS are not unduly burdensome, the reviewers concluded that the in-person dispensation requirement should be removed and replaced with a pharmacy certification system (Review of the One Year [1st] Single Shared System REMS Assessment Report for Mifepristone, December 2021 [Reference ID FDACDER006331-FDACDER006354]). Under this approach, pharmacies would be required to obtain certification, which typically involves agreeing to specified dispensing and recordkeeping requirements. Documents detailing the specific operationalization of the pharmacy certification system were not included in our analysis. The final recommendations from the internal FDA team also included retaining the patient agreement form. The agency announced these changes in December 2021 but did not formally implement them until January 2023, following the sponsors' submission and the FDA's approval of regulatory materials reflecting the updated REMS elements.

Key Themes

Internal FDA documents offer a rare opportunity to examine how the agency made decisions over time about mifepristone, a medicine that has been the subject of intense debate. At key moments, agency scientists reviewed extensive evidence about the agency's controls on mifepristone access and made decisions regarding whether to maintain stricter requirements for mifepristone than for most other medicines, whether to expand the condition of use, whether to adapt to the pandemic, and whether to lift certain provisions as clinical experience accumulated. Three key themes emerged from our analysis.

Consistent Findings on Safety

The FDA has monitored mifepristone's safety through multiple complementary mechanisms, including spontaneous adverse event reports, clinical studies, published literature, and information submitted by professional organizations and advocacy groups (Letter from Select Health Care Practitioners, March 2021 [Reference ID FDACDER006463-FDACDER006750]; Letter from the American College of Obstetricians and Gynecologists and Society for Maternal Fetal Medicine, April 2020 [Reference ID FDACDER006391-FDACDER006445]). From the drug's original approval in 2000 through 2016, the REMS assessment plan required the sponsor to provide summaries of spontaneous adverse event reports and updates on any postapproval studies. In 2016, the agency continued to obtain these data through annual reports, routine pharmacovigilance, and other mechanisms.

The documents we examined underscore the repeated regulatory finding by FDA scientists that mifepristone's safety is well-characterized, serious adverse events have rarely occurred, and best-practice guidelines address major risks.

Lack of Ideological Bias in Staff Scientists' Recommendations

Staff scientists at the FDA based their recommendations on comprehensive reviews of evidence, making decisions that were not consistently on one side or the other of the debate taking place outside the agency regarding mifepristone regulation.

For example, FDA scientists supported removing the in-person dispensation requirement, first in June 2020 during the pandemic, then again in April 2021, and again, following a comprehensive review, in November 2021. These decisions have drawn criticism from abortion opponents, who have pressed for a return to more restrictive regulation.

At the same time, FDA scientists continued to endorse multiple elements to support safe use, including provisions requiring prescriber certification and completion of the patient agreement form. In each case, the agency cited the need for additional data to justify any reconsideration of these provisions. These determinations have been criticized by ACOG and other professional groups, who have called for them to sunset.

The Question of Political Interference

In our document review, we identified 2 moments of potential intervention from FDA political appointees on decisions that ran contrary to the perspective of agency scientists on appropriate evidence-based regulation. In 2016, the FDA commissioner decided, over the apparent objections of the review division, to maintain a requirement for a patient agreement form. The commissioner justified this decision on the grounds that it would promote understanding without interfering with access. Several years later, FDA scientists would endorse continuing with this requirement to best ensure patient understanding of the risks of the product.

In June 2020, the scientific team's conclusion that in-person dispensation was not required during the COVID-19 pandemic was not adopted as the agency's position in response to a court challenge by ACOG against the continuation of this requirement during the pandemic. On the same day that a memo from the scientific team concluded that the in-person dispensation requirement was not needed, the agency filed a brief opposing the challenge. We did not identify documents to explain the timing of these decisions or their provenance.

What might have been a moment of interference with the scientific team's approach was forestalled by the court's action to block the in-person requirement from July 2020 to January 2021. With the exception of the period from January 2021, when the Supreme Court reinstated the in-person requirement, until April 2021, when the FDA chose not to enforce it, we found no documentary evidence of political intervention that substantially affected access to the medication.

Looking Ahead

Litigation on mifepristone access continues to generate uncertainty. Several active cases seek the removal of the REMS requirements altogether. Other cases have been directed at restricting or revoking FDA approval of the drug—most notably, *Alliance for Hippocratic Medicine v FDA*.[17] Although the Supreme Court unanimously dismissed the case in June 2024 on procedural grounds, its decision left the door open for future plaintiffs to revisit similar arguments. Three states are currently challenging the FDA's approval

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of mifepristone.[18] These cases are occurring alongside broader campaigns targeting abortion providers and access, state efforts to restrict mifepristone availability, mounting pressures on the health care system, and deepening disparities in reproductive care.[19]

On September 19, 2025, Department of Health and Human Services Secretary Robert F. Kennedy Jr and FDA Commissioner Martin Makary indicated that the FDA is undertaking a new evaluation of mifepristone's safety and effectiveness.[20] Kennedy has said that key decisions would be up to the president himself.[21] A reversal of FDA policy on mifepristone by political leaders or appointees would represent a significant break from the last quarter century of mifepristone oversight.

Limitations

Our analysis has several limitations. Documents that we received through our FOIA request included redactions that limited our ability to fully understand the factors the FDA considered and its internal deliberations with regard to those factors. In some instances, entire pages were redacted, preventing us from understanding regulatory decision-making and presenting gaps in our review. Additionally, there may be documents that were not provided to us or internal discussion related to mifepristone regulation that was not captured in the written documents. Our interpretation of the documents necessarily reflects judgments about the weight and meaning of regulatory actions over time. Consequently, our analysis may not fully capture the complexity of agency decision-making or the influence of external pressures, including political or legal considerations, that are not explicitly documented. Moreover, our study was not designed to be comparative, and we did not evaluate how the mifepristone REMS compares with REMS programs for other drugs.

Conclusions

Mifepristone's regulatory trajectory offers an instructive case study of how the FDA has conducted drug safety oversight in a politicized environment: cautiously and with the support of evidence and regulatory judgment. Our analysis of internal agency documents spanning more than a decade shows that while the FDA has consistently affirmed mifepristone's safety, changes to its REMS were often made conservatively, incrementally, and in response to external events such as the COVID-19 pandemic. While the FDA considered more radical changes at several key moments, it opted against them to better balance various considerations. As the FDA prepares to review the safety data again, as legal challenges are expected to continue, and as state policies diverge, mifepristone will likely remain a flashpoint in reproductive health policy. Maintaining integrity in this process will require a continued commitment to scientific evidence and an avoidance of political interference.[22]

ARTICLE INFORMATION

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Data Sharing Statement: Researchers interested in accessing specific documents may contact G. Caleb Alexander (galexan9@jhmi.edu). Please include the applicable reference numbers for the requested materials and the basis for the request.

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EXHIBIT F

UCLA School of Law Center on Reproductive Health, Law, and Policy

ANSIRH ADVANCING NEW STANDARDS IN REPRODUCTIVE HEALTH

August 27, 2025

Submitted Electronically
Division of Dockets Management
U.S. Food and Drug Administration
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Reproductive Health Researchers' Comment

The UCLA Law Center for Reproductive Health, Law, and Policy and UCSF Advancing New Standards in Reproductive Health submit this comment on behalf of the below signed 263 reproductive health researchers trained and experienced in conducting or evaluating clinical and social science studies on reproductive health issues, including studies on the safety and effectiveness of mifepristone.[1] Signatories share a commitment to evidence-based reproductive health care and FDA decision-making based on sound and transparent science. Signatories submit this comment in support of pending citizen petitions (FDA-2025-P-0377-0001; FDA-2025-P-1576-0001; FDA-2025-P-2162-0001) that, among other steps to ensure medication abortion remains accessible, ask the FDA to refrain from imposing additional or increased restrictions on mifepristone. Specifically, signatories submit this comment to contextualize the relevant research and to explain the flaws in recent reports on mifepristone that are not grounded in gold standard science or transparent and reliable data and analysis.

I. Decades of Voluminous Gold Standard Science Support the Safety and Effectiveness of Mifepristone, Including Through Telehealth

Decades of conclusive scientific evidence amassed through more than one hundred rigorous studies based on hundreds of thousands of patient outcomes have overwhelmingly established the safety and effectiveness of mifepristone for medication abortion and management of early pregnancy loss. The FDA has reviewed that large and sound body of science at many junctures over the past 25 years and, at each moment,

[1] The institutional affiliations of signatories are for identification purposes only and the views expressed in this letter do not necessarily reflect the views of signatories' affiliated institutions.

confirmed the safety and effectiveness of mifepristone generally[2] and, time and time again, the FDA has found complications and serious adverse events associated with mifepristone extremely rare.[3] Based on this body of evidence, the FDA has modified mifepristone labeling, and eased specific REMS restrictions when science proved they were unnecessary to protect patient safety and unduly restricted access.[4]

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[2] *See* American College of Obstetricians and Gynecologists, Society of Family Planning, and Society for Maternal Fetal-Medicine. (2025, Jan. 31). *Citizen Petition, Document FDA-2025-P-0377*, at pp. 3-11. FDA. https://www.regulations.gov/document/FDA-2025-P-0377-0001 (hereinafter "ACOG Petition"); Commonwealth of Massachusetts, California, New Jersey, and New York. (2025, June 5). *Citizen Petition, Document FDA-2025-P-1576*, at pp. 2-3, 10-11, 12-15. FDA. https://www.regulations.gov/document/FDA-2025-P-1576-0001; GenBioPro. (2025, Jul. 3). *Citizen Petition, Document FDA-2025-P-2162-0001*, at pp. 4-14. FDA. https://www.regulations.gov/document/FDA-2025-P-2162-0001 (hereinafter "GenBioPro Petition"); *see also* Kulier, R., Kapp, N., Gülmezoglu, A. M., Hofmeyr, G. J., Cheng, L., & Campana, A. (2011). Medical methods for first trimester abortion. *The Cochrane Database of Systematic Reviews*, *2011*(11), CD002855. https://doi.org/10.1002/14651858.CD002855.pub4 (systematic review); *The Safety and Quality of Abortion Care in the United States* (with Committee on Reproductive Health Services: Assessing the Safety and Quality of Abortion Care in the U.S., Board on Population Health and Public Health Practice, Board on Health Care Services, Health and Medicine Division, & National Academies of Sciences, Engineering, and Medicine). (2018). National Academies Press. https://doi.org/10.17226/24950 (systematic review); Chen, M. J., & Creinin, M. D. (2015). Mifepristone With Buccal Misoprostol for Medical Abortion: A Systematic Review. *Obstetrics and Gynecology*, *126*(1), 12–21. https://doi.org/10.1097/AOG.0000000000000897 (systematic review); Raymond, E. G., Shannon, C., Weaver, M. A., & Winikoff, B. (2013). First-trimester medical abortion with mifepristone 200 mg and misoprostol: A systematic review. *Contraception*, *87*(1), 26–37. https://doi.org/10.1016/j.contraception.2012.06.011 (systematic review).

[3] U.S. Food and Drug Administration/Center for Drug Evaluation and Research ("FDA/CDER"). (2016, Mar. 29) *Application No. 020687Orig1s020 Medical Review(s)*, at p. 12. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf (hereinafter "FDA/CDER 2016") (concluding medication abortion's "efficacy and safety have become well-established by both research and experience, and serious complications have proven to be extremely rare"); *id.* at p. 47 (serious adverse events "exceedingly rare"): U.S. Food and Drug Administration ("FDA"). (2024). *Mifepristone U.S. Post-Marketing Adverse Events Summary Through 12/31/2024*, at p. 1. https://www.fda.gov/media/185245/download (discussing rarity of serious adverse events, that there is no established causal relationship between those events and medication abortion and that, rather, the "critical risk factor" is pregnancy itself); *see also* Kulier et al., 2011, *supra* note 2 (systematic review finding "serious adverse events are rare"); GenBioPro Petition, *supra* note 2, at pp. 12-14 (summarizing evidence on serious adverse events).

[4] *See, e.g.* FDA/CDER 2016, *supra* note 3, at p. 47; *Letter from Janet Woodcock, Acting Commissioner of Food & Drugs, to Maureen Phipps, Chief Executive Official, American College of Obstetricians & Gynecologists, and William Grobman, President, Society for Maternal Fetal Medicine*, (Apr. 12, 2021). https://www.aclu.org/sites/default/files/field_document/fda_acting_commissioner_letter_to_acog

The evidence supporting the safety and effectiveness of telehealth provision of medication abortion is part of this body of sound, gold standard science.[5] The FDA has reviewed the safety of telehealth provision of mifepristone multiple times, each time reaffirming the safety and effectiveness. In April 2021, the FDA reviewed clinical outcome data for over 50,000 instances of medication abortion provision in rigorous studies that evaluated the safety and effectiveness of care delivered in-person, via telehealth, with pharmacist dispensing of mifepristone, and through hybrid options both before and during the COVID-19 public health emergency. In that review, the FDA concluded that studies of telehealth provision and real world postmarketing adverse event data did not show increases in safety concerns.[6] Again in December 2021, the FDA further reviewed some of the studies it

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examined in its April 2021 determination plus additional studies that looked at hundreds of additional patient experiences and postmarketing adverse event data, all of which found comparable effectiveness rates to models of care with in-clinic dispensing of mifepristone and very low rates of serious adverse events.[7] Between December 2021 and January 2023 when the FDA ultimately announced its decision to formally remove the in-person dispensing requirement, additional rigorous studies involving thousands more patient abortion outcomes confirmed the safety and effectiveness of telehealth provision of mifepristone and very low rates of serious adverse events.[8] Unsurprisingly, a June 2025

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provision, finding effectiveness (98%) and very low rates of serious adverse events, with only two patients (0.3% being admitted to the hospital)).

[7] *See supra* note 4 (citing multiple FDA reviews from 2016 to 2023); *see also* Chong et al., 2021, *supra* note 6; Kerestes et al., 2021, *supra* note 6; Raymond, E., Chong, E., Winikoff, B., Platais, I., Mary, M., Lotarevich, T., Castillo, P. W., Kaneshiro, B., Tschann, M., Fontanilla, T., Baldwin, M., Schnyer, A., Coplon, L., Mathieu, N., Bednarek, P., Keady, M., & Priegue, E. (2019). TelAbortion: Evaluation of a direct to patient telemedicine abortion service in the United States. *Contraception*, *100*(3), 173–177. https://doi.org/10.1016/j.contraception.2019.05.013 (among 190 patients, finding 93% effectiveness and only two serious adverse events (1%)); Grossman, D., Raifman, S., Morris, N., Arena, A., Bachrach, L., Beaman, J., Biggs, M. A., Hannum, C., Ho, S., Schwarz, E. B., & Gold, M. (2022). Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. *Contraception*, *107*, 36–41. https://doi.org/10.1016/j.contraception.2021.09.008 (among 224 patients whose eligibility was assessed in an in-person visit but received medication through a mail-order pharmacy rather than in-clinic, finding 96.9% effectiveness and only two serious adverse events (0.9%)); Upadhyay, U. D., Koenig, L. R., & Meckstroth, K. R. (2021). Safety and efficacy of telehealth medication abortions in the US during the COVID-19 pandemic. *JAMA Network Open*, *4*(8), e2122320. https://doi.org/10.1001/jamanetworkopen.2021.22320 (among 110 patients receiving medication abortion delivered by a mail-order pharmacy after online evaluation, finding 95% effectiveness and no serious adverse events were reported); Grossman, D., Baba, C. F., Kaller, S., Biggs, M. A., Raifman, S., Gurazada, T., Rafie, S., Averbach, S., Meckstroth, K. R., Micks, E. A., Berry, E., Raine-Bennett, T. R., & Creinin, M. D. (2021).). Medication Abortion With Pharmacist Dispensing of Mifepristone. *Obstetrics and Gynecology*, *137*(4), 613–622. https://doi.org/10.1097/AOG.0000000000004312 (among 260 patients provided mifepristone through retail pharmacies after in-clinic evaluation, finding 93.5% effectiveness and no serious adverse events).

[8] *See* Upadhyay, U. D., Raymond, E. G., Koenig, L. R., Coplon, L., Gold, M., Kaneshiro, B., Boraas, C. M., & Winikoff, B. (2022). Outcomes and Safety of History-Based Screening for Medication Abortion. *JAMA Internal Medicine*, *182*(5), 482–491. https://doi.org/10.1001/jamainternmed.2022.0217 (among 3,779 patients receiving medication abortion with history-based screening for eligibility in different settings, finding similar effectiveness and rare serious adverse events when medications dispensed via mail and in-person); Peña, M., Figueroa Flores, K., Muñoz Ponce, M., Facio Serafín, D., Camarillo Zavala, A. M., Ruiz Cruz, C., Ortiz Salgado, I. G., Ochoa Rosado, Y., Socarras, T., Pacheco López, A., & Bousiéguez, M. (2022). Telemedicine for medical abortion service provision in Mexico: A safety, feasibility, and acceptability study. *Contraception*, *114*, 67–73.

rigorous systematic Cochrane Review concluded that "the use of telemedicine for medical abortion in early pregnancy is generally safe, effective, and acceptable," that the review's findings were "consistent with the conclusions of previous work on the topic, including

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https://doi.org/10.1016/j.contraception.2022.06.009 (among 330 patients finding 93% effectiveness with only one serious adverse event (0.3%)); Schummers, L., Darling, E. K., Dunn, S., McGrail, K., Gayowsky, A., Law, M. R., Laba, T.-L., Kaczorowski, J., & Norman, W. V. (2022). Abortion Safety and Use with Normally Prescribed Mifepristone in Canada. *The New England Journal of Medicine*, *386*(1), 57–67. https://doi.org/10.1056/NEJMsa2109779 (study of nearly 280,000 abortions before and after Canada eliminated its REMS-like restrictions on mifepristone and made it available with normal prescriptions, finding no material changes in incidence of serious adverse events). Since then, even *more* studies have confirmed the safety of telehealth provision of mifepristone and that serious adverse events are rare. *See, e.g.,* Koenig, L. R., Becker, A., Ko, J., & Upadhyay, U. D. (2023). The Role of Telehealth in Promoting Equitable Abortion Access in the United States: Spatial Analysis. *JMIR Public Health and Surveillance*, *9*(1), e45671. https://doi.org/10.2196/45671 (finding virtual care particularly beneficial for younger patients, those living in rural areas, those experiencing food insecurity, and those living far from the nearest abortion facility); Koenig, L. R., Raymond, E. G., Gold, M., Boraas, C. M., Kaneshiro, B., Winikoff, B., Coplon, L., & Upadhyay, U. D. (2023). Mailing abortion pills does not delay care: A cohort study comparing mailed to in-person dispensing of abortion medications in the United States. *Contraception*, *121*, 109962. https://doi.org/10.1016/j.contraception.2023.109962 (dispensing mifepristone via mail does not delay care); Pearlman Shapiro, M., Dethier, D., Kahili-Heede, M., & Kaneshiro, B. (2023). No-Test Medication Abortion: A Systematic Review. *Obstetrics and Gynecology*, *141*(1), 23–34. https://doi.org/10.1097/AOG.0000000000005016 (medication abortion performed without prior pelvic examination or ultrasonogram is a safe and effective); Upadhyay, U. D., Koenig, L. R., Meckstroth, K., Ko, J., Valladares, E. S., & Biggs, M. A. (2024). Effectiveness and safety of telehealth medication abortion in the USA. *Nature Medicine*, *30*(4), 1191–1198. https://doi.org/10.1038/s41591-024-02834-w (study of over 6,000 patients receiving medication abortion via asynchronous telemedicine, finding 97.7% effectiveness and only 0.25% with serious adverse events, with no significant differences between synchronous and asynchronous models of care); Srinivasulu, S., Nyandak, D., Fiastro, A. E., MacNaughton, H., Tressan, A., & Godfrey, E. M. (2024). Telehealth Medication Abortion in Primary Care: A Comparison to Usual in-Clinic Care. *Journal of the American Board of Family Medicine: JABFM*, *37*(2), 295–302. https://doi.org/10.3122/jabfm.2023.230178R1 (among 184 patients comparing in-clinic care to telehealth care with medication mailing, finding telehealth was "as effective, timelier, and potentially more accessible than in-clinic" care); Grossman, D., Raifman, S., Morris, N., Arena, A., Bachrach, L., Beaman, J., Biggs, M. A., Collins, A., Hannum, C., Ho, S., Seibold-Simpson, S. M., Sobota, M., Tocce, K., Schwarz, E. B., & Gold, M. (2024). Mail-Order Pharmacy Dispensing of Mifepristone for Medication Abortion After In-Person Screening. *JAMA Internal Medicine*, *184*(8), 873–881. https://doi.org/10.1001/jamainternmed.2024.1476 (among 510 medication abortions where eligibility was assessed in an in-person visit but patients received medication through a mail-order pharmacy rather than in-clinic, finding 97.8% effectiveness and only three serious adverse events (0.6%)).

more recent non-comparative studies," and that "serious adverse events are rare."[9] Telehealth for medication abortion is an accepted, standard method of abortion provision in the United States and around the world.[10]

The White House has recently directed that agencies must produce and act upon sound, gold standard science. A recent Executive Order defines gold standard science as science with data and methods that are, among other criteria, "reproducible," "transparent," "communicative of error and uncertainty," "skeptical of its findings and assumptions," and "subject to unbiased peer review," so that federal decisions can be "informed by the most credible, reliable, and impartial scientific evidence available.[11] An Office of Science and Technology Policy Memorandum further directs agencies to use gold standard science as defined by nine tenets that include reproducibility, transparency, and unbiased peer review.[12] Moreover, when federal agencies use scientific information to inform agency decision-making, federal employees are directed to apply a "'weight of scientific evidence' approach."[13] FDA Commissioner Makary recently declared his pride in the FDA taking action grounded in "transparency [and] gold-standard science."[14]

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[9] Cleeve, A., Lavelanet, A., Gemzell-Danielsson, K., & Endler, M. (2025). The use of telemedicine services for medical abortion. *The Cochrane Database of Systematic Reviews*, *2025*(6), CD013764. https://doi.org/10.1002/14651858.CD013764.pub2.

[10] American College of Obstetricians and Gynecologists. (2020). Medication abortion up to 70 days of gestation. ACOG Practice Bulletin No. 225. *Obstet Gynecol* 2020;136:e31–47. https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2020/10/medication-abortion-up-to-70-days-of-gestation ("Medication abortion can be provided safely and effectively by telemedicine with a high level of patient satisfaction"); World Health Organization. (2022). *Abortion Care Guideline*, at p. 95. https://www.who.int/publications/i/item/9789240039483 (recommending the option of telemedicine to deliver medical abortion services); National Abortion Federation. (2024). *Clinical Policy Guidelines for Abortion Care*, at p. 1 ("[t]elemedicine can be safely used to provide abortion care, including medication abortion provision, informed consent, and follow-up").

[11] White House. (2025, May 23). *Executive Order: Restoring Gold Standard Science*., at Sections 1; 3(i)(ii) & (vii). https://www.whitehouse.gov/presidential-actions/2025/05/restoring-gold-standard-science/.

[12] White House, Office of Science and Technology Policy. (2025, June 23). *Agency Guidance for Implementing Gold Standard Science in the Conduct & Management of Scientific Activities*., at pp. 2-5. https://www.whitehouse.gov/wp-content/uploads/2025/03/OSTP-Guidance-for-GSS-June-2025.pdf.

[13] White House, 2025, *supra* note 11, at Sections 2(e) &4(f).

[14] *See* FDA. (2025, July 10). *A Statement from FDA Commissioner Marty Makary, M.D., M.P.H: 100 Days of Embracing Gold-Standard Science, Transparency and Common Sense*.

We strongly believe that the lynchpin of sound science is whether the data and methods are transparent, the work is reproducible by other scientists, and the work has been subject to the rigors of unbiased peer review. We are extremely concerned that the FDA may be considering significant action to reverse previous mifepristone REMS and label updates based on unverified and unreliable reports and studies that do not satisfy gold science standards. For the reasons discussed below, significant federal action based on these recent reports, or others that similarly lack scientific rigor and reliability, would be inappropriate and unsound federal agency decision-making.

II. New Research That is Not Reproducible, is Methodologically Flawed, or Both, Does Not Outweigh the Overwhelming Body of Rigorous Evidence on Mifepristone's Safety and Effectiveness

A. The Self-Published Analysis of Unknown Data by the Ethics and Public Policy Center is Not Verifiable or Reproducible and Suffers Multiple Methodological Flaws

In support of its recommendation that the FDA reinstate a regulatory protocol from when mifepristone was first approved over 20 years ago, the Ethics and Public Policy Center (EPPC)[15] has self-published two position papers on medication abortion – one on occurrences of serious adverse events[16] and one on the occurrence of failure.[17] In these papers, EPPC presents its findings and conclusions as the product of the "largest-known study of the abortion pill" derived from its "analysis of data from an all-payer insurance

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https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-marty-makary-md-mph-100-days-embracing-gold-standard-science-transparency.

[15] According to EPPC, its mission is "to apply the riches of the Jewish and Christian traditions to contemporary questions of law, culture, and politics" in America. *See* Ethics & Public Policy Center (n.d.). *Our Mission*. Retrieved August 25, 2025, from https://eppc.org/about/. EPPC's "The Life and Family Initiative," which produced the recent reports on mifepristone, is "committed both to ensuring the equal protection of unborn children in law and to providing concrete support to families by advancing a pro-life, pro-family agenda that takes our duties in justice to the unborn and to families seriously." *See* Ethics & Public Policy Center (n.d.). *Life and Family Initiative*. Retrieved August 25, 2025, from https://eppc.org/program/life-and-family-initiative/.

[16] Hall, J. B., & Anderson, R. T. (2025). The Abortion Pill Harms Women: Insurance Data Reveals One in Ten Patients Experiences a Serious Adverse Event. *Ethics & Public Policy Center*. https://eppc.org/publication/insurance-data-reveals-one-in-ten-patients-experiences-a-serious-adverse-event/ (hereinafter "EPPC Report on Serious Adverse Event").

[17] Hall, J. B., & Anderson, R. T. (2025). The Abortion Pill Harms Women: Insurance Data Reveals Repeated Abortion Attempts Due to High Failure Rate. *Ethics & Public Policy Center*. https://eppc.org/publication/the-abortion-pill-harms-womeninsurance-data-reveals-repeated-abortionattempts-due-to-high-failure-rate/ (hereinafter "EPPC Report on Failure Rate").

claims database."[18] However, as discussed below, these reports lack basic information and disclosures that reputable studies provide for transparency and reproducibility. Moreover, several claimed findings and conclusions appear to be based on errors and/or flawed assumptions drawn from the undisclosed data source and guided by an unnamed research team. Given these serious deficiencies, EPPCs position papers do not credibly call into question, let alone outweigh, the consistent findings from an overwhelming body of rigorous scientific studies and methodologically transparent data demonstrating that mifepristone, including when provided through telehealth, is safe and effective.

Below we summarize some of the most serious concerns and questions about the underlying data and analysis from which these position papers draw their conclusions and upon which they base sweeping recommendations to more heavily regulate mifepristone.

1. The Data and Analyses Used by EPPC are Not Disclosed and Cannot be Verified or Reproduced

In its first self-published report of insurance data for medication abortion prescriptions, EPPC claims that its analysis shows 10.93% of patients experienced "a serious adverse event" after a mifepristone abortion.[19] This purported finding is the foundation of their claim that the "real-world rate of serious adverse events following mifepristone abortions is at least 22 times as high as reported on the drug label."[20] But the report does not provide reliable evidence to support this claim, nor does any published literature.

In describing their data and methodology, the authors assert the data came from an "all-payer insurance claims database," from which they analyzed data of 865,727 "prescribed mifepristone abortions from 2017-2023," and that their analysis was "conducted and validated" by a research team of "data scientists, analysts, and engineers, with assistance from our clinical team of board-certified obstetricians and gynecologists."[21] However, the EPPC report authors do not identify the name of the database or the researchers and their affiliations, nor do they share the coding they used to generate the study cohort and analyze the data. Likewise, two follow-on explainers[22] and the second report on emergency

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[18] EPPC Report on Serious Adverse Event, *supra* note 16, at p. 1.

[19] EPPC Report on Serious Adverse Event, *supra* note 16, at p. 1.

[20] *Id.*

[21] *Id.* at pp. 1, 6.

[22] Hall, J. B., & Anderson, R. T. (2025). Fact Sheet: Excluded Adverse Events in Real-World Study of Mifepristone. *Ethics & Public Policy Center*. https://eppc.org/publication/fact-sheet-excluded-adverse-events-in-real-world-study-of-mifepristone/ (hereinafter "EPPC Fact Sheet"); Hall, J. B., & Anderson, R. T. (2025). Frequently Asked Questions About the Largest Study on Chemical Abortion.

visits following failed medication abortion[23] do not share any of this information and thus offer no greater transparency or ability to verify and reproduce the data and analysis.

One of the most problematic aspects of representing their analysis as a scientifically validated large-scale study is that they do not provide the source of the all-payer insurance claims database, precluding the ability of other researchers and scientists to independently verify their analysis and results. Despite a statement in the Frequently Asked Questions ("FAQ") release that: "We have made our study fully replicable for anyone who wants to analyze the insurance claims data" and the "dataset is available for purchase and our methodology is public,"[24] the information simply is not provided in any of these reports and explainers. Additionally, EPPC has stated publicly that it will not reveal the dataset used to identify patient outcomes.[25]

And while EPPC suggests this singular database is readily identifiable, to the best of our knowledge that is not the case. Signatories to this letter, which includes numerous researchers who regularly analyze insurance and medical claims data in their work, do not know of a single "commercially available all-payer health insurance claims database" that includes both private and public health insurance "data for all U.S. patients"[26] as described by EPPC.

Assuming the EPPC research team did acquire data from a commercial compilation of Medicaid and several private insurance claim datasets or databases, it is crucial to know which ones were relied upon and included in the study. There are known methodological

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Ethics & Public Policy Center. https://eppc.org/publication/frequently-asked-questions-about-the-largest-study-on-chemical-abortion/ (hereinafter "EPPC FAQ").

[23] EPPC Report on Failure Rate, *supra* note 17.

[24] EPPC FAQ, *supra* note 22, at pp. 3-4.

[25] EPPC repeatedly told journalists it could not reveal the dataset or even its source. *See, e.g.,* Glenn Kessler, *Digging Into the Math of a Study Attacking the Safety of the Abortion Pill*, WASH. POST (May 12, 2025), https://www.washingtonpost.com/politics/2025/05/12/abortion-pill-medication-abortion-study-mifepristone ("[EPPC's spokesperson] cited a confidentiality agreement with the vendor. . . . 'we do not view the confidentiality of our specific dataset as a barrier for others interested in obtaining similar data and replicating or extending this research.'"); Keren Landman, *A Convenient Piece of Junk Science,* ATLANTIC, (May 24, 2025), https://www.theatlantic.com/health/archive/2025/05/mifepristone-abortion-rfk-fda/682939/ ("In an email, Hunter Estes, EPPC's communications director, told [the Atlantic] that the center's contract with their data vendor prevents EPPC from sharing the name of the database or even of the vendor."). And at least one signatory to this comment directly contacted the authors asking for information on the database but received no answer.

[26] EPPC Serious Adverse Event, *supra* note 16, at p. 5.

limitations of some databases for analyzing abortion claims data. For example, some commercially available sources of Medicaid claims data are over-representative of "Hyde exceptions" because many states only provide Medicaid coverage for abortions in situations of rape, incest, or life endangerment.[27] Medicaid claims data thus overrepresent abortions to prevent life-threatening health risks and are not representative of abortion cases overall. Likewise, patients covered by Medicaid often present with more complex needs and additional health conditions that can contribute to a higher risk of complications as compared to the general population. Thus, for patients with Medicaid coverage, abortions – like any healthcare – can result in a greater need for follow-up care. Accordingly, in a retrospective review of insurance or medical claims, it is standard to disclose the different payer and billing sources and to identify and address any inherent limitations in the data such as over- or under-representation of certain populations or regions of the country, or potential for claims misclassifications in particular datasets.

Additionally, it is highly problematic that EPPC does not disclose the full list of diagnosis and procedure codes used in its analyses, nor many other standard disclosures like the coding they used to analyze data, information about their study cohort (such as comorbidities), or how that cohort was created. Full disclosure of methods for creating the study cohort and lists of the diagnoses and procedure codes for measuring both exposures and outcomes is standard practice in analyses of insurance claims data. But EPPC simply states that it "identified relevant ICD-10 diagnoses codes and CPT/HCPCS procedures codes from multiple sources," (including from CDC, CMS, FDA and "codes suggested by our doctors")[28] without listing each diagnosis and procedure code used or saying more about its study cohort.

In standard studies of medication abortion safety, researchers use treatment codes to identify serious adverse events, given that diagnosis codes alone may not indicate the degree of seriousness of an event.[29] A lack of treatment indicates the encounter did not

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[27] Frederiksen, B., Dennis, E., Liu, G., Leslie, D., Salganicoff, A., & Roberts, S. (2025). The limitations of using Medicaid administrative data in abortion research. *Contraception*, *142*, 110704. https://doi.org/10.1016/j.contraception.2024.110704.

[28] EPPC Report on Serious Adverse Event, *supra* note 16, at p. 5.

[29] Taylor, D., Upadhyay, U. D., Fjerstad, M., Battistelli, M. F., Weitz, T. A., & Paul, M. E. (2017). Standardizing the classification of abortion incidents: The Procedural Abortion Incident Reporting and Surveillance (PAIRS) Framework. *Contraception*, *96*(1), 1–13. https://doi.org/10.1016/j.contraception.2017.05.004. The full list of diagnosis and procedure codes is also important to verify if the medications or procedures provided to a patient were in fact related to an abortion. Some medications and procedures commonly used in abortion are also commonly

involve a serious adverse event. For example, given the variety of definitions of hemorrhage, it would be inaccurate to consider a hemorrhage diagnosis a serious adverse event if it did not require any treatment. Thus, when classifying adverse events, it is critical to examine treatment/procedure codes, not only diagnosis codes. While EPPC's subsequent FAQ claims its analysis was based on "diagnosis and procedure codes" and only counted "treatment for a serious complication,"[30] it never identifies a single treatment code that was used as part of that methodology, let alone discloses all the treatment codes considered under each category it counts as a serious adverse event.

Finally, contrary to standards for transparency in scientific studies, the EPPC report has no discussion of the limitations of its analysis. For example, EPPC does not address how the serious adverse event rate they report is impacted by exclusion of certain populations from an insurance claims database, such as patients who pay out of pocket.[31] Some public and private insurance plans cover abortions only in limited circumstances, such as when continuing the pregnancy poses a serious health risk. Pregnant people who do not qualify will be among those who pay out of pocket for abortion. Thus, people more likely to have pregnancy complications or require more complex abortion treatment are overrepresented in insurance claims data.

2. EPPC's Findings and Conclusions, to the Extent Explained, are Inconsistent and Unsound

To the extent possible given the summary description of the data purchased, and the piecemeal explanations of the methodology used, we outline several additional concerns related to specific unexplained variables, assumptions, findings, and conclusions made by EPPC in its reports:

Lack of definitions and methodology to identify hemorrhage: The authors do not sufficiently define hemorrhage. This category accounts for 28,658 of the 94,605 "serious adverse events," which is one of the three largest categories of serious adverse events in their report.[32]

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used for other indications unrelated to pregnancy. For example, a uterine aspiration may be performed to evaluate and treat heavy menstrual bleeding when a patient is not pregnant.

[30] EPPC FAQ, *supra* note 22, at p. 1.

[31] The authors state that the data excludes "cash pay transactions (which are disproportionately common for abortion)." EPPC Report on Serious Adverse Event, *supra* note 16, at p. 5. But there is no discussion of how that, or other excluded populations, impacts their findings.

[32] EPPC Report on Serious Adverse Event, *supra* note 16, at Fig. 1.

A successful medication abortion always involves some bleeding. When a patient presents with complaints of bleeding, it could be excessive bleeding or it could be the expected amount.[33] Without a standardized definition,[34] EPPC is likely misclassifying many cases of normal bleeding that occur with a medication abortion. Indeed, the FDA has previously addressed the problem of mischaracterizing or misclassifying treatment for heavy bleeding after medication abortion as a serious adverse event: "Heavy bleeding or hemorrhage after medical abortion is a small subset of bleeding and can require a surgical procedure due to ongoing pregnancy or incomplete expulsion; these are considered failed treatment rather than adverse events and are not characterized using the [Council for International Organizations of Medical Sciences'] definitions. Even if heavy, bleeding after medical abortion may not be considered a serious adverse event unless clinically diagnosed as hemorrhage or requiring a transfusion."[35]

EPPC's Fact Sheet claims that they "excluded non-serious bleeding" such as "typical expected bleeding," [36] but does not confirm how their methodology ensured this was done reliably. For example, relying only on diagnostic codes – as they seem to have done – could erroneously elevate the hemorrhage category numbers. For example, a patient could present after an episode of heavy bleeding after using medication abortion. A clinician may use the diagnosis code of "hemorrhage" to justify checking the patient's blood count. But if the patient is clinically stable, bleeding resolves, blood count is normal, and no treatment for hemorrhage is provided, this would not be a serious adverse event. Again, this is why it

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[33] Arey, W., Lerma, K., & White, K. (2024). Self-diagnosing the end of pregnancy after medication abortion. *Culture, Health & Sexuality*, *26*(3), 405–420. https://doi.org/10.1080/13691058.2023.2212298.

[34] *See, e.g.,* Taylor et al., 2017, *supra* note 29; Kerns, J. L., Brown, K., Nippita, S., & Steinauer, J. (2024). Society of Family Planning Clinical Recommendation: Management of hemorrhage at the time of abortion. *Contraception*, *129*, 110292. https://doi.org/10.1016/j.contraception.2023.110292.

[35] *Letter from Patrizia A. Cavazzoni, M.D., Director Center for Drug Evaluation and Research to Donna J. Harrison, M.D., Executive Director American Association of Pro-Life Obstetricians and Gynecologists*, (Dec. 16, 2021), at pp. 36-37. https://downloads.regulations.gov/FDA-2019-P-1534-0016/attachment_1.pdf (hereinafter "FDA Letter 2021").

[36] EPPC Fact Sheet, *supra* note 22, at p. 2. Nor does their statement that they only used codes "related to hemorrhage or serious bleeding (according to the FDA definition)" help clarify what definition they are using. *Id*. They do not describe or cite to any FDA definition of "hemorrhage or serious bleeding" and the FDA guidance on serious adverse events that they cite to elsewhere does not include such a definition. *See* FDA. (2023). *What is a Serious Adverse Event?* https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event.

is imperative to look at diagnosis and treatment codes together to ensure proper classification.

Likely inclusion of emergency room visits unrelated to serious adverse events: Abortion-related emergency room (ER) visits were counted as serious adverse events. At a count of 40,960, this is the second largest category included in their report.[37]

While the FDA collects, reviews, and includes on the mifepristone labeling information about ER visits related to medication abortion, when evaluating real-world safety and effectiveness it considers whether those visits are accompanied by other serious adverse events.[38] FDA guidance states: "Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event)."[39]

Research shows that many people go to an emergency room after a medication abortion to get immediate care for symptoms, or to ask questions, or to confirm they are no longer pregnant, without receiving any treatment.[40] This is more common when the patient lives far from the abortion provider.[41] ER visits are more common among people with Medicaid coverage, as many do not have a primary healthcare provider.[42] Additionally, the time period of the data analyzed, 2017-2023, overlaps with the height of the COVID pandemic,

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[37] EPPC Report on Serious Adverse Event, *supra* note 16, at Fig. 1.

[38] *See, e.g.,* FDA Letter 2021, *supra* note 35, at pp. 26-34, 35 (explaining recent review of safety and effectiveness of dispensing mifepristone by mail and finding, "[a]lthough the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other serious adverse events related to mifepristone use").

[39] FDA 2023, *supra* note 36.

[40] Upadhyay, U. D., Desai, S., Zlidar, V., Weitz, T. A., Grossman, D., Anderson, P., & Taylor, D. (2015). Incidence of emergency department visits and complications after abortion. *Obstetrics and Gynecology*, *125*(1), 175–183. https://doi.org/10.1097/AOG.0000000000000603; Upadhyay, U. D., Johns, N. E., Barron, R., Cartwright, A. F., Tapé, C., Mierjeski, A., & McGregor, A. J. (2018). Abortion-related emergency department visits in the United States: An analysis of a national emergency department sample. *BMC Medicine*, *16*(1), 88. https://doi.org/10.1186/s12916-018-1072-0.

[41] Upadhyay, U. D., Johns, N. E., Meckstroth, K. R., & Kerns, J. L. (2017). Distance Traveled for an Abortion and Source of Care After Abortion. *Obstetrics and Gynecology*, *130*(3), 616–624. https://doi.org/10.1097/AOG.0000000000002188.

[42] Mortensen, K., & Song, P. H. (2008). Minding the gap: A decomposition of emergency department use by Medicaid enrollees and the uninsured. *Medical Care*, *46*(10), 1099–1107. https://doi.org/10.1097/MLR.0b013e318185c92d.

during which the implementation of social distancing policies created barriers for in-office primary care visits,[43] which could have led to an increase in ER visits for routine follow-up care.

While EPPC later states in its Fact Sheet that it excluded ER visits that did not include serious adverse events,[44] for reasons addressed above, it is impossible to verify how this was done. For example, as already explained, their definition of hemorrhage remains unclear and unreliable. Thus, it is possible that billing for an ER visit with an initial diagnosis of hemorrhage, but which self-resolved and did not require treatment, was included. Likewise, infection is another category that requires more explanation to determine the extent to which the EPPC reporting of a 1.34% rate of infection might be inflated by inclusion of non-serious conditions like yeast vaginitis and urinary tract infections.[45] Further, their decision to rely on NIH's Common Terminology Criteria for Adverse Events raises further questions about the reliability of their coding analysis. Those codes originated in connection with cancer treatment and research and are not commonly used in connection with ER care.

"Other abortion-specific complications" are not clearly defined: There is a need for greater transparency around this "other" category. This is likely where EPPC included the unidentified "codes suggested by our doctors," contributing to greater confusion and obscurity around the methods used. This is the largest category of serious adverse events, accounting for 49,169 of the 94,605 serious adverse events counted by EPPC.[46]

Because no information about the researchers or doctors who did this coding was offered, we are unable to evaluate their expertise in abortion care or what they relied upon to designate abortion-specific complications for this category. Relatedly, and deeply problematic, they included diagnosis codes for homicidal and suicidal ideation as two of

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[43] Alexander, G. C., Tajanlangit, M., Heyward, J., Mansour, O., Qato, D. M., & Stafford, R. S. (2020). Use and Content of Primary Care Office-Based vs Telemedicine Care Visits During the COVID-19 Pandemic in the US. *JAMA Network Open*, *3*(10), e2021476. https://doi.org/10.1001/jamanetworkopen.2020.21476.

[44] *See* EPPC Fact Sheet, *supra* note 22, at p. 1.

[45] *See* EPPC Report on Serious Adverse Event, *supra* note 16, at Fig. 1. While neither the initial EPPC report, the EPPC Fact Sheet, nor the EPPC FAQ say anything about what types of infections were excluded, an EPPC spokesperson answering questions about the possible inclusion of yeast or urinary tract infections identified only one such diagnosis – vaginitis – that was excluded. *See* Kessler, *supra* note 25.

[46] EPPC Report on Serious Adverse Event, *supra* note 16, at Fig. 1.

the diagnosis codes qualifying as abortion-specific complications.[47] By including these codes, the EPPC team either misrepresents, or misunderstands, the evidence on abortion and the types of serious adverse events that relate to abortion. Rigorous published research overwhelmingly establishes that serious mental health crises are not a complication of abortion.[48] Thus, there is no basis for suggesting such events are related to an abortion because it was diagnosed within 45 days of an abortion, and it is irresponsible and misleading to suggest it does.[49]

Mischaracterizing subsequent treatment to complete a medication abortion as a serious adverse event and/or "repeated abortion": EPPC alternately counts any procedural abortion within 45 days following a medication abortion as a serious adverse event or as evidence that an initial medication abortion failed. But characterizing follow-up treatment for an incomplete or failed medication abortion as a serious adverse event is inconsistent with published literature and FDA guidance.

In their first report, EPPC counted "Repeated (surgical) abortion" after a medication abortion as a serious adverse event. Specifically, they assert procedural abortions account for 24,563 of the 94,605 serious adverse events in their findings.[50] Subsequently, in their second report claiming to identify the "real-world failure rate," of mifepristone abortion, they present this number differently. In the second report, EPPC claims "5.26 percent of women undergo a second abortion attempt within 45 days of the first," (this includes a

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[47] EPPC FAQ *supra* note 22, at p.3.

[48] *See, e.g.*, Biggs, M. A., Upadhyay, U. D., McCulloch, C. E., & Foster, D. G. (2017). Women's Mental Health and Well-being 5 Years After Receiving or Being Denied an Abortion: A Prospective, Longitudinal Cohort Study. *JAMA Psychiatry*, *74*(2), 169–178. https://doi.org/10.1001/jamapsychiatry.2016.3478; Steinberg, J. R., Laursen, T. M., Lidegaard, Ø., & Munk-Olsen, T. (2024). Medication and procedural abortions before 13 weeks gestation and risk of psychiatric disorders. *American Journal of Obstetrics and Gynecology*, *231*(4), 437.e1-437.e18. https://doi.org/10.1016/j.ajog.2024.05.025; Steinberg, J. R., Laursen, T. M., Adler, N. E., Gasse, C., Agerbo, E., & Munk-Olsen, T. (2019). The association between first abortion and first-time non-fatal suicide attempt: A longitudinal cohort study of Danish population registries. *The Lancet. Psychiatry*, *6*(12), 1031–1038. https://doi.org/10.1016/S2215-0366(19)30400-6; Biggs, M. A., Rowland, B., McCulloch, C. E., & Foster, D. G. (2016). Does abortion increase women's risk for post-traumatic stress? Findings from a prospective longitudinal cohort study. *BMJ Open*, *6*(2), e009698. https://doi.org/10.1136/bmjopen-2015-009698.

[49] Notably, a spokesperson for the authors admitted "there were zero instances of patients with those two SAE mental health diagnosis codes" within their data analysis. Kessler, *supra* note 25. This, however, does not minimize the harm of suggesting it is a risk related to medication abortion.

[50] EPPC Report on Serious Adverse Event, *supra* note 16, Fig. 1.

second abortion by either mifepristone and/or surgical procedure).[51] They then conclude that: "13.51 percent of women – roughly one in seven – experience at least one serious adverse event or repeated abortion attempt within 45 days of first attempting a mifepristone abortion."[52] While this new presentation of the data seems to acknowledge not all treatments to complete an abortion are serious adverse events, in their conclusion they once again assert, as they do in their first report, that the "real-world rate of serious adverse events following mifepristone abortions is at least 22 times as high as reported on the drug label."

It is known and expected that about 3-5% of patients will need additional medications or a procedure to complete the abortion.[53] And while EPPC's report of a five percent real-world failure rate is within the range of some prior clinical studies on effectiveness, it cannot be evaluated or verified for the reasons already explained regarding the unknown dataset and methodologies for data analysis.

Whether wrongly counting treatment for completing a medication abortion as a "serious adverse event," using that data to suggest mifepristone is not effective, or combining and presenting the data in a conflicting and inconsistent way, the EPPC's interpretation of insurance claims regarding treatment for incomplete abortions and ongoing pregnancy is misleading.

Problems identifying miscarriage treatment and other uses of mifepristone: One of the three ways EPPC says they identified medication abortions was a prescription for mifepristone with or without misoprostol within the next 3 days.[54] But mifepristone is used for other indications, including for miscarriage management and induction termination, along with misoprostol.[55] Additionally, mifepristone is frequently used for cervical priming

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[51] EPPC Report on Failure Rate, *supra* note 17, at p. 2 and Table 1.

[52] *Id.* at p. 2.

[53] Chen & Creinin, 2015, *supra* note 2; Raymond et al., 2013, *supra* note 2; Upadhyay et al., 2015, *supra* note 40.

[54] EPPC Report on Serious Adverse Event, *supra* note 16, at p. 4.

[55] *See, e.g.*, Boos, E. W., Horta, M., Thompson, I., Dusetzina, S. B., & Leech, A. A. (2023). Trends in the Use of Mifepristone for Medical Management of Early Pregnancy Loss From 2016 to 2020. *JAMA*, *330*(8), 766–763. https://doi.org/10.1001/jama.2023.13628; Tarleton, J. L., Benson, L. S., Moayedi, G., Trevino, J., & with the assistance of Leah Coplon, Anitra Beasley, and Elise Boos on behalf of the Society of Family Planning Clinical Affairs Committee. (2025). Society of Family Planning Clinical Recommendation: Medication management for early pregnancy loss. *Contraception*, *144*, 110805. https://doi.org/10.1016/j.contraception.2024.110805; Nobles, J., Hwang, S., Bennett, E., & Jacques, L. (2024). Abortion Restrictions Threaten Miscarriage Management In The United States. *Health Affairs (Project Hope)*, *43*(9), 1219–1224. https://doi.org/10.1377/hlthaff.2023.00982;

before procedural abortion in the second trimester.[56] Any of these uses could have been captured in this study. In general, miscarriage and treatment for miscarriage are associated with slightly higher complication rates than for abortion,[57] which would erroneously inflate the "serious adverse event" rate reported by the study.

EPPCs follow-up explanations only add to the confusion and further highlight potential problems in their analysis. In the subsequent FAQ, EPPC states it "was very careful to exclude miscarriage care in our report by requiring any mifepristone only prescription was accompanied by a Z332 code (encounter for elective termination of pregnancy) or Z640 (problems related to unwanted pregnancy)."[58] But mifepristone along with misoprostol is a recommended standard of care for miscarriage management,[59] which means patients experiencing a miscarriage will commonly be prescribed both medications. Yet, EPPC does not say it ensured there was an accompanying Z332 or Z640 code when a patient was prescribed both medications. Thus, it seems, EPPC has not excluded cases of standard

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Schreiber, C. A., Creinin, M. D., Atrio, J., Sonalkar, S., Ratcliffe, S. J., & Barnhart, K. T. (2018). Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss. *The New England Journal of Medicine*, *378*(23), 2161–2170. https://doi.org/10.1056/NEJMoa1715726; Chu, J. J., Devall, A. J., Beeson, L. E., Hardy, P., Cheed, V., Sun, Y., Roberts, T. E., Ogwulu, C. O., Williams, E., Jones, L. L., La Fontaine Papadopoulos, J. H., Bender-Atik, R., Brewin, J., Hinshaw, K., Choudhary, M., Ahmed, A., Naftalin, J., Nunes, N., Oliver, A., … Coomarasamy, A. (2020). Mifepristone and misoprostol versus misoprostol alone for the management of missed miscarriage (MifeMiso): A randomised, double-blind, placebo-controlled trial. *Lancet (London, England)*, *396*(10253), 770–778. https://doi.org/10.1016/S0140-6736(20)31788-8; Zwerling, B., Edelman, A., Jackson, A., Burke, A., & Prabhu, M. (2023). Society of Family Planning Clinical Recommendation: Medication abortion between 14 0/7 and 27 6/7 weeks of gestation: Jointly developed with the Society for Maternal-Fetal Medicine. *American Journal of Obstetrics and Gynecology*. https://doi.org/10.1016/j.ajog.2023.09.097; American College of Obstetricians and Gynecologists. (2013). Second-Trimester Abortion. ACOG Practice Bulletin No. 135. *Obstet Gynecol* 2013;121(6):1394-1406.

[56] Diedrich, J. T., Drey, E. A., & Newmann, S. J. (2020). Society of Family Planning clinical recommendations: Cervical preparation for dilation and evacuation at 20-24 weeks' gestation. *Contraception*, *101*(5), 286–292. https://doi.org/10.1016/j.contraception.2020.01.002.

[57] Roberts, S. C. M., Beam, N., Liu, G., Upadhyay, U. D., Leslie, D. L., Ba, D., & Kerns, J. L. (2020). Miscarriage Treatment–Related Morbidities and Adverse Events in Hospitals, Ambulatory Surgery Centers, and Office-Based Settings. *Journal of Patient Safety*, *16*(4), e317–e323. https://doi.org/10.1097/PTS.0000000000000553.

[58] EPPC FAQ, *supra* note 22, at p. 2.

[59] Chu et al., 2020, *supra* note 55; Schreiber et al., 2018, *supra* note 54; Neilson, J. P., Hickey, M., & Vazquez, J. (2006). Medical treatment for early fetal death (less than 24 weeks). *The Cochrane Database of Systematic Reviews*, *2006*(3), CD002253. https://doi.org/10.1002/14651858.CD002253.pub3 (meta-analysis).

miscarriage treatment, or the corresponding problem of an erroneously inflated rate of serious adverse events.

"Other life-threatening adverse events" are not necessarily abortion related: This category accounts for 1,956 of the 94,605 "serious adverse events" in the report.[60] The analysis captures chronic issues, including cardiac and pulmonary events, as "serious adverse events," but there is no indication that they are abortion related. In fact, patients with these conditions may be more likely to have an abortion to avoid exacerbating their chronic condition, and thus, the direction of causality between the abortion experience and the serious adverse event is ambiguous. As explained above, it is quite likely these types of cases are over-represented in the database because many public and private insurance plans cover abortions only if a pregnancy is causing or exacerbating serious health issues. Again, without a clear list of each specific diagnosis and the corresponding treatment for claims included in this category, or description of the study cohort's characteristics, including existing comorbidities, it is impossible to determine if these are appropriately categorized as abortion-related complications simply by virtue of occurring within 45 days of an abortion.

EPPC makes sweeping conclusions and recommendations not supported by their stated evidence: The policy implications stated do not follow from the authors' own analyses, even if one were to take the reported findings at face value.

For instance, they find no evidence to support that a return to in-person dispensing of mifepristone for a medication abortion would reduce adverse events; the analysis does not stratify by the location of mifepristone dispensing so there is no evidence that adverse events would be different based on in-person versus remote dispensing of mifepristone. Likewise, they do not report serious adverse events by year, so there is no support for their conclusion that removing restrictions on mifepristone has resulted in increased adverse event rates. They also have no findings to support the recommendation that only physicians should provide mifepristone. The analysis does not look at or address whether a medication abortion was provided by a physician or an advanced practice clinician. Similarly, their analysis does not examine adverse events by pregnancy duration, and thus, their recommendation that medication abortion be restricted to the first seven weeks is unsupported by the analysis conducted.

[60] EPPC Report on Serious Adverse Event, *supra* note 16, at Fig. 1.

Finally, as EPPC itself acknowledges, ectopic pregnancy is not caused by or a complication of medication abortion,[61] and evidence establishes that abortion medications do not create harm if taken by someone with an ectopic pregnancy.[62] Yet EPPC makes the baseless claim that "use of mifepristone by a woman with an ectopic pregnancy poses extraordinary, heightened risk to her health."[63]

B. One New Study that Evaluates Emergency Department Visits Related to Abortion is Deeply Flawed

We are also aware of one new study published this year which sought to identify the prevalence and severity of emergency department ("ED") visits by patients who have taken mifepristone for medication abortion: *Determining the Period Prevalence and Acuity of Emergency Department Visits Following Induced Abortion Mistakenly Identified as Spontaneous Abortions: An Analytical Observational Prospective Cohort Study*.[64] In this paper, lead author James Studnicki and co-authors, all affiliated with the Charlotte Lozier Institute (the research and education institute of Susan B. Anthony Pro-Life America), conclude that ED visits following induced abortion have high severity, and that rates of such outcomes are being deflated and concealed due to high rates of miscoding and misattributing these visits as related to a spontaneous abortion (miscarriage). But the authors' interpretation of the data and findings rest on serious methodological flaws and

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[61] *See* EPPC FAQ, *supra* note 22, at p. 2.

[62] Shannon, C., Brothers, L. P., Philip, N. M., & Winikoff, B. (2004). Ectopic pregnancy and medical abortion. *Obstetrics and Gynecology*, *104*(1), 161–167. https://doi.org/10.1097/01.AOG.0000130839.61098.12.

[63] EPPC FAQ, *supra* note 22, at p. 2.

[64] Studnicki, J., Fisher, J. W., Cox, T. L., Cirucci, C. A., Reardon, D. C., Skop, I., Louttit, C., Harrison, D. J., & Craver, C. (2025). Determining the Period Prevalence and Acuity of Emergency Department Visits Following Induced Abortion Mistakenly Identified as Spontaneous Abortion: An Analytic Observational Prospective Cohort Study. *Family Medicine and Primary Care: Open Access,* *9*(282). https://doi.org/10.29011/2688-7460.100282. The authors of this study are largely the same authors of prior studies attempting to show a higher rate of emergency department visits related to medication abortion that were retracted because of fundamental problems with the study design and methodology. Retraction Notice. (2024). *Health Services Research and Managerial Epidemiology*, *11*, 23333928231216699. https://doi.org/10.1177/23333928231216699. Moreover, in this newest study, they again use the same methods as used in one of the studies that was retracted. Studnicki, J., Longbons, T., Harrison, D. J., Skop, I., Cirucci, C., Reardon, D. C., Craver, C., Fisher, J. W., & Tsulukidze, M. (2022). A Post Hoc Exploratory Analysis: Induced Abortion Complications Mistaken for Miscarriage in the Emergency Room are a Risk Factor for Hospitalization. *Health Services Research and Managerial Epidemiology*, *9*, 23333928221103107. https://doi.org/10.1177/23333928221103107 (Retraction published 2024, *Health Services Research and Managerial Epidemiology, 11*).

unreliable data that undermine their conclusions. As a result, the study does not credibly support their conclusion that use of mifepristone for induced abortion represents a "serious risk factor," and does not undermine the overwhelming body of scientific evidence demonstrating the safety of medication abortion with mifepristone.

1. **The Methodology Used by the Authors to Code for Acuity of Emergency Department Visits is Gravely Inaccurate**

The authors of this study are misclassifying acuity of patient outcomes and interventions to draw sweeping conclusions. Core to the conclusions of the paper are its determinations of acuity, or severity level, of patient emergency department visits following an induced abortion (as determined by the study authors, although this categorization is also flawed, see below). However, the study methodology misclassifies acuity based on use of Current Procedural Terminology (CPT) codes that do not support their determinations.

The study methodology classifies CPT codes 99284 and 99285 as "severe" or "critical" and thus labels any visit with one of these acuity codes as having high acuity.[65] However, these codes do not always support such categorization. CPT codes are used to describe emergency department visits for the evaluation and treatment of a patient, and the specific code is primarily determined on initial presentation of the patient and reflects the amount of cognitive work required for the ED clinician to evaluate the patient and make a diagnosis, not the severity of the overall visit once treatment is provided. These CPT codes have nothing to do with the seriousness of the final diagnosis and treatment. For example, an ED visit where detailed history, examination, urine and blood testing, and moderately complex medical decision making is required can push the CPT code to 99284 or 99285, but it does not necessarily indicate a serious adverse event or severe medical condition experienced by the patient. Additionally, the study does not disaggregate among all visits it categorizes as "high acuity," to show how many were put in that category because of CPT code 99284 versus CPT code 99285.

More generally, it is imprecise to use any single CPT code to determine the severity or acuity of an emergency department visit. It is critical to look at all treatment codes that patients receive in an emergency department to determine severity and acuity as accurately as possible. Comprehensively looking at multiple codes is also important to

[65] Studnicki et al., 2025, *supra* note 64, at p. 3.

mitigate the possibility that some higher acuity codes are inaccurate. Research shows that there is a growing trend of providers and hospitals using higher acuity codes.[66]

Despite the ability to conduct a comprehensive review of all treatment codes, the authors of this study did not. The authors pulled data from the Centers for Medicare and Medicaid Services (CMS),[67] which is a data source that includes access to all billing information for included visits. Thus, the researchers could and should have used this data source to determine the nature of each adverse event, rather than relying on CPT codes that do not accurately or sufficiently describe acuity level. The failure to do so, in combination with the authors' misclassification of at least some CPT codes, render the authors' findings that most emergency department visits after abortion were high acuity unsupported by the study itself and inconsistent with methodology and conclusions in previous research.

2. The Determination of What Counts as a "Miscode," Relies on Flawed Methodology and Bad Faith Assumptions About Patients and Providers

The authors' methodology for classifying a "miscode" is flawed and undermines the credibility and reliability of the authors' staggering claim that 18% of all ED visits following medication abortion were miscoded.[68] The study authors identify a cohort of patients who had a medication abortion using a single Healthcare Common Procedure Coding System (HCPCS) code (HCPCS code S0190, which is the code for mifepristone).[69] However, mifepristone is not exclusively used to induce abortion, it is also increasingly used to treat miscarriages.[70] As a result, many of the uses of that code may in fact be actual miscarriages. But the authors only make the miscoding assumption in one direction – a direction that necessarily inflates the prevalence of ED visits related to induced abortion.

One major error is the authors' failure to account for the complexity of billing data and coding. Billing data for a single emergency department visit contains multiple claims, sometimes even hundreds of rows of claims for different tests, medications, IV fluids, etc., each of which will have a different claim and diagnosis or treatment code. In practice, this means that there may be some discrepancy between each claim for an emergency

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[66] *See e.g.*, Ruxin, T., Feldmeier, M., Addo, N., & Hsia, R. Y. (2023). Trends by Acuity for Emergency Department Visits and Hospital Admissions in California, 2012 to 2022. *JAMA Network Open*, *6*(12), e2348053. https://doi.org/10.1001/jamanetworkopen.2023.48053.

[67] Studnicki et al., 2025, *supra* note 64, at p. 2.

[68] *Id.* at p. 3.

[69] *Id.* at p. 2.

[70] *See supra* note 59 (citing multiple studies documenting increased use of mifepristone for miscarriage care).

department visit due to the number of claims related to each visit. For example, if a patient's urine goes to the emergency department lab for pregnancy testing, it is possible that the wrong diagnosis code could be used in that single claim, but that does not mean that the entire visit was miscoded. Nonetheless, in this study, the presence of a single code for miscarriage alongside a single code for induced abortion led authors to classify the entire visit as a "miscode." This methodological error undergirds a misunderstanding of the fundamental coding processes as used in the emergency department context.

The presence of codes for both induced abortion and miscarriage does not mean that the entire visit was miscoded, particularly in the emergency department context. Emergency department visits with severe acuity – which can include miscarriages – will have many, many claims, and thus an even greater likelihood of at least one claim being attributed to an induced abortion rather than a miscarriage, particularly given that the two conditions present very similarly. For the same reason, visits the authors consider to have been "miscoded" are also likely to be ones that present with higher acuity codes and have more claims associated with them.

Additionally unfounded, and especially concerning, is the authors' underlying assumption and premise that miscodes result from intentional deception for "concealment of the abortion."[71] Foundational to the study's results and recommendations is the authors' postulation that these miscodes result from patients lying to the emergency department doctors and/or health care workers lying in their coding in order to attribute visits to miscarriages rather than induced abortions. The authors inappropriately assume bad faith of patients and providers[72] and fail to adequately consider the likelihood of human error, given how easy it is to code incorrectly in one of the many claims associated with an ED visit (as described above). By way of example, even if ten codes are used and nine signal miscarriage, if one signals induced abortion, it appears as if the study authors consider the entire visit as purposeful lying or attempts to hide an abortion.

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[71] Studnicki et al., 2025, *supra* note 64, at p. 6. Relatedly, the authors assert that miscoding has created a problem for reliably researching prevalence rates of abortion complications, stating: "miscoded abortion complications remain invisible to research scientists resulting in large underestimation of actual abortion complications." *Id.* But, as described above, many researchers have used more rigorous methods to assess abortion complications. These researchers have examined actual treatment codes and reviewed comprehensive claims data to see whether an ED visit led to a hospital admission in order to accurately determine complications. *See, e.g.,* FDA/CDER 2016, *supra* note 3; FDA 2024, *supra* note 3; Kulier et al., 2011, *supra* note 2; GenBioPro Petition, *supra* note 2, at pp. 12-14.

[72] Studnicki et al., 2025, *supra* note 64, at p. 6.

3. The Study Lacks Reliable Data to Reproduce or Verify its Results

In addition to the above ways in which the study methodology is obscure and flawed, the study's reliance only on Medicaid administrative data for abortion is unreliable. The study draws data from the CMS Transformed Medicaid Statistical Information System Analytical Files (TAF) for 2016-2021 and from the discontinued Medicaid Analytic eXtract (MAX) files for 2004-2015.[73] However, the use of Medicaid administrative data for abortion rates has been shown to be inaccurate. Research has shown that this dataset is unreliable for abortion-related studies.[74] In a recent study, researchers compared the number of abortions counted in the MAX and TAF datasets to the number of expected abortions covered by Medicaid nationwide and by state. The study found that MAX identified only 11% of expected Medicaid-covered abortions in 2009 and 13% in 2010, while TAF identified 25% of expected Medicaid-covered abortions in 2020, which constituted only 7% of total abortions in the United States for that year.[75] Thus the study authors concluded that these databases significantly undercount abortion covered by Medicaid and cautioned against use of MAX or TAF data for abortion-related research. Given that the Studnicki study relies solely on these databases, both the numerator and denominator used for their article are likely wrong.

CONCLUSION

Standard practices in epidemiology emphasize the importance of transparency in methodological approaches to ensure the reliability, reproducibility, and credibility of research findings.[76]

The issues discussed above reflect just some of the most serious transparency, reproducibility, and methodology problems that make any reliance on the recent EPPC papers, Studnicki study, or other research with similar flaws wholly inconsistent with FDA standards and obligation to rely on sound, gold standard science in its decision-making.

These shortcomings are even more problematic where, as here, claimed findings contradict consistent and overwhelming findings of decades of rigorous, transparent, and

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[73] Studnicki et al., 2025, *supra* note 64, at p. 2.

[74] Frederiksen et al., 2025, *supra* note 27.

[75] *Id.* at p. 3.

[76] *See, e.g.*, S. V., & Pottegård, A. (2024). Building transparency and reproducibility into the practice of pharmacoepidemiology and outcomes research. *American Journal of Epidemiology*, *193*(11), 1625–1631. https://doi.org/10.1093/aje/kwae087.

reproducible research on the safety and effectiveness of medication abortion with mifepristone.

Sincerely,

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EXHIBIT G

IN THE SUPREME COURT OF THE UNITED STATES

U.S. Food and Drug Administration, *et al.*, *Applicants*	
v.	No. 22A-
Alliance for Hippocratic Medicine, *et al.*, *Respondents*	

DECLARATION OF JANET WOODCOCK, M.D.

I, Janet Woodcock, M.D., of the U.S. Food and Drug Administration (FDA), pursuant to 28 U.S.C. § 1746, declare under penalty of perjury that the following is true and correct to the best of my knowledge:

1. I am the Principal Deputy Commissioner of FDA. I began working at FDA in 1986 in FDA's Center for Biologics Evaluation and Research ("CBER"). From 1994 to 2004 and 2007 to 2020, I served as the Director of FDA's Center for Drug Evaluation and Research ("CDER"). I served as the Acting Commissioner of Food and Drugs from January 20, 2021 to February 17, 2022. During my tenure at FDA, I have also held the positions of Deputy Commissioner, Chief Medical Officer, and Director of the Office of Therapeutics Research and Review in CBER.

2. I received my medical degree from Northwestern University Medical School, and my undergraduate degree from Bucknell University. I have held teaching appointments at Pennsylvania State University and the University of California at San Francisco.

3. CDER regulates over-the-counter and prescription drugs by, among other things, overseeing the development of new and generic medications, evaluating applications for FDA approval, and monitoring drugs' safety once they are marketed.

4. In my role as the Director of CDER, I provided overall direction to all CDER activities to help ensure that safe and effective drug products are available to improve the health of consumers, and that prescription and over-the-counter drug products, both brand name and generic, work effectively and that the health benefits of these products outweigh the known risks.

5. As a result of my experience, particularly through my official duties at FDA, I am familiar with FDA's drug approval process generally and with FDA's ongoing efforts to monitor the safety and efficacy of approved drugs. I am also familiar with Risk Evaluation and Mitigation Strategies, also known as REMS. *See* 21 U.S.C. § 355-1.

6. I am familiar with the new drug application ("NDA") for Mifeprex (mifepristone) Tablets, 200 mg, including the supplemental NDA ("sNDA") approved in 2016, and the abbreviated new drug application ("ANDA") for Mifepristone Tablets, 200 mg approved in 2019.

7. I submit this declaration in support of FDA's Application for a Stay in the above-captioned matter. This declaration is based on my personal knowledge, my background, training, and experience, and my review and consideration of information available to me in my official capacity, including information furnished by FDA personnel in the course of their official duties.

8. FDA-approved drug applications include specified conditions of use that define the scope of the approval. Changing the approved conditions of use of a drug product requires action by both the sponsor and FDA; neither party can make such changes unilaterally. The sponsor must propose the changes in a supplemental application, and FDA must then review and approve the proposed changes. See, e.g., 21 U.S.C. §§ 355, 355-1; 21 C.F.R. § 314.70. FDA may notify the sponsor that changes are required and direct the sponsor to submit them. 21 U.S.C. §§ 355-1(g)(4)(B) and 355(o)(4).

9. Mifeprex has been subject to restrictions on its use since approval in 2000, initially under 21 C.F.R. § 314.520 and later under a REMS under 21 U.S.C. § 355-1. The sNDA that FDA approved in 2016 modified the conditions of use, including the REMS. Those modifications included: changing the dose and dosing regimen for Mifeprex and the second drug in the approved regimen (misoprostol), changing the gestational age for which the product is approved (from through 49 days gestation to through 70 days gestation), requiring only one clinic or office visit rather than three, removing a requirement to administer mifepristone and misoprostol in the office or clinic, providing greater flexibility on the timing and method of follow up care, and allowing any healthcare provider licensed to prescribe medications under state law (rather than just physicians) to become certified to prescribe mifepristone.

10. The Memorandum Opinion and Order issued by the United States District Court for the Northern District of Texas on April 7, 2023 stated, "the Court hereby STAYS the effective date of FDA's September 28, 2000, Approval of mifepristone and all subsequent challenged actions related to that approval – i.e., the 2016 Changes, the 2019 Generic Approval, and the 2021 Actions." Mem. Op. at 67. The District Court stayed its Order until April 15 at 12:01 am, Central Time. I understand that the U.S. Court of Appeals for the Fifth Circuit stayed the District Court's order regarding the 2000 approval of mifepristone, but allowed the District Court's order to go into effect in all other respects. I am informed that this means that FDA's 2016 and subsequent modifications to the conditions of use, including the REMS, will be stayed, absent intervention from this Court. I understand that if the District Court and Fifth Circuit orders go into effect, FDA's approval of Mifepristone Tablets, 200 mg, will be stayed, and FDA's approval of Mifeprex will cover only the conditions of use, including the REMS, that were in place prior to FDA's approval of the 2016 Mifeprex sNDA.

11. I have been informed that the Fifth Circuit's Order assumes that the conditions of use for Mifeprex, including the REMS, could simply snap back to what they were prior to FDA's 2016 approval of labeling changes (including dose and dosing regimen changes) and REMS modification ("2016 action"). The reality is far more disruptive, given the interrelatedness of the REMS and FDA-approved product labeling, among other factors. In this Declaration, I describe the practical consequences and disruption of requiring the conditions of use (including the REMS) to revert to those in place prior to FDA's approval of the sNDA in 2016.

12. Although the 2019 Citizen Petition submitted to FDA by the American Association of Pro-Life Obstetricians and Gynecologists and the American College of Pediatricians did not question the change in the dose and dosing regimen approved in 2016 (*see* Citizen Petition at 1-2, reciting requested actions), and neither court concluded that FDA erred in changing the dose and dosing regimen, based on the Fifth Circuit panel's partial stay opinion, FDA's understanding is that the labeling for Mifeprex would need to be revised to reflect the dose and dosing regimen in place pre-2016. Specifically, reverting to the pre-2016 conditions of use would require the Mifeprex labeling to be changed to reflect that a patient be given a substantially higher dose of mifepristone, and to reflect a different overall dosing regimen for mifepristone and misoprostol (the second drug in the approved dosing regimen) and a lower dose of misoprostol, administered by a different route. Prior to the 2016 supplement approval, the approved Mifeprex labeling included the following approved conditions of use: a 600 mg. dose of mifepristone, followed 48 hours later by a 400 mcg dose of misoprostol, both taken orally. In 2016, the labeling for Mifeprex was revised to reflect the following revised conditions of use: a 200 mg. oral dose of mifepristone, followed 24-48 hours later by a 800 mcg dose of misoprostol administered buccally (dissolved in the cheek pouch). In the absence of a stay, the prescribing

information for medical providers would need to be revised to reflect a dose and a dosing regimen that have not been in place for years and that will be unfamiliar to many certified prescribers today. This also would result in the drug's prescribing information providing for higher doses of mifepristone than what we now know are needed for the intended use.

13. The conditions for use (including the REMS) are reflected in multiple documents: the FDA-approved prescribing information, the Medication Guide, the REMS Document (which sets out the REMS requirements), the Prescriber Agreement Form, and the Patient Agreement Form. In the absence of a stay, the sponsor would be required to submit a supplement to revise all these documents and obtain FDA approval in order to distribute a product whose labeling conforms with the pre-2016 conditions of approval (including the REMS) and the District Court's and Fifth Circuit's orders.

14. The Prescriber Agreement Form, which is part of the REMS, would need to be changed, because the current Prescriber Agreement Form imposes different requirements from the Prescriber Agreement Form pre-2016. For example, the pre-2016 prescribing guidelines describe the need for a follow-up visit at approximately 14 days after treatment, and a requirement for prescribers to report any serious adverse events to the sponsor. By signing the Prescriber Agreement Form, a prescriber agrees to follow those guidelines. At least some current prescribers likely never completed the Prescriber Agreement Form that was approved pre-2016, because they did not become certified prescribers until 2016 or later, or even if they did, they would have subsequently signed the newer Prescriber Agreement Form, thereby agreeing to different terms. The combination of the District Court's and Fifth Circuit's orders thus arguably requires all current prescribers to be re-certified. And if the scope of the stay pending appeal is later revised, they may need to become recertified again.

15. There are significant practical consequences for the sponsor to change the above-described documents. In the absence of a stay, when the administrative stay expires, the sponsors' drug products immediately would become misbranded and thus unlawful to introduce in interstate commerce. The FDCA requires that drugs bear labeling containing adequate directions for use. 21 U.S.C. § 352(f)(1); 21 C.F.R. 201.5 (defining "adequate directions for use" as "directions under which the layman can use a drug safely and for the purposes for which it is intended"). For prescription drugs, like mifepristone, adequate directions for use cannot be written for a layperson. *See* 21 U.S.C. § 353(b)(1). Thus, all prescription drugs are misbranded under 21 U.S.C. § 352(f)(1) unless they fall within one of the exemptions from the requirement for adequate directions for use, *see, e.g.*, 21 C.F.R. § 201.100(c)(2). As a result of the courts' orders, Mifepristone Tablets, 200 mg, will be misbranded because FDA's approval of the generic application will be stayed. A new approval would be required unless the District Court's stay of the approval is lifted. And as a result of the courts' orders, Mifeprex also will be misbranded until the sponsor submits a supplemental application proposing changes to the conditions of use consistent with the courts' orders, FDA reviews and approves that supplement, and the sponsor incorporates those changes into the labeling and packaging for the product. The sponsor would also need to post and disseminate new Prescriber and Patient Agreement Forms and, as noted above, most prescribers would need to become recertified. Difficult and novel questions would need to be resolved, such as whether the combination of the courts' orders compels reversion to the pre-2016 labeling for Mifeprex even though it contains information that is now scientifically out-of-date, for example, by failing to reflect current scientific data on the safety and efficacy of the drug. It would also require FDA to reinstate a superseded dosing regimen, requiring a substantially *higher* dose of the drug than FDA has deemed necessary. We estimate that this

process would take months, at minimum, due to the logistics of effectuating such changes, including Danco's printing of new drug labels and labeling. And if a later court order reinstates the scope and conditions of FDA's Mifeprex approval as of 2023, the sponsor and FDA would need to start this process over again, with the sponsor crafting and submitting a new sNDA and, once approved, printing new labels and labeling once again while prescribers adjust again to changes in the approved dosing regimen.

16. The Fifth Circuit's partial stay order also will, if allowed to remain in place, create significant chaos for patients, prescribers, and the health care delivery system. As noted above, I have been informed that the order will result in Mifeprex being misbranded overnight and will stay the approval of the generic product (issued in 2019) altogether, leaving prescribers, patients, and the health care delivery system to face substantial uncertainty as to the legal status and appropriate options with regard to existing stores of the drug.

Dated: April 14, 2023



Janet Woodcock, M.D.
Principal Deputy Commissioner
United States Food and Drug Administration

EXHIBIT H

Docusign Envelope ID: 46AF7693-3C4C-4C75-B832-DB4C87E29467

January 31, 3025

CITIZEN PETITION

Pursuant to 21 C.F.R. § 10.30, the American College of Obstetricians and Gynecologists, Society of Family Planning, and Society for Maternal-Fetal Medicine submit this petition, together with an appendix of supporting studies and documents, to request that the Food and Drug Administration ("FDA"): (1) remove the Mifepristone Shared System Risk Evaluation and Mitigation Strategy ("REMS"), including all of its Elements to Assure Safe Use ("ETASU"); or (2) in the alternative, at a minimum, refrain from taking any action that would further reduce patient access to mifepristone[1] and/or increase the burdens associated with prescribing or dispensing mifepristone.

Over more than two decades, hundreds of medical studies and vast amounts of data have confirmed that mifepristone, in combination with misoprostol, is a safe and effective way to terminate an early pregnancy. The scientific evidence is overwhelming: major adverse events occur in ***less than 0.32%*** of patients.[1] The risk of death is almost non-existent. Few drugs have been so extensively studied after their approval by FDA and few can boast such a clear and compelling record of safe use. Access to mifepristone enables practitioners to provide safe, medically-appropriate, evidence-based, and effective care. Indeed, mifepristone, in combination with misoprostol, constitutes the most common form of abortion in the United States, accounting for nearly two out of every three abortions.

[1] Petitioners use "mifepristone" herein to refer to both Mifeprex (NDA 020687) and its generic (ANDA 091178).

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FDA itself determined in 2016, based on more than 2.5 million uses, that the drug's "efficacy and safety have become well established by both research and experience, and serious complications have proven to be extremely rare."[2] Yet, despite this record, FDA continues to subject mifepristone to unique regulatory requirements that impose burdens on health care providers and hamper patients' access to this medication. Particularly in light of rising maternal mortality across the country, access to mifepristone is a crucial component of comprehensive reproductive health care. Leading medical associations agree that, given mifepristone's outstanding safety record and its critical importance for reproductive health care, it is past time for FDA to fully lift the mifepristone REMS.[3] Consistent with this medical community consensus, Petitioners respectfully request that FDA eliminate its existing medically unnecessary barriers to mifepristone, or at minimum, take no further steps that would reduce access to this safe, essential medication.

ACTION REQUESTED

Petitioners request that FDA remove the Mifepristone Shared System REMS Program, including but not limited to the three ETASU requiring prescriber certification, pharmacy certification, and a patient agreement form. In the alternative, Petitioners request that FDA, at a minimum, take no action imposing greater burdens on patient access to mifepristone, and no action increasing burdens on the health care system relating to the provision of mifepristone, including but not limited to (a) adding new ETASU, (b) reinstating former mifepristone ETASU that are not currently part of the January 2023 REMS, (c) making the existing ETASU more onerous, or (d) modifying the REMS or labeling for mifepristone in a manner inconsistent with prevailing standards of evidence-based care.

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STATEMENT OF GROUNDS

A. Mifepristone is extremely safe

Twenty-five years ago, FDA approved mifepristone (under the brand name Mifeprex) as part of a two-drug regimen for medication abortion.[4] In that regimen, which now is FDA-approved through ten weeks of pregnancy, mifepristone blocks a hormone necessary to sustain pregnancy, and misoprostol causes contractions and bleeding that empty the uterus.[5] As of December 31, 2024, approximately 7.5 million U.S. patients had used this regimen for medication abortion.[6] High-quality studies also support the use of mifepristone with misoprostol specifically for managing early pregnancy loss.[7]

While all abortion is very safe, FDA acknowledges that medication abortion with mifepristone provides a "meaningful therapeutic benefit" to some patients and may be "preferable and safer in [a patient's] particular situation."[8] Some patients, for instance, who have been the victims of rape or sexual assault may prefer to avoid the use of medical instruments in a procedural abortion; others may have uterine abnormalities that are contraindications for procedural abortion; still others may use medication abortion to avoid the risks of any anesthesia or sedation associated with abortion procedures.

As is the case for all drugs sold in the United States, the FDA-approved labeling for mifepristone warns of the drug's risks.[9] For mifepristone, the boxed warning in the labeling lists: "serious and sometimes fatal infections or bleeding," both of which FDA accurately described in 2016 as "exceedingly rare, generally far below 0.1% for any individual adverse event."[10] As the labeling makes plain, these risks arise whenever the pregnant uterus is evacuated, whether by "miscarriage, surgical abortion, medical abortion, or childbirth."[11] The labeling confirms: "[n]o causal relationship between the use of [Mifepristone tablets 200mg] and misoprostol and [serious infections and bleeding] has been established."[12] Indeed, FDA concluded in 2016 that the "critical

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risk factor" for certain rare serious infections following mifepristone use "[wa]s pregnancy itself," not the medication.[13] After nearly 25 years of mandatory reporting of deaths potentially associated with mifepristone, the associated fatality rate is 0.00048%—and not one of the infinitesimally small number of deaths can be "causal[ly]" attributed to mifepristone.[14]

Mifepristone is as safe or safer than common drugs like Tylenol, Viagra, and penicillin—some of which are sold without a prescription and none of which has a REMS.[15] And mifepristone is far safer than hundreds of opioid analgesics that are subject to *less stringent* ETASU than mifepristone, even as opioids claim lives at such "a staggering rate" that they are "reducing life expectancy in the United States."[16]

B. Mifepristone's safety profile has remained strong and stable even after FDA removed certain medically unnecessary restrictions

Mifepristone's safety record has remained remarkably stable since FDA's original approval in 2000, including after FDA lifted some of its initial restrictions on the drug.

Since acknowledging in 2016 that mifepristone's safety profile is "well-characterized" and "has not changed over the period of surveillance,"[17] FDA has made three principal changes to the mifepristone REMS: (1) in 2016, FDA allowed all health care professionals with prescriptive authority under state law to become certified prescribers; (2) that same year, FDA eliminated the requirement that prescribers report serious adverse events potentially associated with mifepristone other than death; and (3) in 2021, FDA suspended and then, in 2023, permanently lifted the requirement that mifepristone be dispensed to patients only in person at a hospital, clinic, or medical office. In addition, in 2016, FDA made numerous changes to mifepristone's labeling, including updating the dosing and the route of misoprostol administration, removing the indication for multiple follow-up visits, and changing the gestational age indication from 49 days to 70 days.

There is no evidence that eliminating any of the former REMS restrictions (or changing

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the label indications) reduced mifepristone's safety.[18] To the contrary, and as further detailed below, high-quality research and real-world data from both the United States and globally confirm that mifepristone remains one of the safest medications used in medical practice.[19]

1. Mifepristone is safe when prescribed and dispensed by qualified advanced practice clinicians

In 2016, FDA correctly concluded that advanced practice clinicians ("APCs") with prescriptive authority under state law could safely prescribe and dispense mifepristone. When FDA implemented this change, it relied upon three randomized controlled studies[20] and one comparative study[21] to support the conclusion that medication abortion is safe and effective when provided by APCs.[22] The success rates for medication abortions provided by APCs were greater than 96% across all the studies, and were similar to the success rates for physician-prescribed abortions.[23]

Since then, additional high-quality, peer reviewed studies further confirm FDA's 2016 finding that mifepristone remains safe and effective when prescribed and dispensed by qualified nonphysicians. A comprehensive, peer-reviewed review of the safety and effectiveness of medication abortion, conducted by the National Academies of Science, Engineering, and Medicine—an independent organization dedicated to providing objective expert advice on scientific, engineering and medical issues to inform public policy—concluded that "both trained physicians (OB/GYNs, family medicine physicians, and other physicians) and advanced practice clinicians (APCs) (physician assistants, certified nurse-midwives, and nurse practitioners) can provide medication and aspiration abortions safely and effectively."[24] A retrospective observational cohort study of medication abortion between 2009 to 2018 concluded that the safety and effectiveness of APC-provided medication abortion are within the established medical benchmarks.[25] And in the event that uterine aspiration is needed to complete the evacuation of a patient's uterus, studies show that the very low complication rate for aspiration procedures is "not

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significantly different" whether performed by an APC or by a doctor.[26] The latter finding is consistent with research comparing the safety of aspiration abortion procedures when performed by physicians and APCs.[27]

Moreover, rescinding the ability of APCs to prescribe mifepristone would burden patient access by reducing the number of certified prescribers without increasing safety or efficacy.[28] And the burden would fall most heavily on underserved rural and remote populations.[29] Given the significant data showing that APCs offer improved access without compromising safety or efficacy, there is no reason for FDA to restrict the ability of APCs to provide medication abortions where permitted by state law.

2. The elimination of the in-person dispensing ETASU did not impact the safety of mifepristone

Telehealth for medication abortion is now a standard method of providing abortion care in the United States and around the world.[30] As in other areas of medicine provided by telehealth, reproductive health clinics and providers have developed specific protocols and technologies for telehealth care to ensure adequate patient contact and monitoring, such as health questionnaires, specialized patient platforms (*e.g.*, a patient "portal"), messaging and chat functions, and phone or video calls, all of which enable care to be provided with fewer or no in-person visits.

Critically, telehealth protocols for medication abortion offer the same patient protections as in-person dispensing and provide an equivalent level of patient care. Just as would happen during in-person care, patients are evaluated by a clinician who screens the patient to confirm pregnancy (relying on, *e.g.*, medical history, self-reported symptoms, and results of an at-home pregnancy test), assesses the duration of pregnancy, and identifies contraindications such as a potential ectopic pregnancy or other medical conditions or drug allergies.[31] Where clinically appropriate, the patient is advised to obtain in-person testing before proceeding.[32]

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After the patient's eligibility for medication abortion has been confirmed and the patient has provided informed consent, the clinician either sends the appropriate medications to the patient directly or transmits a prescription to a mail-order or retail pharmacy.[33] And just as would happen during in-person care, the clinician advises the patient about follow-up care, including instructions for confirming that the pregnancy has terminated and what to do if they experience signs and symptoms of complications.[34] The percentage of patients that visit an emergency room for *any* abortion-related reason is exceedingly small,[35] and, as detailed below, the manner in which mifepristone is prescribed or dispensed does not alter its safety profile.

a. *Telehealth medication abortion is safe and effective*

After reviewing (a) REMS assessment data, (b) data from FDA's Adverse Event Reporting System ("FAERS") during the period when the in-person dispensing ETASU was not being enforced during the COVID-19 pandemic, and (c) numerous published studies, FDA concluded in December 2021 that "mifepristone will remain safe and effective for medication abortion if the in-person dispensing requirement is removed."[36] Specifically, FDA's analysis relied upon six studies that "generally support a conclusion that dispensing by mail is safe."[37] FDA stated that it would permanently remove the in-person dispensing requirement to "render the REMS less burdensome to healthcare providers and patients," enabling prescribers to provide medication abortion by telehealth where permitted by state law.[38] FDA formalized that change when it published the updated REMS in January 2023.

FDA's decision to eliminate this ETASU was strongly supported by the scientific evidence available as of December 2021. Research published since then further confirms that direct-to-patient telemedicine for medication abortion is safe and effective.[39]

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For instance, a peer-reviewed study of over 6,000 telehealth patients in 20 states and Washington DC treated by three different online clinics between April 2021 and January 2022 found that "telehealth for abortion is effective and safe, with [safety and efficacy] rates similar to in-person care."[40] This study evaluated both "synchronous" telehealth care (where the provider communicates with the patient either by video or phone call) and "asynchronous" telehealth care (where the communication is by text message),[41] and further found that both "synchronous and asynchronous care are comparably effective and safe."[42] Specifically, the rates for both serious adverse events (0.25%) and ectopic pregnancy (0.14%) were "similar to previous studies of in-person medication abortion care," published in 2013 to 2015, which had found adverse event rates of 0.2–0.5%, and ectopic pregnancy rates of 0.2%.[43]

Other high-quality studies have come to similar conclusions. For instance, one study that compared in-person medication abortion care with telehealth care without in-person diagnostic or screening tests concluded that "medication abortion [performed through] telehealth screening and mail-order pharmacy dispensing of medications was associated with similar rates of complete abortion as in-person care with ultrasonography, met the prespecified threshold for noninferiority, and had low rates of [adverse events] overall."[44] A smaller study of medication abortion in primary care settings found that medication abortion provided by telehealth was "as effective, timelier and potentially more accessible than in-clinic care."[45] Another study comparing abortion outcomes between screening approaches across five telehealth sites showed no difference in serious adverse events between patients who received pre-abortion ultrasound or pelvic exams and those who did not.[46] And a systematic review and meta-analysis of the literature on medication abortion by telehealth confirms that telehealth abortion care is as safe and effective as in-person care, with a "shorter waiting time for medication delivery."[47]

All of these studies confirm that FDA was correct in determining that removal of the in-person dispensing requirement did not impact the safety and effectiveness of medication abortion.

b. *Telehealth for medication abortion improves access to care with high patient satisfaction*

At the same time, research also confirms that the availability of medication abortion by telehealth improves patient access to mifepristone and reduces burdens on the health care delivery system while maintaining or improving patient satisfaction. Accordingly, any reversion to an in-person dispensing requirement would burden patient access and the health care system, contrary to the statutory standards that govern FDA's imposition of ETASU. *See* 21 U.S.C. § 355-1(f)(2).

Telehealth increases access to abortion care by eliminating the need to travel to a health care provider. Thus, it offers a particular benefit for patients living in rural and medically underserved areas where there is no access to in-person abortion care,[48] as well as for patients who find it challenging to take time off from work or arrange for childcare in order to travel for abortion care.[49] Without associated travel, patients do not have to incur any expenses for transportation, gas, and lodging, incur fewer expenses for child care, and lose fewer wages.[50] In other words, telehealth eliminates or mitigates many of the burdens that can deter and delay abortion access for the low-income populations that comprise a majority of abortion seekers.[51] Telehealth also reduces delays in obtaining care because it enables patients to avoid long wait times at physical clinics[52]—a particularly urgent concern since *Dobbs v. Jackson Women's Health Organization*, as state abortion bans have increased demand for abortion care in many states where abortion remains lawful.[53] Reinstating in-person dispensing—which would lead to even more in-person visits at brick-and-mortar clinics already stretched thin—would increase burdens on the health care system and impede patient access.

Even without considering the time and expense of having to travel for abortion care, medication abortion care is typically more affordable for patients when provided through telehealth than through in-person care.[54] In 2023, pricing data collected from brick-and-mortar clinics that offered both in-person and telehealth care revealed that they were able to offer telehealth abortion services at a lower rate than in-person medication abortion services.[55] Given the longstanding prohibition on using federal funds to pay for abortion, managing the cost of abortion care is essential to ensure that patients with fewer resources are able to access the care they need.

In general, telehealth offers many opportunities for patients and providers to build trust and rapport—and that observation holds true in the context of medication abortion. In a qualitative study of 1,600 patients who received abortion care through telemedicine, "nearly all participants were very satisfied with telehealth abortion," with 98% of those surveyed reporting that they trusted their provider.[56] Patients further reported that choosing telehealth not only made abortion care more accessible, but also allowed them to receive care more quickly and with greater privacy in the comfort of their own home.[57]

Studies also show that telehealth abortion care offers patients other significant advantages. In a survey of medication abortion patients, those who received services by telehealth felt that the option "allowed them to talk more freely and openly, and feel more confident about the privacy of their abortion decision."[58] Indeed, a recent qualitative study of telehealth patients found that telehealth mitigates some manifestations of abortion stigma by eliminating the need to visit a physical clinic and thus reducing the visibility of one's abortion decision.[59] This benefit is all the more essential given increased rates of anti-abortion violence and harassment at brick-and-mortar clinics—violence and harassment specifically designed to deter or prevent access to reproductive

care.[60] In short, depriving mifepristone patients of the telehealth option would impede patient access in violation of FDA's congressional mandate not to impede access.

3. Evidence supports FDA's elimination of non-fatal mandatory adverse event reporting for mifepristone

FDA determined in 2016 that it was unnecessary to require prescribers of mifepristone to report non-fatal adverse events following the use of mifepristone given mifepristone's stable risk profile reflected in 15 years of mandatory serious-adverse-event reporting.[61] Since then, multiple data sources confirm that mifepristone continues to be extremely safe. FDA correctly lifted the broad adverse-event reporting requirement in 2016, and the ongoing requirement that mifepristone prescribers report the miniscule number of deaths following mifepristone use is extraneous.

First, FDA continues to collect data on adverse events for mifepristone through multiple data sources, including FAERS and case reports in published medical literature, just as it does for other drugs. *See* 21 U.S.C. § 355(k); 21 C.F.R. §§ 314.80, 314.81. FDA regularly relies upon stable FAERS data in determining whether a REMS may be removed.[62] Second, the medical literature shows an adverse event rate for mifepristone when prescribed pursuant to updated standards of evidence-based care, and in the absence of prior REMS requirements, that is comparable to the real-world clinical data reported to FDA prior to 2016. For example, a recent large prospective cohort study of over 6,000 patients who obtained medication abortion by telehealth had a serious adverse event rate of only 0.25%, comparable to the rate for in-person care included in the mifepristone labeling based on pre-2016 studies.[63] In other words, there is no reason to believe that the complication rate materially changed following the elimination of the pre-2016 adverse event reporting requirement. And, given the infinitesimal death rate associated with (and not proven to be caused by) mifepristone after millions of uses and decades of mandatory reporting, there is likewise no reason to maintain this special REMS reporting requirement.

C. A REMS is not necessary to ensure that mifepristone's benefits outweigh its risks, and the mifepristone ETASU do not fit the statutory profile

Given mifepristone's safety, FDA has not gone far enough in eliminating burdensome, medically unnecessary restrictions on this safe medication. As detailed below, the prescriber certification, patient agreement, and pharmacy certification ETASUs do not enhance safety—but *do* impede patient access and burden the health care delivery system. Indeed, FDA still regulates mifepristone more stringently than nearly any other of the 20,000 drugs it regulates. Unlike the 97% of prescription drugs without a REMS—including, to take just two examples, Viagra (with a fatality rate six-times that of mifepristone) and Jeuveau (a drug that temporarily improves the appearance of wrinkles and whose labeling features a black-box warning of "life threatening" breathing difficulties)—mifepristone is among the tiny fraction of medications subject to such regulation, alongside highly addictive and dangerous opioids.

A REMS is not necessary for mifepristone under the statutory scheme Congress has mandated to guide FDA's balancing of a medication's risks and benefits. Specifically, a REMS is permitted only if "necessary to ensure that the benefits of [a] drug outweigh [its] risks…." 21 U.S.C. § 355-1(a)(1); *accord id.* § 355-1(g)(4)(B)(i). Among other factors, Congress directed FDA to consider the "seriousness of any known or potential adverse events" and "the background incidence of such events in the population likely to use the drug, *id*.—a particularly meaningful consideration here since the serious adverse events associated with mifepristone are risks of "pregnancy itself."[64] Congress further limited FDA's authority to impose ETASU, permitting them only where "necessary to assure safe use of the drug, because of its inherent toxicity or potential harmfulness," and only where "required as part of [a] strategy to mitigate a specific serious risk listed in the labeling of the drug." 21 U.S.C. §355-1(f)(1). Moreover, ETASU may be imposed only when they are "commensurate with the specific serious risk[s] listed in the labeling"; must,

"to the extent practicable," "conform with [ETASU] for other drugs with similar, serious risks"; and may "not be unduly burdensome on patient access," "considering in particular … patients who have difficulty accessing health care (such as patients in rural or medically underserved areas)." *Id.* §355-1(f)(1)-(2). Petitioners respectfully submit that the mifepristone REMS and ETASU do not meet these statutory requirements.

1. Prescriber Certification

The Prescriber Certification ETASU requires would-be prescribers to fax a form to the drug distributor attesting that they can date a pregnancy and diagnose an ectopic pregnancy; can ensure patient access to a uterine evacuation procedure in cases of incomplete abortion or severe bleeding and to medical facilities equipped to provide blood transfusions and resuscitation if necessary; and have read and understood the prescribing information. Clinicians also agree to review the Patient Agreement with the patient, answer the patient's questions, obtain a signature, retain the signed form, and provide the patient a copy; and (as discussed in Section B.3, above), to report any patient deaths to the drug sponsor. As of 2023, this ETASU also requires clinicians to fulfill certain obligations if a pharmacy will dispense the mifepristone, including providing the pharmacy with their signed Prescriber Certification form and communicating directly with the pharmacy if the pharmacy cannot ensure delivery within four calendar days.

For 99.5% of the over 20,000 prescription drugs it regulates, FDA does not impose a prescriber certification ETASU.[65] This is true even for drugs that, unlike mifepristone, require diagnostic tests or special screening before they can be safely prescribed. FDA has retained the Prescriber Certification ETASU because it assumes that certification is necessary to assure that only qualified providers will prescribe mifepristone.[66] The facts, however, show otherwise. For instance, in 2017, Canada removed its REMS-like requirements, which included a prescriber certification requirement. While eliminating those restrictions significantly increased access to

mifepristone, it had no negative impact on mifepristone's safety or efficacy.[67]

Contrary to FDA's assumption, the Prescriber Certification ETASU is unnecessary to assure that health care professionals prescribe mifepristone only when competent to do so because *all* clinicians are ethically obligated to provide only medically necessary and appropriate care within the scope of their training and competence.[68] There are countless medications not subject to a Prescriber Certification ETASU that can be safely prescribed only when the clinician makes a proper diagnosis, screens for contraindications, and provides instructions for any necessary follow-up or emergency care—and there is nothing unique about prescribing mifepristone that makes this burdensome ETASU necessary. To the contrary, as Petitioner ACOG noted in a letter to FDA nearly a decade ago, "[a] standard clinical license should be sufficient to ensure that a practitioner meets qualifications for prescribing mifepristone."[69] Nor is it necessary to assure that a health care professional will obtain a patient's informed consent for mifepristone when medical ethics and professional guidelines already require informed consent as an essential practice across all areas of medicine, including abortion care.[70] Indeed, FDA has recognized that there is "strong adherence to evidence-based guidelines" by clinicians who provide abortion care.[71]

The Prescriber Certification ETASU also impedes patient access to mifepristone by chilling a health care provider's decision to offer this medication. Nearly one in ten OBGYNs responding to a survey of Petitioner ACOG's members were deterred from prescribing mifepristone because of the requirement that they register with the drug sponsor.[72] A qualitative survey of family practitioners concluded that removal of the in-person dispensing requirement would not eliminate the distinct deterrent effect of prescriber certification on would-be prescribers.[73]

It is well-documented that many would-be prescribers do not register to prescribe mifepristone because they fear anti-abortion threats and violence if their registrations became

public.[74] Moreover, the Pharmacy Certification ETASU requires prescribers to send their certification form to every pharmacy that will dispense mifepristone to their patients and requires the pharmacy to keep that form on file. Notwithstanding the important confidentiality safeguards contained in the Pharmacy Certification's ETASU requirement, this protocol multiplies the possibility of a data breach and amplifies providers' concerns for their safety and the safety of their families. In the aftermath of the *Dobbs* decision, acts of anti-abortion violence and harassment have increased dramatically in states where abortion access is protected by state law.[75] The Prescriber Certification ETASU persists in deterring providers from prescribing mifepristone and impeding patient access.

2. Pharmacy Certification

The Pharmacy Certification ETASU is largely a means of enforcing the Prescriber Certification requirement by "ensur[ing] that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers."[76] As detailed above, there is no valid reason for maintaining Prescriber Certification, undermining any justification for this derivative ETASU. Meanwhile, the Pharmacy Certification ETASU compounds the burdens on providers and the health care delivery system. As Petitioners and other commenters have previously warned, the extra costs and administrative burdens that this ETASU imposes on pharmacies disincentivizes pharmacies from dispensing mifepristone—an assessment that FDA seemingly shared when it found that the Pharmacy Certification would "likely limit" "pharmacies choosing to certify."[77]

Critically, FDA has not reckoned with the significant burdens the Pharmacy Certification ETASU imposes on patients—particularly those who already face significant obstacles in obtaining needed health care—despite a statutory requirement to assess those burdens. *See* 21 U.S.C. §355-1(f)(2)(C)(ii). First, the strong disincentivizing effect of the ETASU on brick-and-mortar pharmacies leaves telehealth patients dependent on mail-order (*i.e.*, online) pharmacies to

access mifepristone. While it is critical that patients retain the option to have their mifepristone mailed to them, this model does not work for everyone, as Petitioners' members see in their practices. Individuals who lack stable housing may not have a physical address to which a package can be securely and confidentially mailed. Patients experiencing abuse in their household may not be able to rely on mail delivery if they need to keep their pregnancy and abortion decision confidential for their own safety. Patients who lack facility with computers[78] or who lack reliable internet access, such as those living in rural areas, are more likely to depend on neighborhood retail pharmacies to access mifepristone. In such situations, the inability to use an online pharmacy may impede access altogether.

Moreover, the Pharmacy Certification ETASU places significant burdens on the health care delivery system by, for example, mandating that pharmacies either ensure delivery to the patient within four days of receiving the prescription or contact the prescriber to confirm that later delivery is acceptable. In their discussions with FDA, the drug sponsors noted that this means a default of "two-day or next day shipping," and noted concerns about the resulting "affordability of shipping services."[79] Indeed, this four-day requirement makes expedited delivery the default option—effectively increasing shipping costs for all patients—even when delivery on a longer timeline is clinically appropriate. To be sure, Petitioners are deeply invested in ensuring timely access to health care. But mifepristone is no different from the countless other time-sensitive medications dispensed through pharmacies without a Pharmacy Certification ETASU mandating such deadlines.[80] As the sponsors made clear, "the professional practice of pharmacy requires that pharmacies promptly dispense products to patients upon receiving the prescription or swiftly communicate with the patient and prescriber if that is not possible within the appropriate clinical window."[81] And FDA found no increase in adverse events when mail-order pharmacies dispensed

mifepristone during the COVID-19 pandemic with no delivery-date mandate.[82] At bottom, while timely access to health care is certainly critical, it is not in mifepristone patients' best interests for FDA to impose delivery restrictions that needlessly increase the cost of abortion care and deter pharmacies from dispensing this medication.

Additionally, the Pharmacy Certification ETASU means that prescribers cannot simply issue a prescription to the patient's preferred pharmacy location, as they do with virtually all other medications (including other time-sensitive medications). Instead, they have to contact any pharmacy their patients may seek to use in order to identify one that is certified to dispense mifepristone. As a practical matter, since so few pharmacies are certified, the Pharmacy Certification ETASU results in additional burdens and delay.

3. Patient Agreement

The Patient Agreement ETASU requires the patient to sign an FDA-approved form stating that they are taking mifepristone because they have "decided ... to end [their] pregnancy," that they will follow a particular clinical protocol, and that they understand when and how to seek follow-up or emergency care. Notably, in 2016, FDA's own scientific review team determined that this ETASU was "duplicative" of the Medication Guide that every patient receives and "does not add to safe use conditions" and, accordingly, recommended its elimination.[83] However, FDA's Commissioner at the time overrode the review team's recommendation, leading FDA to maintain this ETASU.[84]

In choosing to again retain this requirement in 2023, FDA speculated that *new* mifepristone prescribers might not provide appropriate counseling and obtain informed consent absent the Patient Agreement ETASU.[85] FDA's speculation, however, cannot be reconciled with the Agency's recognition that, in general, "informed consent in medicine is an established practice."[86] As noted above in Section C.1, informed consent is part of the professional guidelines governing abortion

care.[87] And, as FDA recognizes, the "same risk information" contained in the Patient Agreement is contained in the Medication Guide that all patients receive.[88] FDA did not identify any evidence suggesting that new prescribers of mifepristone would shirk these professional norms; in fact, the Agency routinely approves entirely new drugs without a patient agreement ETASU, even though every prescriber will be unfamiliar with that new medication. This evidence justifies "remov[ing] this REMS requirement[] . . . based on the integration of the REMS safe use condition into clinical practice,[89] as the Agency has done for other drugs.

FDA acknowledged in 2016 that the Patient Agreement ETASU "is a burden for patients."[90] It can also be a burden for qualified health care providers who seek to prescribe mifepristone, since they often must struggle with administrative complexities associated with integrating the Patient Agreement form into existing clinical record systems.[91] In the course of its reviews of the mifepristone REMS, the Agency has never explained why it believes this ETASU's burdens are essential to ensure that mifepristone's benefits outweigh its risks.

D. FDA should have reviewed *all* relevant data in its most recent REMS review

During FDA's most recent REMS review, FDA excluded from consideration information that was directly relevant to the Agency's statutory obligation to ensure that an ETASU is "not … unduly burdensome on patient access" (especially for those patients in "rural or medically underserved areas"), as well as the requirement that FDA "minimize the burden on the health care delivery system" when imposing ETASU. 21 U.S.C. §§ 355-1(f)(2)(C), (D).[92] That information included input from Petitioners and other associations of health care professionals on the burdens imposed by the REMS, as well as "[d]ata on the logistics of accessing abortion care in general, such as time to appointment or the distance traveled to obtain care."[93]

These exclusions prevented FDA from accurately assessing the burdens that the mifepristone ETASU impose on patient access and the health care system. Petitioners respectfully

submit that this was a significant misstep, which deprived FDA of information directly relevant to the applicable statutory requirements. Petitioners therefore urge FDA to revisit this highly relevant evidence from 2022 or earlier as well as the more recent evidence cited above confirming that mifepristone remains extremely safe and effective after FDA's 2016 and 2023 changes to the REMS and mifepristone label and that those regulatory updates reduced needless burdens.

E. In the alternative, and at an absolute minimum, FDA must maintain the status quo with respect to mifepristone

At the very minimum, based on the evidence detailed above of mifepristone's ongoing safety and efficacy, there is no medical basis to further restrict access beyond the status quo as of January 2023 by, for instance, reinstating any previously withdrawn ETASU; increasing the burdens of the existing ETASU; imposing a new ETASU; or modifying the mifepristone labeling to be inconsistent with prevailing standards of evidence-based care. As discussed in Section B, numerous high-quality studies show that mifepristone's safety profile remained strong and stable even after FDA removed the special non-fatal adverse-event reporting requirement, permitted APCs to independently prescribe mifepristone where permitted by state law, and eliminated the in-person dispensing requirement. To be sure, anti-abortion activists have pointed to other publications in support of their efforts to reinstate previous, superseded ETASU, such as the five articles attached to the complaint in *Alliance v. Hippocratic Medicine*, No. 2:22-cv-00223-Z (N.D. Tex.). But as FDA recognized at the time, none of these articles contains "safety data relevant to" the removal of the in-person dispensing requirement.[94]

Conversely, the evidence is clear that reinstating the prior ETASU would impede patient access. For example, one recent study found that telehealth plays an "instrumental role in obtaining an abortion among patient populations who are known to face the most structural barriers to abortion care," particularly "those residing in rural areas, and those who resided far from an

abortion facility."[95] Reinstating the prior ETASU would demonstrably impede patient access, particularly for "patients who have difficulty accessing health care," in violation of the statutory command of 21 U.S.C. § 355-1(f)(2).

ENVIRONMENTAL IMPACT

Petitioners' proposal is categorically exempt from the requirement of an environmental impact statement under 21 C.F.R. § 25.31(a) or 21 C.F.R. § 25.31(b).

ECONOMIC IMPACT

No information required at this time.

CERTIFICATION

Petitioners certify that, to the best of our knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Signed:

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[1] Ushma D. Upadhyay et al., *Incidence of Emergency Department Visits and Complications After Abortion*, 125 Obstetrics & Gynecology 175, 181 (2015) (study of nearly 55,000 abortions found a major complications rate of 0.31% for medication abortion).

[2] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., No. 020687Orig1s020, Mifeprex Medical Review(s) 1, 12 (Mar. 29, 2016).

[3] Am. Coll. of Obstetricians & Gynecologists et al., *Leading Medical Organizations Call for the FDA to Permanently Remove Restrictions on Mifepristone* (June 18, 2024), https://www.acog.org/news/news-releases/2024/06/leading-medical-organizations-call-for-fda-to-permanently-remove-restrictions-on-mifepristone.

[4] U.S. Food & Drug Admin., Mem. re approval action concerning NDA 20-687 MIFEPREX (mifepristone) 1, 1-8 (Sept. 28, 2000).

[5] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., U.S. Food & Drug Admin., Joint Summary Review for Mifepristone REMS, at 4 (Jan. 3, 2023); World Health Org., *Medical Management of Abortion*, at 1 (2018).

[6] U.S. Food & Drug Admin., NDA 020687 & ANDA 091178, Mifepristone U.S. Post-Marketing Adverse Events Study through 12/31/2024 (2025).

[7] Courtney A. Schreiber et al., *Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss*, 378 N. Eng. J. Med. 2161 (2018); Justin J. Chu, et al., *Mifepristone and misoprostol versus misoprostol alone for the management of missed miscarriage (MifeMiso): a randomised, double-blind, placebo-controlled trial*, 396 Lancet 770 (2020).

[8] Janet Woodcock, M.D., Dir., Ctr. for Drug Evaluation & Rsch., Citizen Petition Denial, at 5 (Mar. 29, 2016); *see also* Am. Coll. of Obstetricians & Gynecologists & Soc'y of Family Planning, Prac. Bull. No. 225, *Medication Abortion Up to 70 Days of Gestation*, 136 Obstetrics & Gynecology 1 (Oct. 2020, *reaff'd* 2023); Nathalie Kapp & Patricia A. Lohr, *Modern methods to induce abortion: Safety, efficacy and choice*, 63 Best Prac. & Rsch. Clinical Obstetrics & Gynaecology 37 (2020); World Health Org., *Medical Management of Abortion* (2018); Elizabeth G. Raymond & David A. Grimes, *The Comparative Safety of Legal Induced Abortion and Childbirth in the United States*, 119 Obstetrics & Gynecology 215 (2012).

[9] U.S. Food & Drug Admin., Development & Approval Process (Aug. 8, 2022), https://www.fda.gov/drugs/development-approval-process-drugs.

[10] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Research, Application No. 020687Orig1s020 Medical Review(s), at 47 (Mar. 29, 2016).

[11] Mifepristone 2023 Labeling and Medication Guide, at 16.

[12] Mifepristone 2023 Labeling and Medication Guide, at 2, 5.

[13] Janet Woodcock, M.D., Dir., Ctr. for Drug Evaluation & Rsch., U.S. Food & Drug Admin., Citizen Petition Denial, at 25-26 (Mar. 29, 2016).

[14] Mifepristone 2023 Labeling and Medication Guide, at 1-2, 5; U.S. Food & Drug Admin., NDA 020687 & ANDA 091178, Mifepristone U.S. Post-Marketing Adverse Events Study through 12/31/2024 (2025) (36 reported deaths after approximately 7.5 million uses of mifepristone for medical termination of pregnancy).

[15] Nat'l Acad. of Sci., Eng'g & Med., *The Safety & Quality of Abortion Care in the United States*, at 79 (2018) (risks of mifepristone are "similar in magnitude" to "antibiotics and NSAIDs"); Advancing New Standards in Reprod. Health, UCSF, *Analysis of Medication Abortion Risk and the FDA report "Mifepristone U.S. Post-Marketing Adverse Events Summary through 12/31/2022,"* Issue Brief, at 3 (May 2024) (Viagra and penicillin have fatality rates "several times higher" than mifepristone); Gregory Lowe, et al., *10-Year analysis of adverse event reports to the Food and Drug Administration for phosphodiesterase type-5 inhibitors* 9 J. of Sexual Med. 265 (2012) (fatality rates for Viagra); Alfred Neugut, et al., *Anaphylaxis in the United States: an investigation into its epidemiology*, 161 Archives of Internal Med. 15 (2001) (fatality rates for penicillin).

[16] U.S. Food & Drug Admin., *Opioid Medications*, (2021), https://www.fda.gov/drugs/information-drug-class/opioid-medications; U.S. Food & Drug Admin., *REMS Document*, *Opioid Analgesic REMS Program*, (2021),

https://www.accessdata.fda.gov/drugsatfda_docs/rems/Opioid_Analgesic_2021_04_09_REMS_Document.pdf; U.S. Food & Drug Admin., *Opioid Analgesic REMS*, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=17 (last updated Oct. 31, 2024) ("Products" tab).

[17] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., No. 020687Orig1s020, Mifeprex Medical Review(s), at 88 (Mar. 29, 2016).

[18] *See, e.g.*, U.S. Food & Drug Admin., REMS Modification Rationale Review (Dec. 16, 2021), at 12 (noting that the results of two pre-2016 studies "not captured in [FDA's] 2016 literature search . . . are consistent with the existing safety profile of the approved medical abortion regimen."); *id*. at 21-22 (finding "no new safety concerns with the use of mifepristone for medical termination of pregnancy" between January 2020 and September 2021 based on data from the FDA Adverse Event Reporting System or the "published medical literature"); U.S. Food & Drug Admin., *Pharmacovigilance Memorandum: Mifepristone, All Adverse Events* (Apr. 12, 2022) at 6 (same as to period from October 2021 to December 2022).

[19] *See. e.g.*, Laura Schummers et al., *Abortion Safety and Use with Normally Prescribed Mifepristone in Canada*, 386 New Eng. J. Med. 57, (2022) (in Canada, lifting all REMS-like restrictions resulted in no change to mifepristone's safety profile); Ushma Upadhyay et al., *Effectiveness and Safety of Telehealth Medication Abortion in the United States*, 30 Nature Medicine 1191, 1191 (2024) (in US, "[t]elehealth medication abortion is effective, safe and comparable to safety and efficacy of in-person medication abortion care.").

[20] Claudia D. Olavarrieta et al., *Nurse versus physician-provision of early medical abortion in Mexico: a randomized controlled non-inferiority trial*, 93 Bull World Health Org. 249 (2015); H. Kopp Kallner et al., *The Efficacy, Safety and Acceptability of Medical Termination of Pregnancy Provided by Standard Care by Doctors or by Nurse-Midwives*, 122 BJOG: Int'l J. Obstetrics & Gynecology 510 (2015); IK Warriner et al., *Can Midlevel Health-Care Providers Administer Early Medical Abortion as Safely and Effectively as Doctors? A Randomised Controlled Equivalence Trial in Nepal*, 377 Lancet 1155 (2011).

[21] Mahesh Puri et al., *The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal*, 22 Reprod. Health Matters 94 (2015).

[22] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Research, Application No. 020687Orig1s020 Cross Discipline Team Leader Review (Mar. 29, 2016), at 16-17.

[23] *Id*. at 17.

[24] Nat. Acad. Sci., Eng'g, & Med., *The Safety and Quality of Abortion Care in the United States* 1, 165 (2018).

[25] L. Porsch et al., *Advanced Practice Clinicians and Medication Abortion Safety: A 10-Year Retrospective Review*, 101 Contraception 357 (2020).

[26] Amy Levi et al., *Training in Aspiration Abortion Care*, 88 Int'l J. Nursing Studies 55, 57 (2018).

[27] Eva Patil et al., *Aspiration Abortion with Immediate Intrauterine Device Insertion: Comparing Outcomes of Advanced Practice Clinicians and Physicians*, 61 J. Midwifery & Women's Health 325 (2016).

[28] L. Porsch et al., *Advanced Practice Clinicians and Medication Abortion Safety: A 10-Year Retrospective Review*, 101 Contraception 357 (2020).

[29] Lydia Mainey, et al., *The Role of Nurses and Midwives in the Provision of Abortion Care: A Scoping Review*, 29 J. of Clinical Nursing 1513 (2020); Nat. Acad. Sci., Eng'g, & Med., *The Safety and Quality of Abortion Care in the United States* 1, 114-17 (2018).

[30] Am. Coll. Obstetricians & Gynecologists, *Medication Abortion Up to 70 Days of Gestation*, Practice Bulletin No. 225, at e35 (Oct. 2020, *reaff'd* 2023), https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2020/10/medication-abortion-up-to-70-days-of-gestation ("Medication abortion can be provided safely and effectively by telemedicine with a high level of patient satisfaction"); World Health Organization, Abortion Care Guideline, 95 (March 8, 2022), https://www.who.int/publications/i/item/9789240039483 (recommending the option of telemedicine to deliver medical abortion services).

[31] Elizabeth G. Raymond et al., *Commentary: No-Test Medication Abortion: A Sample Protocol Increasing Access During a Pandemic and Beyond*, 101 Contraception 361, 362 (2020).

[32] *Id*. at 362-63 (recommending in-person testing for patients with significant symptoms of or risk factors for ectopic pregnancy; recent vaginal bleeding or pelvic pain, prior permanent contraception, prior ectopic pregnancy, or intrauterine device in place at conception); *id*. at 363 (in a small number of cases, the clinician may advise the patient to obtain Rh testing for the purpose of determining whether treatment with Rh D immune globulin is appropriate); *see also* Am. Coll. Obstetricians & Gynecologists, *RhD Immune Globulin Administration After Abortion or Pregnancy Loss at Less Than 12 Weeks of Gestation*, Clinical Practice Update, at e140 (Dec. 2024) (suggesting that "Rh testing and RhIg administration can be considered on an individual basis" for patients at less than 12 weeks gestation and need not be performed routinely); Nat'l Abortion Fed., *Clinical Policy Guidelines for Abortion Care* at 12 (2024) ("Below 12 weeks from the last menstrual period, patients and providers may forego Rh testing and anti-D immune globulin for patients who are Rh negative").

[33] Elizabeth G. Raymond et al., *Commentary: No-Test Medication Abortion: A Sample Protocol Increasing Access During a Pandemic and Beyond*, 101 Contraception 361, 364 (2020); Alice Mark et al., *The Future Of Abortion Is Now: Mifepristone By Mail And In-Clinic Abortion Access In The United States*, 104 Contraception 38 (2021).

[34] Elizabeth G. Raymond et al., *Commentary: No-Test Medication Abortion: A Sample Protocol Increasing Access During a Pandemic and Beyond*, 101 Contraception 361, 363–64 (2020).

[35] Ushma Upadhyay et al., *Abortion-Related Emergency Department Visits in the United States: An Analysis of a National Emergency Department Sample*, 16 BMC Med. 1, 7-10 (2018). The majority of these visits involved "observation care only," likely because some patients do not appreciate that normal post-abortion symptoms include "ongoing uterine cramping and bleeding." *Id*. at 9.

[36] U.S. Food & Drug Admin., REMS Modification Rationale Review, NDA 020687 & 91178, at 39 (Dec. 16, 2021).

[37] *Id*. (referring to Holly A. Anger et al., *Clinical and Service Delivery Implications Of Omitting Ultrasound Before Medication Abortion Provided Via Direct-To-Patient Telemedicine And Mail In The U.S.*, 104 Contraception 659 (2021); Elizabeth Raymond et al., *TelAbortion: evaluation of a direct to patient telemedicine; abortion service in the United States*, 100 Contraception 173 (2019); Erica Chong et al., *Expansion of a direct-to-patient telemedicine abortion service in the United States and experience during the COVID-19 pandemic*, 104 Contraception 43 (2021); Daniel Grossman et al., *Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment*, 107 Contraception 36 (2021); Courtney Kerestes et al., *Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models*, 104 Contraception 49 (2021); Paul Hyland et al., *A direct-to-patient telemedicine abortion service in Australia: Retrospective analysis of the first 18 months*, 58 The Austl. & N.Z. J. of Obstetrics & Gynaecology 335 (2018); Courtney Kerestes et al., *Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models*, 104 Contraception 49 (2021); Paul Hyland et al., *A direct-to-patient telemedicine abortion service in Australia: Retrospective analysis of the first 18 months*, 58 The Austl. & N.Z. J. of Obstetrics & Gynaecology 335 (2018)).

[38] *Id*.

[39] *See, e.g*., Ushma Upadhyay et al., *Effectiveness and safety of telehealth medication abortion in the USA*, 30 Nature Med. 1191 (2024); Lauren J. Ralph et al., *Comparison of No-Test Telehealth and In-Person Medication Abortion*, 332 JAMA 898 (2024), https://jamanetwork.com/journals/jama/article-abstract/2820321; Silpa Srinivasulu et al., *Telehealth Medication Abortion in Primary Care: A Comparison to Usual in-Clinic Care*, 37 J. of the Am. Board of Fam. Med. 295 (2024).

[40] Ushma Upadhyay et al., *Effectiveness and safety of telehealth medication abortion in the USA*, 30 Nature Med. 1191, 1197 (2024).

[41] *Id*.

[42] *Id.* at 1197.

[43] *Id*. at 1194.

[44] Lauren J. Ralph et al., *Comparison of No-Test Telehealth and In-Person Medication Abortion*, 332 JAMA 898, 903 (2024).

[45] Silpa Srinivasulu et al., *Telehealth Medication Abortion in Primary Care: A Comparison to Usual in-Clinic Care*, 37 J. of the Am. Board of Fam. Med. 295, 299 (2024). While the study was too small to draw conclusions about safety, its safety data was "within the range of other studies evaluating complete abortion after [medication abortion] in primary care." *Id*. at 299.

[46] Holly A. Anger & Elizabeth G. Raymond, *Clinical and service delivery outcomes following medication abortion provided with or without pretreatment ultrasound or pelvic examination: An updated comparative analysis*, 140 Contraception 1 (2024); *see also* Lauren J. Ralph et al., *Comparison of No-Test Telehealth and In-Person Medication Abortion*, 332 JAMA 898 (2024).

[47] *See* Leonardo Cely-Andrade et al., *Telemedicine For The Provision Of Medication Abortion To Pregnant People At Up To Twelve Weeks Of Pregnancy: A Systematic Literature Review And Meta-Analysis*, 21 Reprod. Health 136, 155 (2024) (meta-analysis of 21 articles published between 2011 and 2022, concluding there are no significant differences in safety, effectiveness, or patient satisfaction when comparing telehealth to in-person abortion care).

[48] Leah R. Koenig et al., *The role of telehealth in promoting equitable abortion access in the United States: spatial analysis*, 9 JMIR Public Health Surveillance e45671 (2023).

[49] Amy Tressan et al., *Telemedicine Abortion in Primary Care: An Exploration of Patient Experiences*, 22 Annals of Fam. Med. 19 (2024) (Table 1); Rachel K. Jones, *Medicaid's Role In Alleviating Some Of The Financial Burden Of Abortion: Findings From The 2021-2022 Abortion Patient Study*, 56 Persp. on Sexual & Reprod. Health 244, 245 (2024) (fifty-five percent of abortion seekers had experienced a prior birth).

[50] Erica Chong et al., *Expansion of a direct-to-patient telemedicine abortion service in the United States and experience during the COVID-19 pandemic*, 104 Contraception 43, 44 (2021).

[51] Guttmacher Inst., *Abortion in the United States* (June 2024), https://www.guttmacher.org/fact-sheet/induced-abortion-united-states (stating that "[s]ome 41% of people obtaining abortions had an income below the federal poverty level (FPL) and 30% had incomes between 100% and 199% of the FPL").

[52] Andréa Becker et al., *"It Was So Easy in a Situation That's So Hard": Structural Stigma and Telehealth Abortion*, 0 J. of Health & Soc. Behav. 1 (2025).

[53] Rachel K. Jones et al., *The Number of Brick-and-Mortar Abortion Clinics Drops, as US Abortion Rate Rises: New Data Underscore the Need for Policies that Support Providers* (June 2024), https://www.guttmacher.org/report/abortion-clinics-united-states-2020-2024 (noting that "[s]ome states that share a border with one or more ban states absorbed the additional patients with little or no increase in the numbers of brick-and-mortar clinics between 2020 and March 2024").

[54] *See* Erica Munson & Kelli S. Hall, *Opportunities for Increasing Access to Person-Centered Abortion Care Through Telehealth*, 114 Am. J. of Public Health 152 (2024).

[55] Ushma Upadhyay et al., *Pricing of medication abortion in the United States, 2021–2023*, 56 Persp. on Sexual & Reprod. Health 282 (2024).

[56] Leah R. Koenig et al., *Patient Acceptability of Telehealth Medication Abortion Care in the United States, 2021-2022: A Cohort Study*, 114 Am. J. Pub. Health 241, 247-248 (2024) (Table 2).

[57] *Id*. at 248.

[58] Emily M. Godfrey et al., *Patient Perspectives Regarding Clinician Communication During Telemedicine Compared With In-Clinic Abortion*, 141 Obstetrics & Gynecology 1139, at 1143 (2023).

[59] Andréa Becker et al., *"It Was So Easy in a Situation That's So Hard": Structural Stigma and Telehealth Abortion*, 0 J. of Health & Social Behav. 1 (2025).

[60] Nat'l Abortion Fed., *2022 Violence & Disruption Statistics Report* at 9, 11(2023).

[61] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., No. 020687Orig1s020, Mifeprex Medical Review(s), at 88 (Mar. 29, 2016).

[62] *See, e.g.*, U.S. Food & Drug Admin., Lotronex (alosetron hydrochloride) Information at 2-3 (Sept. 8, 2023), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/lotronex-alosetronhydrochloride-information (citing as support for removing the REMS that reporting of adverse events in FAERS "has been stable since 2002 and an increase in severe outcomes has not been observed"); Chisato Fukazawa et al., *Factors Influencing Regulatory Decision-Making in Signal Management: Analysis Based on the Signals Identified from the FAERS*, 55 Therapeutic Innovation & Regul. Sci. 685 (Mar. 2021) (analyzing regulatory actions taken based on signals FDA identified from FAERS, including labeling changes, REMS modifications, product recall, and withdrawal).

[63] Ushma Upadhyay et al., *Effectiveness and Safety of Telehealth Medication Abortion in the United States*, 30 Nature Med. 1191, 1194 (2024).

[64] Janet Woodcock, M.D., Dir., Ctr. for Drug Evaluation & Rsch., U.S. Food & Drug Admin., Citizen Petition Denial, at 25-26 (Mar. 29, 2016).

[65] U.S. Food & Drug Admin., *Approved REMS*, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm (sum of drugs with "ETASU A" reflected under REMS Materials, divided by 20,000).

[66] U.S. Food & Drug Admin., REMS Modification Rationale Review, NDA 020687 & 91178, at 13 (Dec. 16, 2021).

[67] Laura Schummers et al., *Abortion Safety and Use with Normally Prescribed Mifepristone in Canada*, 386 New Eng. J. Med. 57, 63-66 (2022). Another Canadian study underscored "the apparent overall short-term safety of accessible first-trimester" abortion, and concluded that serious adverse events associated with the mifepristone/misoprostol regimen were "very rare." Ning Liu et al., *Short-Term Adverse Outcomes After Mifepristone–Misoprostol Versus Procedural Induced Abortion: A Population-Based Propensity-Weighted Study*, 176 Annals of Internal Med. 145, 151 (2023).

[68] Am. Med. Assoc., AMA Principles of Medical Ethics, Principle I ("A physician shall be dedicated to providing competent medical care...").

[69] Hal C. Lawrence, III, MD, Exec. VP & CEO, ACOG, Letter to FDA re recommendations regarding safety, effectiveness, and use of mifepristone, at 2 (Nov. 4, 2015); *see also* Am. Coll. Obstetricians & Gynecologists, *Medication Abortion Up to 70 Days of Gestation, Practice Bulletin No. 225*, at e34 (Oct. 2020, *reaff'd* 2023), https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2020/10/medication-abortion-up-to-70-days-of-gestation ("Any clinician with the skills to screen patients for eligibility for medication abortion and to provide appropriate follow-up can provide medication abortion").

[70] Nat'l Abortion Fed., *2024 Clinical Policy Guidelines for Abortion Care*, at 4 (2024) (at a minimum, patient must be informed of the risks of hemorrhage, infection, continuing pregnancy and death); Am. Coll. of Obstetricians & Gynecologists Comm. Op. No. 819, *Informed Consent and Shared Decision Making in Obstetrics and Gynecology*, 130 Obstetrics & Gynaecology e34 (2021).

[71] U.S. Food & Drug Admin., REMS Modification Rationale Review, NDA 020687 & 91178, at 17 (Dec. 16, 2021).

[72] Daniel Grossman et al., *Induced Abortion Provision Among a National Sample of Obstetrician–Gynecologists*, 133 Obstetrics & Gynecology 477, 482 (2019).

[73] Na'amah Razon et al., *Exploring the impact of mifepristone's risk evaluation and mitigation strategy (REMS) on the integration of medication abortion into US family medicine primary care clinics*, 109 Contraception 19, 23 (2022) ("the physicians we interviewed still encountered a range of barriers to provide medication abortions that the revised REMS will not alleviate").

[74] Citizen Petition from Am. Coll. of Obstetricians & Gynecologists, at 13-14 (Oct. 4, 2022); Dr. Graham Chelius, Soc'y for Fam. Planning & Cal. Acad. of Fam. Physicians, Letter to FDA re: Evidence Supporting Elimination of the Mifepristone REMS, at 5 (Sept. 29, 2021); Suzanne Robottom et al., U.S. Food & Drug Admin., Div. of Risk Management, *Risk Management Review – Korlym (mifepristone)*, at 9 (Jan. 27, 2012).

[75] Nat'l Abortion Fed., *2022 Violence & Disruption Statistics Report*, at 8 (2023).

[76] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., Joint Summary Review, at 13-14 (Jan. 3, 2023); Citizen Petition from Am. Coll. of Obstetricians & Gynecologists, at 15-16 (Oct. 4, 2022); Letter from Maureen G. Phipps, CEO, Am. Coll. Obstetricians & Gynecologists, & James L. Madara, CEO, Am. Med. Assoc., to Dr. Robert Califf, Comm'r, U.S. Food & Drug Admin. re: Actions Related to Mifepristone, at 3 (June 21, 2022).

[77] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch, Joint Summary Review, at 14 (Jan. 1, 2023); Citizen Petition from Am. Coll. of Obstetricians & Gynecologists, at 15-16 (Oct. 4, 2022); Letter from Maureen G. Phipps, CEO, Am. Coll. of Obstetricians & Gynecologists, & James L. Madara, CEO, Am. Med. Assoc., to Dr. Robert Califf, Comm'r, U.S. Food & Drug Admin., re: Actions Related to Mifepristone, at 3 (June 21, 2022).

[78] Saida Mamedova et al., *A Description of U.S. adults who are not digitally literate*, Nat'l Ctr. for Educ. Stat., at 5 (2018).

[79] U.S. Food & Drug Admin., *Single Shared System Risk Evaluation & Mitigation Strategy (REMS) Supporting Document* at 7; Sponsors Response to Agency Correspondence Following 9/19/2022 Meeting, at 2 (Oct. 19, 2022); *Mifepristone SSS REMS, Sponsors' Aug. 26, 2022 Resp. to FDA's Information Request Dated July 22, 2022*, at 17 (Aug. 26, 2022).

[80] U.S. Food & Drug Admin., *Approved REMS*, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm.

[81] U.S. Food & Drug Admin., *Single Shared System Risk Evaluation & Mitigation Strategy (REMS) Supporting Document*, at 7; Sponsors Response to Agency Correspondence Following 9/192022 Meeting, at 2 (Oct. 19, 2022); *Mifepristone SSS REMS, Sponsors' Aug. 26, 2022 Resp. to FDA's Information Request Dated July 22, 2022*, at 17 (Aug. 26, 2022).

[82] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., Joint Summary Review, at 5-6 (Jan. 1, 2023); U.S. Food & Drug Admin., REMS Modification Rationale Review (Dec. 16, 2021); U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., Joint Summary Review, at 23 (Jan. 3, 2023); U.S. Food & Drug Admin., REMS Modification Rationale Review (Dec. 16, 2021); U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., Joint Summary Review, at 38 (Jan. 1, 2023).

[83] Janet Woodcock, MD, Dir., Ctr. for Drug Evaluation & Rsch., U.S. Food & Drug Admin., Letter re: NDA 020687, Supp 20 (Mar. 28, 2016); U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., Application No. 020687Orig1s020 Summary Review, at 25 (Mar. 29, 2016).

[84] Janet Woodcock, MD, Dir., Ctr. for Drug Evaluation & Rsch., U.S. Food & Drug Admin., Letter re: NDA 020687, Supp 20 (Mar. 28, 2016).

[85] U.S. Food & Drug Admin., REMS Modification Rationale Review, NDA 020687 & 91178, at 18 (Dec. 16, 2021).

[86] U.S. Food & Drug Admin., REMS Modification Rationale Review, NDA 020687 & 91178, at 17 (Dec. 16, 2021).

[87] Nat. Acad. Sci., Eng'g, & Med., *The Safety and Quality of Abortion Care in the United States*, at 11, 13 (2018); Citizen Petition from Am. Coll. of Obstetricians & Gynecologists, at 13 (Oct. 4, 2022); Citizen Petition Consult re: Prescriber Certification and Adverse Event Reporting, at 8 (Dec. 16, 2021).

[88] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., Application No. 020687, Clinical Review, at 89 (Mar. 28, 2016).

[89] U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., Application No. 020687Orig1s020 Cross Discipline Team Leader Review, at 25 (Mar. 29, 2016).

[90] Janet Woodcock, MD, Dir., Ctr. for Drug Evaluation & Rsch., U.S. Food & Drug Admin., Letter re: NDA 020687, Supp 20 (Mar. 28, 2016); U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., Application No. 020687Orig1s020 Summary Review, at 25 (Mar. 29, 2016).

[91] Na'amah Razon et al., *Exploring the impact of mifepristone's risk evaluation and mitigation strategy (REMS) on the integration of medication abortion into US family medicine primary care clinics*, 109 Contraception 19, 23 (2022) ("The ongoing requirement for patients to sign a Patient Agreement Form may also limit the ability of family

physicians to provide medication abortion, especially since having this form on site and incorporating it into medical records requires the involvement of clinical administrators.").

[92] U.S. Food & Drug Admin., REMS Modification Rationale Review, NDA 020687 & 91178, at 11-12, 45-49 (Dec. 16, 2021).

[93] U.S. Food & Drug Admin., REMS Modification Rationale Review, NDA 020687 & 91178, at 45-49 (Dec. 16, 2021).

[94] U.S. Food & Drug Admin., Memorandum to File re Referenced Publications, at 2–3 (Dec. 30, 2022) (referring to Studnicki, et al., *A Longitudinal Cohort Study of Emergency Room Utilization Following Mifepristone Chemical and Surgical Abortions, 1999–2015* (2021); Studnicki, et al., *A Post Hoc Exploratory Analysis: Induced Abortion Complications Mistaken for Miscarriage in the Emergency Room are a Risk Factor for Hospitalization* (2022); Rafferty et al., *#AbortionChangesYou: A Case Study to Understand the Communicative Tensions in Women's Medication Abortion Narratives* (2020); Aultman et al., *Deaths and Severe Adverse Events after the use of Mifepristone as an Abortifacient from September 2000 to February 2018* (2019); Cirucci, et al., *Mifepristone Adverse Events Identified by Planned Parenthood in 2009 and 2010 Compared to Those in the FDA Adverse Event Reporting System and Those Obtained Through the Freedom of Information Act* (2021)). The two Studnicki studies were later retracted by the publisher, who relied in part on a post-publication peer review by two independent experts who "identified fundamental problems with the study design and methodology, unjustified or incorrect factual assumptions, material errors in the authors' analysis of the data, and misleading presentations of the data that, in their opinions, demonstrate a lack of scientific rigor and invalidate the authors' conclusions in whole or in part." Retraction Notice, 11 *Health Services Research and Managerial Epidemiology* (2024), https://journals.sagepub.com/doi/10.1177/23333928231216699.

[95] Leah R. Koenig et al., *The role of telehealth in promoting equitable abortion access in the United States: spatial analysis*, 9 JMIR Public Health Surveillance e45671 (2023).

EXHIBIT I

October 6, 2025

Martin Makary, MD, MPH
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-002

Dear Commissioner Makary,

We submit this comment in support of pending citizen petitions (FDA2025-P-0377-0001; FDA-2025-P-1576-0001; FDA-2025-P-2162-0001) regarding FDA regulation of mifepristone. We support Petitioners' request that the Food and Drug Administration (FDA): (1) remove the Mifepristone Shared System Risk Evaluation and Mitigation Strategy (REMS), or (2) in the alternative, at a minimum, refrain from taking any action that would further reduce patient access to mifepristone and/or increase the burdens associated with prescribing or dispensing mifepristone.

We conduct research on access to mifepristone as part of the Reproductive Health Outcomes and Disparities (RHOADs) Research Lab at the University of Chicago, which works to generate new knowledge to improve reproductive health care and outcomes and reduce racial and socioeconomic disparities. As part of this work, we have researched the use of a learning collaborative to support evidence-based use of mifepristone for early pregnancy loss and abortion in primary care and have conducted research to explore the provision of mifepristone across other settings. We have expertise in providing mifepristone, training others to provide it, and researching barriers and facilitators to access in diverse settings, including telehealth, pharmacy, and primary care.(1–6)

Mifepristone is among the most thoroughly studied medications approved by the FDA, with a strong scientific consensus affirming its safety and effectiveness, as outlined in Citizen Petition FDA-2025-P-0377-0001. Beyond the safety and efficacy of mifepristone, its availability, along with the drug misoprostol, has expanded access to abortion; the most recent research suggests that medication abortion makes up more than 60% of abortions in the U.S.(7) Additional regulations on mifepristone or removal of FDA approval could dramatically reduce access to abortion, delaying care, or preventing access entirely.

Our research and that of others has found that prior ETASU requiring in-person dispensing created barriers to access, including reducing the number of qualified mifepristone providers.(1,5,8–11) For instance, a national study of ob-gyns conducted before the in-person dispensing requirement was lifted found that among those not providing medication abortion, 28% said they would if they could write a prescription for mifepristone.(8) Similarly, interviews with ob-gyns in Massachusetts found that the most common barriers to using mifepristone to manage early pregnancy loss were barriers related to the REMS program.(9,12)

Among primary care providers, the REMS requirements have also been cited as barriers to integrating mifepristone into regular care. One 2019 study among primary care providers interested in reproductive health care found only one-third stocked mifepristone and a key barrier identified was the in-person dispensing requirement. Providers in this study also believed that lack of mifepristone access resulted in negative patient experiences, including disrupted continuity of care, medically-unnecessary appointments, and undesired aspiration procedures.(10) Another study involving interviews with family physicians across the U.S. found that 41% raised the REMS criteria as a barrier to providing medication abortion in primary care by adding administrative burdens and bureaucratic complexity that discouraged uptake.(11)

The FDA is authorized to impose a risk evaluation and mitigation strategy (REMS) program when it determines that restrictions are necessary, including additional regulations known as Elements to Assure Safe Use (ETASU). 21 U.S.C. § 355-1(a) and 21 U.S.C. § 355-1(f)(1)(A). However, any ETASU must "not be unduly burdensome on patient access to the drug, considering in particular…patients who have difficulty accessing health care (such as patients in rural or medically underserved areas)." 21 U.S.C. § 355-1(f)(2)(C)(ii) (cite) In the case of mifepristone, the FDA must consider whether ETASU unduly burden patient access to medication abortion, particularly among those patients who have difficulty accessing care. And as explained in detail below, further restrictions on medication abortion, including but not limited to restrictions on access to telehealth, could unduly burden patient access.

Extensive research has demonstrated the significant burdens for patients and their families when abortion access is restricted, including access to medication abortion with mifepristone. Such research has identified the burdens to pregnant people, their children, and families in terms of maternal and child health, emotional well-being, physical safety, socio-economic security, and educational opportunities.

Abortion restrictions lead to abortion delays and denial. Years of research demonstrate that restrictions on abortion access—including restrictions on medication abortion, gestational limits, waiting periods, restrictions on facilities providing abortion, limits for minors, and outright bans—lead to people experiencing delays or denied access to desired abortion care. For example, one study demonstrated that states with regulations targeting abortion facilities saw the largest declines in number of available clinics.(13) Research in states with laws requiring two-trip mandatory waiting periods found that restrictions delay and prevent abortions and increase births, with one national study finding an increase in second-trimester abortions by 18%, reduction in abortions by 9-11%, and an increase in births by 2%.(14–19) Furthermore, increases in births were larger in counties further away from clinics or that had lower socioeconomic status, suggesting that the greater the financial and logistical barriers, the more likely that abortion care was denied.(19) Similarly, a study in Texas found that an increase in travel distance from 0–50 miles to 50–100 miles reduced abortion rates by 16%.(20–22) Recent research on the effects of state abortion bans post-*Dobbs* also suggest such bans lead to increases in births, from 1-3.2% depending on distance and appointment availability.(23)

Similarly, FDA restrictions that interfere with access to mifepristone and medication abortion, or make it unavailable altogether, risk the same delays and denials of abortion care and the same range of harmful consequences for patients, as outlined below.

Abortion restrictions lead to increases in live births and infant deaths. In the U.S., infant mortality (i.e., death before age 1 year) has generally been declining, with 5.6 infant deaths per 1000 live births in 2022 (down from 6.9 in 2000).(24) Abortion restrictions, however, can lead to increased infant deaths through the continuation of pregnancies with congenital malformations, the leading cause of infant mortality in the U.S.(25,26) Restrictions may also limit access to high-risk pregnancy care, which could result in maternal health complications linked to adverse infant outcomes.(27–30) Further, restrictions on abortion access may exacerbate disparities in infant mortality because individuals who are unable to overcome barriers to abortion access are often from the same groups that experience higher rates of infant mortality, including racially minoritized individuals, those without a college degree, and individuals using public health insurance.(25,31–35) In fact, research following abortion restrictions in Texas prior to the *Dobbs* decision estimated a 6% to 13% increase in infant mortality above expectation while another study showed a 7% increase in infant mortality nationwide following the *Dobbs* decision, with the predominant cause from all three studies being death associated with congenital malformations.(36–38) This research has been affirmed by recent national findings: researchers analyzing birth certificate data between 2012-2023 estimate that abortion bans in 14 states resulted in 22,180 additional live births and 478 additional infant deaths above what would have been expected.(39) The impacts were greater in certain populations; Black infants died at a rate 11% higher than would have been expected.(40)

Denying access to abortion also contributes to worsening maternal health outcomes. Numerous studies have demonstrated how the inability to access abortion can affect maternal mortality and morbidity, as well as longer-term physical and mental health outcomes. For instance, results from the seminal Turnaway Study[1] indicate that people who were denied an abortion and gave birth reported more life-threatening complications like eclampsia and postpartum hemorrhage and more chronic headaches or migraines, joint pain, and gestational hypertension.(41,42) Similarly, an analysis of Vital Statistics Natality data up through 2017 found that laws targeting abortion providers increased rates of adverse cardiovascular health outcomes among birthing people by 11–16%.(43)

Additional analysis of national statistical data find associations between abortion restrictions and maternal mortality. Results from a study using 2007–2015 National Vital Statistics System microdata mortality files from 38 states and DC found states that enacted legislation to restrict

[1] The Turnaway Study followed 1,000 women for five years and compared outcomes of individuals seeking abortions who either received or were denied care. This rigorous study provides critical data on the long-term adverse effects of abortion denial, including serious physical and mental health challenges as well as economic hardship and insecurity.

abortion based on gestational age increased the maternal mortality rate by 38%.(44) Another study using 2015-2018 National Center for Health Statistics maternal mortality data examined the associations between the state abortion policy context and maternal death and found that states with a higher number of abortion-restricting policies had a 7% increase in total maternal mortality (defined as a death while pregnant or within 1 year following the end of a pregnancy, from any cause related to or aggravated by the pregnancy or its management).(45) At the same time research has shown that expanded access to abortion results in lower maternal mortality and morbidity.(46,47)

Research has also identified adverse mental health outcomes for people denied abortion access. A recent review of the literature suggested that women who obtain abortions do not have worse mental health outcomes related directly to abortion and that those denied access to abortion have worse initial adverse psychological outcomes.(48) Research on outcomes following denial of abortion come largely from the Turnaway Study. Findings suggest that women denied abortion showed a less steep decline in baseline depression or anxiety symptoms and also faced greater initial levels of anxiety, lower self-esteem, and lower life satisfaction.(49–54) Research also found that women who were denied abortion initially reported more negative emotions.(55)

Denying abortion access contributes to adverse outcomes for children. Researchers compared children born after an abortion denial to children born later from subsequent pregnancies to women who received an abortion. Children born after a denial were more likely to experience poor maternal bonding (9% vs 3%) and have more reported injuries in early life (6% vs 3%).(56) They were also more likely to live in households unable to cover basic living expenses. Abortion restrictions have also been shown to increase racial disparities in infant health outcomes at birth – increasing gaps in premature birth and low birthweight between Black and white infants by 3–6 %.(43) Other research confirms that children from unintended pregnancies face additional challenges and disadvantages: they are more likely to be reported in less than excellent health, have extreme activity levels (either too active or too inactive), which is associated with behavioral and developmental challenges, and they also have higher odds of scorning below the median on standardized developmental assessments.(57)

Denying abortion access can increase poverty and developmental delays for existing children. The majority of abortion patients are already parents.(58) Studies show that when women are denied an abortion, their existing children have more economic insecurity and are more likely to be living below the federal poverty line compared to the children of women who received a desired abortion.(59) Likely due to financial and emotional stress, these children also have comparatively more challenges meeting developmental milestones.(59)

Denying abortion access can result in system-level impacts on children and families. Beyond harms to individual households, abortion restrictions have been associated with greater family instability and added strain on child welfare systems, while also exacerbating inequities across communities. A recent national cohort study found that the enactment of TRAP laws—state restrictions on abortion providers—was associated with an 11% increase in foster care

placements, often due to housing inadequacy, with more significant effects for Black and other racial and ethnic minority children.(60) Restrictions have also been linked to child maltreatment, where longer travel distances to abortion facilities have been associated with increases in reports of neglect and physical abuse, especially for infants and non-white children.(61) Research has also suggested associations between state abortion restrictions and increased homicide deaths among children age 0-5.(62) In contrast, legalization of abortion has historically been associated with about a 10% decline in reported child abuse and neglect.(63)

Restricted access to abortion and increase risks of intimate partner violence.
Homicide is already a leading cause of death during pregnancy and the postpartum period in the United States. Pregnancy and the postpartum period are times of elevated risk for homicide among all females of reproductive age; one study examining homicide rates during and following pregnancy found that the majority occurred in the home, implicating involvement by known persons.(64) For women who give birth after being denied an abortion, ongoing contact with the man involved in the pregnancy results in continued exposure to violence. Research found that having an abortion was associated with a reduction over time in physical violence from the man involved in the pregnancy, while giving birth was not, suggesting that having a baby from an unwanted pregnancy appears to result in sustained violence.(65) Along the same lines, research found that women denied abortions were slower to end their romantic relationships than women having abortions.(66) Conversely, women who receive wanted abortions are more likely to describe themselves as being in very good relationships years later compared to women who are denied an abortion.(65–67) Access to abortion care is particularly important for survivors of intimate partner violence, especially those whose unintended pregnancies resulted from reproductive coercion or rape. In cases where a survivor needs privacy around her abortion decision out of fear of abuse, mifepristone offers a safe and private abortion option. As set forth in greater detail in the Comment in Support of Citizen Petition No. FDA-2025-P-0377-0001from Legal Voice, women are more likely to experience intimate partner violence during pregnancy and access to abortion can play a critical role in escaping the harms of such violence.

Research identifies numerous socio-economic costs of abortion delay and denial. Being denied a wanted abortion can significantly curtail educational attainment, labor force participation, and achievement of aspirational life goals.(68–72) The Turnaway Study found that women denied an abortion who gave birth experienced an increase in household poverty lasting at least four years, were more likely to not have enough money to cover basic living expenses, and were more likely to have a lower credit score.(70,73,74) Researchers also found that being denied an abortion increased a woman's amount of debt and increased the number of their negative public financial records, such as bankruptcies and evictions.(74) After being denied an abortion, women had more than three times greater odds of being unemployed and were more likely to be enrolled in public safety net programs.(70)

Restrictions on abortion access can also derail educational opportunities. One study found that regulations on abortion providers, which often lead to clinic closures, increased births among teens

by more than 3%. The same study reported that living in states with such laws before age 18 reduced college initiation by 2.1%, and college completion by 5.8% among Black women in particular.(75)

In addition to the socio-economic costs when abortion is denied, barriers to access caused by abortion restrictions can increase burdens for those who still ultimately obtain abortions. Restrictions can result in delays to care and associated costs, including possibly pushing a person beyond the gestation eligible for a medication abortion, requiring more expensive procedures or greater travel to an appropriate clinic setting. Regulations that would remove access to mifepristone via telehealth services could also cause delay and require people to travel to an in-person clinic site, increasing burdens and costs. Research on the burdensome consequences of additional costs in seeking abortion care are detailed further below.

Access to mifepristone through telehealth abortion services alleviates burdens; if access is removed, burdens will increase. The use of telehealth for abortion care has been demonstrated as safe and effective.(76) It has also become a common way to access abortion. The number of abortions delivered via telehealth has increased since April 2022; by the end of 2024, 1 in 4 abortions was provided via telehealth. In states where abortion and telehealth were permitted, on average, 15% of abortions were provided via telehealth each month.(77) If the FDA imposes REMS or ETASU such that mifepristone can no longer be accessed via telehealth, this will have a burdensome impact on patients in states where abortion remains legal, but access to in-person services can prove difficult due to cost, geography, or other logistical barriers. In states with few abortion providers or large rural areas like Colorado, Minnesota, Alaska, Wisconsin, Hawaii, Ohio, Pennsylvania, Utah, and Virginia, telehealth abortion numbers have steadily increased over time, suggesting increasing reliance on this service.(77)

Research has proven that cost poses a barrier to abortion; restrictions that would limit access to telehealth abortion and require more travel could increase costs, resulting in delays and denials of care and the harmful consequences described above. Abortion is often not covered by insurance, and, for many, the out-of-pocket cost of an abortion can be considered a catastrophic health expenditure (CHE), according to one study that looked at whether abortion costs exceeded 40% of average monthly income. (78) One cross-sectional study of U.S. patients seeking abortion found that 42% of individuals were estimated to incur CHEs as part of care-seeking.(79) Findings from a systematic review by Barr-Walker et al (2019) describe the range of financial and logistical burdens of abortion travel pre-*Dobbs*, including planning and paying for accommodations, transit, and childcare along with compensating from time away from work.(80) Financial obstacles can result in delays, affect method choice, lead to financial stress, and result in inability to obtain care altogether.(78,81–84) Delay and denial of abortion care resulting from financial obstacles result in the same harmful consequences of delayed and denied access described above.

In conclusion, decades of research demonstrate the harmful impacts for patients when abortion access is restricted. Additional regulations that make mifepristone more difficult or impossible to

obtain will unduly burden patients, especially those who already face difficulty in accessing care. We urge the Department to consider the evidence presented in this comment and incorporate it when analyzing the petition. Should you wish to discuss their contents with us further, please reach out to Lee Hasselbacher at lhasselbacher@uchicago.edu.[2]

Sincerely,

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EXHIBIT J

Boston University School of Law
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January 27, 2026

Submitted Electronically

Acting Commissioner of Food and Drugs, Sarah Brenner, MD, MPH
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

Re: Supplemental Comment in Support of Citizen Petition FDA-2025-P-0377-0001

Acting Commissioner Brenner,

The Boston University School of Law's Program on Reproductive Justice (BUPRJ), Immigrants' Rights and Human Trafficking Program (IRHTP), and the Racial Justice and Movement Lawyering Clinic (RJMLC) jointly submit this public comment regarding the pending Citizen Petitions, FDA-2025-P-0377-0001; FDA-2025-P-1576-0001; FDA-2025-P-2162-0001; and FDA-2025-P-3287-0001 ("Petitions"). We previously submitted Public Comment FDA-2025-P-0377-0242 on October 11, 2025.

We now submit this supplemental comment to provide additional analysis and information in light of new research highlighting the connection between intimate partner violence (IPV) and access to reproductive healthcare. We join the aforementioned petitions insofar as they advise the U.S. Food and Drug Administration (FDA) to: (1) eliminate the Mifepristone Shared System Risk Evaluation and Mitigation Strategy (REMS); or (2) at minimum, refrain from imposing additional restrictions on mifepristone.

For the reasons set forth in our prior comment and below, we urge the FDA to swiftly expand access to mifepristone and reproductive healthcare via telehealth and other evidence-based measures, rather than imposing unduly burdensome requirements making it harder for patients to access care.

This supplemental comment highlights recent findings by the National Bureau of Economic Research (NBER) demonstrating that limiting access to reproductive healthcare increases IPV against women. This NBER working paper provides the first comprehensive, causal analysis of how post-*Dobbs* abortion restrictions have affected IPV, the most common form of violence

against women.[1] The NBER study demonstrates that between 2017 and 2023, restrictive abortion policies led to a 7-10% increase of IPV incidents for reproductive-age women.[2] This equates to approximately 9,000 IPV cases, where the abuse rose directly from or correlated with inaccessibility of abortion services.[3] According to the paper, non-Hispanic Black women experienced the highest increase in IPV incidents under these circumstances, reflecting broader disparities to access along lines of race and ethnicity.[4] These findings suggest that barriers to reproductive healthcare access, created by the REMS and other abortion restrictions, likely contribute to violence against pregnant people, with especially stark impacts on historically marginalized communities.

The connection between restricted abortion access and increased IPV, as substantiated in the NBER paper, furthers existing public health research and illustrates the tangible consequences of limiting reproductive healthcare. Abortion restrictions can intensify financial strain, prolong exposure to abuse, and reduce individuals' ability to exit unsafe relationships.[5] The NBER study found that almost 80% of women who were forced to carry a pregnancy to term due to abortion restrictions experienced IPV, highlighting the widespread harm these restrictions can cause.[6] The study also found that abortion restrictions can increase the likelihood of IPV even when they do not ultimately result in a birth.[7] Factors such as stress, prolonged interactions with violent partners, and other burdens imposed by restrictions can also elevate the likelihood of IPV while pregnant.[8] This is particularly alarming given that more than half of all homicides against women are committed by a former or current intimate partner.[9] By creating additional barriers to timely abortion care, policies that restrict access to mifepristone may increase the likelihood that pregnant people remain in dangerous, and even life-threatening, circumstances for longer. These restrictions can essentially confine individuals within unsafe situations by limiting the care they need.

The rise in IPV due to abortion restrictions imposes substantial burdens to the government, as well as disproportionate economic burdens on individuals. Increased IPV imposes sizable fiscal costs on society as a whole. According to the NBER study, restrictions linked to IPV impose approximately $1.24-$1.87 billion in added social costs.[10] Adjusted to the value of the dollar in

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[1] Dhaval M. Dave, Christine Durrance, Bilge Erten, Yang Wang, & Barbara L. Wolfe, *Abortion Restrictions and Intimate Partner Violence in the Dobbs Era* 1-2 (NBER Working Paper No. 33916, 2025).
[2] *Id.* at 3.
[3] *Id.*
[4] *Id* at 12.
[5] *Id.* at 1-2.
[6] *Id.* at 10.
[7] *Id.* at 2-3.
[8] *Id.* at 3-4.
[9] Allison Ertl et al., *Surveillance for Violent Deaths—National Violent Death Reporting System, 32 States, 2016*, 68(SS-9) MMWR Surveillance Summaries 13 (2019).
[10] Dave et al., *supra* note 1, at 17.

2023, the lifetime economic burden amounts to over $4.5 trillion.[11] These costs encompass increased healthcare expenditures, lost productivity and earnings, and significant burdens on public systems such as law enforcement and social services.[12] While these figures highlight strain on public infrastructure, the NBER study also reveals how limited access directly harms individuals. Notably, the financial and social burdens of both IPV and abortion inaccessibility fall disproportionately on low-income individuals, who are more likely to already face barriers to healthcare and lack the resources to travel for care or recover from economic harm.[13] Restricting access to safe, effective, evidence-based reproductive healthcare, thus, risks avoidable economic harm, while undermining patient health and safety.

The FDA should remove unnecessary restrictions on mifepristone to reduce preventable harm and support patient safety. In light of this new research, we reiterate our support for lifting unnecessary REMS requirements and expanding access to medication abortion via telehealth and other equitable, evidence-based mechanisms. Given the growing body of evidence linking abortion restrictions to increased rates of IPV, we strongly urge the FDA to refrain from imposing such restrictions. The FDA should swiftly remove all unwarranted barriers to mifepristone, affirm its safety and efficacy, and promote policies that protect patient health and safety.

Sincerely,



Georgia Aguilar
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Research Assistant with the Program on Rereproductive Justice
Boston University School of Law[14]



Julie Dahlstrom, Esq.
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The Boston University School of Law

[11] *Id.*
[12] *Id.*
[13] *Id.* at 1-3.
[14] Signatories to this comment do so as individuals and representatives of their respective programs. The position articulated in this comment does not represent the views of Boston University or Boston University School of Law.

Caitlin Glass, Esq.
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EXHIBIT K

April 11, 2025

Dr. Martin Makary
Food and Drug Administration
655 15th Street, NW, Suite 503
Washington, DC 20005

RE: Comment in Support of Citizen Petition No. FDA-2025-P-0377-0001

Submitted electronically via regulations.gov

Commissioner Makary,

Pursuant to 21 C.F.R. § 10.30, Legal Voice, Family Violence Appellate Project, Sexual Violence Law Center, and Washington State Coalition Against Domestic Violence, submit this comment in support of the Citizen Petition filed by the American College of Obstetricians and Gynecologists, Society of Family Planning, and Society for Maternal-Fetal Medicine, Petition No. FDA-2025-P-0377-0001. We strongly support Petitioners' request that the Food and Drug Administration (FDA): (1) remove the Mifepristone Shared System Risk Evaluation and Mitigation Strategy (REMS), or (2) in the alternative, at a minimum, refrain from taking any action that would further reduce patient access to mifepristone and/or increase the burdens associated with prescribing or dispensing mifepristone.

Legal Voice advances gender equity throughout the Pacific Northwest through litigation, administrative and legislative advocacy, and public education. Legal Voice advocates and works in Alaska, Idaho, Montana, Oregon, and Washington, all of which have different levels of access barriers to abortion services. Reproductive freedom is fundamental and essential, particularly for Black, Indigenous, and People of Color (BIPOC) women, LGBTQIA+ people, survivors of intimate partner violence (IPV), and those living at the intersection of multiple marginalized identities. Legal Voice is familiar with the challenges that IPV survivors face in exercising their autonomy and understands the barriers that make it especially difficult for IPV survivors to access reproductive health care, including abortion medication.

Family Violence Appellate Project is the only nonprofit organization in California dedicated to representing survivors of domestic violence and other forms of gender-based abuse in civil appeals for free. FVAP is devoted to ensuring domestic violence survivors can live in healthy safe environments, free from abuse. Abuse through reproductive coercion is widespread, and safe access to medication abortion is paramount to survivor safety and health.

Sexual Violence Law Center attorneys represent survivors of sexual violence, domestic violence, and gender-based violence in court on multiple issues, including healthcare autonomy and privacy.

Washington State Coalition Against Domestic Violence (WSCADV) is a statewide network of domestic violence programs, that works to end domestic violence by providing supports to our member programs and engaging in advocacy. Through WSCADV's work with domestic

violence (DV) survivors and their advocates, WSCADV knows that decisions about birth control, pregnancy, and parenting are deeply personal and can be challenging. For survivors of domestic violence, these choices are often taken away, with pregnancy used as a means of control. WSCADV's advocates have seen how non-consensual pregnancies can trap survivors in abusive relationships, making it even harder to escape. Sexual abuse within the relationship can lead to pregnancies, forcing survivors to confront the painful reality that their abuser might have legal rights to visitation or custody. Based on WSCADV's experience working with survivors across Washington, WSCADV believes that access to mifepristone offers hope and vital options for DV survivors, empowering them to make decisions about their reproductive health, access to healthcare, and safety for themselves and their families.

In recent years, the Food and Drug Administration has implemented changes to the Risk Evaluation and Mitigation Strategy for mifepristone, a medication used for medical termination of pregnancy. These changes have eased mifepristone access by allowing direct-to-patient telehealth and pharmacy certification, without compromising patient safety. Interfering with access to mifepristone and reinstating needlessly burdensome, medically unnecessary requirements for in-person dispensing of this safe and effective medication used by millions of American women would have one clear and certain effect: reducing access to medication abortion across the United States.

Restricting access to mifepristone will cause particularly grave harm to IPV survivors by limiting their ability to access abortion care, thus increasing their risk of health complications, violence, and homicide. Abusers often control their partners' reproductive choices by forcing pregnancy and restricting prenatal care. The consequences of such entrapment range from heightened abuse during pregnancy to death. As difficult as it is for all survivors of IPV to escape abusive relationships and exercise their reproductive autonomy, IPV survivors of color—who already experience disproportionately high rates of unintended pregnancy and increased health risks— face systemic inequities that make doing so even harder. Changes in the availability of mifepristone will curtail access to medication abortion with serious consequences for the health and lives of many survivors of IPV.

Intimate Partner Violence Survivors Face Higher Risk of Unintended Pregnancy, Threatening Health and Safety

Intimate partner violence is widespread, leads to increased risk of unintended pregnancy, and results in adverse health outcomes for millions of survivors. Nearly half of women in the United States have been affected by IPV, which the World Health Organization defines as "behaviour by an intimate partner or ex-partner that causes physical, sexual or psychological harm, including physical aggression, sexual coercion, psychological abuse and controlling behaviours."[1] Almost *60 million* American women[2] report that they have experienced sexual violence, physical violence, and/or stalking by an intimate partner

[1] World Health Org., *Violence Against Women* (Mar. 9, 2021), https://www.who.int/news-room/fact-sheets/detail/violence- against-women; *see also* World Health Org., *Understanding and Addressing Violence Against Women: Intimate Partner Violence* 1 (2012), http://apps.who.int/iris/bitstream/10665/77432/1/WHO_RHR_12. 36_eng.pdf.
[2] People of many gender identities experience IPV. This brief specifically references "women" where the underlying research or quoted material focuses on women.

during their lifetimes.[3] Women of color face disproportionately high IPV rates, with over half of multiracial, Native, and Black individuals affected.[4] Noncitizens face added barriers like language, immigration status, and limited legal resources.[5]

In addition to physical abuse, IPV abusers exert "coercive control" over survivors by isolating them from family and friends, monitoring their whereabouts, and restricting their access to money[6] and transportation.[7] Survivors from marginalized communities face systemic inequities that exacerbate the conditions for coercive control.[8] This coercion limits survivors' access to resources needed to escape the abusive relationship.

Poverty and lack of resources make it even more difficult for survivors to escape IPV and women living in poverty are twice as likely to experience IPV.[9] People of color are even more likely to live in poverty if they also are LGTBQ+, disabled, or non-citizens.[10] It takes money to flee an abusive relationship—for hotel rooms, gas, food, and childcare, among other needs.[11] Longer-term costs include mental and physical health care needs, stable housing, legal representation, and finding flexible employers who will accommodate time-off requests for court appearances.[12]

Women living in rural areas experience more frequent and severe rates of IPV than women in urban areas, often making it more difficult for rural survivors to receive needed care.[13] Rural areas also have fewer health care providers and reproductive heath care services tend to be limited for people in rurual areas, even within states that protect abortion access.[14] Additionally rural emergency departments have fewer resources in place to address IPV.[15] These barriers further isolate survivors from necessary resources and highlight the importance of measures, like direct-to-patient telehealth, that reduce barriers to accessing reproductive health care, including medication abortion care.

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[3] *See also* Jamila K. Stockman et al., *Intimate Partner Violence and Its Health Impact on Disproportionately Affected Populations, Including Minorities and Impoverished Groups*, 24 J. Women's Health 62, 62 (2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4302952/pdf/jw h.2014.4879.pdf.
[4] Ruth W. Leemis et al., Ctr. for Disease Control & Prevention, *The National Intimate Partner and Sexual Violence Survey: 2016/2017 Report on Intimate Partner Violence* 7 (2022), https://www.cdc.gov/violenceprevention/pdf/nisvs/NISVSReport onIPV_2022.pdf.
[5] Karla Fischer et al., *The Culture of Battering and the Role of Mediation in Domestic Violence Cases*, 46 SMU L. Rev. 2117, 2121-22 (1993), https://scholar.smu.edu/cgi/viewcontent.cgi?article=2322&conte xt=smulr ; Julie Goldscheid, *Gendered Violence and Work: Reckoning with the Boundaries of Sex Discrimination Law*, 18 Colum. J. Gender & L. 61, 75–77 (2008), https://academicworks.cuny.edu/cgi/viewcontent.cgi?article=116 2&context=cl_pubs; Leigh Goodmark, *A Troubled Marriage: Domestic Violence and the Legal System* 42 (2012).
See also Jamila K. Stockman et al., *Intimate Partner Violence and Its Health Impact on Disproportionately Affected Populations, Including Minorities and Impoverished Groups*, 24 J. Women's Health 62, 62 (2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4302952/pdf/jw h.2014.4879.pdf.
[6] *See id.* at 2121–22; Julie Goldscheid, *Gendered Violence and Work: Reckoning with the Boundaries of Sex Discrimination Law*, 18 Colum. J. Gender & L. 61, 75–77 (2008), https://academicworks.cuny.edu/cgi/viewcontent.cgi?article=116 2&context=cl_pubs; Leigh Goodmark, *A Troubled Marriage: Domestic Violence and the Legal System* 42 (2012).
[7] *See* Goldscheid, *supra* note 8, at 75; Goodmark, *supra* note 8, at 42.
[8] *See generally* Natalie J. Sokoloff & Ida Dupont, *Domestic Violence at the Intersections of Race, Class, and Gender: Challenges and Contributions to Understanding Violence Against Marginalized Women in Diverse Communities*, 11 Violence Against Women 38 (2005), https://pubmed.ncbi.nlm.nih.gov/16043540/.
[9] Erika A. Sussman & Sara Wee, Ctr. for Survivor Agency & Just., *Accounting for Survivors' Economic Security: An Atlas for Direct Service Providers* 1 (2016), https://csaj.org/wp- content/uploads/2021/10/Accounting-for-Survivors-Economic- Security-Atlas-Mapping-the-Terrain-.pdf.
[10] Bianca D.M. Wilson et al., UCLA Williams Inst., *LGBT Poverty in the United States: Trends at the Onset of COVID-19*, 3–4 (2023), https://williamsinstitute.law.ucla.edu/wp- content/uploads/LGBT-Poverty-COVID-Feb-2023.pdf.
[11] Sussman et al., *supra* note 10, at Erika A. Sussman & Sara Wee, Ctr. for Survivor Agency & Just., *Accounting for Survivors' Economic Security: An Atlas for Direct Service Providers* 1 (2016), https://csaj.org/wp- content/uploads/2021/10/Accounting-for-Survivors-Economic- Security-Atlas-Mapping-the-Terrain-.pdf.
[12] Erika A. Sussman & Sara Wee, Ctr. for Survivor Agency & Just., *Accounting for Survivors' Economic Security: An Atlas for Direct Service Providers* 1 (2016), https://csaj.org/wp- content/uploads/2021/10/Accounting-for-Survivors-Economic- Security-Atlas-Mapping-the-Terrain-.pdf.
[13] Corinne Peek-Asa et al., *Rural Disparity in Domestic Violence Prevalence and Access to Resources*, 20 J. Women's Health 1743, 1747 (2011), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3216064/.
23 *Id*. at 1748.
[14] Lillian Mongeau Hughes, *For Many Rural Women, Finding Maternity Care Outweighs Concerns About Abortion Access*, KFF Health News, (Jan. 2, 2025), https://kffhealthnews.org/news/article/maternity-care-rural-desert-abortion-access-oregon-mobile-clinic/view/republish/.
[15] Danielle M. Davidov et al., *Comparison of Intimate Partner Violence and Correlates at Urgent Care Clinics and an Emergency Department in a Rural Population*, 20 Int'l J. Env't Res. & Pub. Health 4554, at 2 (2023), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10002050/.

Survivors of IPV face higher risks of unintended pregnancy due to "reproductive coercion", including birth control sabotage and forced pregnancies by abusive partners. Research from the Centers for Disease Control and Prevention (CDC) shows that nearly 10.3 million women have experienced a partner trying to force pregnancy or refusing to use contraception.[16] Studies have also found that IPV survivors are nearly three times more likely to conceal an abortion from their partners due to safety concerns. Again, systemic inequities further compound the risks. Marginalized communities already experience disproportionately high rates of unintended pregnancy,[17] largely due to a lack of access to sexual health information,[18] health insurance,[19] and affordable contraceptives,[20] as well as a history of coercion by and mistrust of state and medical institutions.[21]

Intimate Partner Violence Survivors Need Abortion Access but Face Major Barriers

Meaningful access to abortion care, while important to all women, is particularly critical for IPV survivors, and especially those whose unintended pregnancies resulted from reproductive coercion or rape. Because pregnancy termination undermines abusers' control, survivors face increased barriers to obtaining abortion care when they need to hide their abortion from their abuser. Mifepristone provides a safe and private abortion option for many people, such that maintaining access to mifepristone is critical for survivors of IPV.

Indeed, many survivors have children whom they already struggle to protect.[22] Among other risks, having a child, or another child, with an abusive partner exacerbates challenges survivors face in finding housing upon leaving the abuser, as they would be limited to shelters which permit children.[23]

It is common for abusers to control prenatal care, which can result in increased complications and adverse health outcomes. Survivors of IPV are at a high risk of depression and post-traumatic stress disorder and at increased risk of having babies preterm and babies with low birth weight.[24] While the United States has a maternal mortality rate over three times that of other developed nations,[25] BIPOC women are disproportionately affected with a higher maternal mortality rate and lower-quality

[16] M.C. Black et al., Ctr. for Disease Control & Prevention, *National Intimate Partner and Sexual Violence Survey: 2010 Summary Report* 48 (2011).
[17] Theresa Y. Kim et al., *Racial/Ethnic Differences in Unintended Pregnancy: Evidence from a National Sample of U.S. Women*, 50 Am. J. Preventative Med. 427, 427 (2016), https://pubmed.ncbi.nlm.nih.gov/26616306/.
[18] Amaranta D. Craig et al., *Exploring Young Adults' Contraceptive Knowledge and Attitudes: Disparities by Race/Ethnicity and Age*, 24 Women's Health Issues 281, 285–87 (2014), https://www.teachtraining.org/wp- content/uploads/2013/10/Exploring-young-adults-contraceptive- knowledge-and-attitudes.pdf.
[19] Latoya Hill et al., Kaiser Fam. Found., *Health Coverage by Race and Ethnicity, 2010–2022* (Jan. 11, 2024), https://www.kff.org/racial-equity-and-health-policy/issue- brief/health-coverage-by-race-and-ethnicity/.
[20] Usha Ranji et al., Kaiser Fam. Found., *Beyond the Numbers: Access to Reproductive Health Care for Low-Income Women in Five Communities* (Nov. 14, 2019), https://www.kff.org/report- section/beyond-the-numbers-access-to-reproductive-health- care-for-low-income-women-in-five-communities-executive- summary/.
[21] Marcela Howell et al., In Our Own Voice: Nat'l Black Women's Reprod. Just. Agenda, *Contraceptive Equity for Black Women* 2– 3 (2020), http://blackrj.org/wp-content/uploads/2020/04/6217- IOOV_ContraceptiveEquity.pdf.
[22] *See, e.g.*, Joan S. Meier, *Domestic Violence, Child Custody, and Child Protection: Understanding Judicial Resistance and Imagining the Solutions*, 11 Am. U. J. Gender Soc. Pol'y & L. 657 (2003), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=1768029 (discussing difficulties parent survivors face in protecting children from physical harm and navigating courts for custody and protective orders).
[23] Naomi R. Cahn, *Civil Images of Battered Women: The Impact of Domestic Violence on Child Custody Decisions*, 44 Vand. L. Rev. 1041, 1051 (1991), https://heinonline.org/HOL/Page?collection=journals&handle=h ein.journals/vanlr44&id=1057&men_tab=srchresults; *see* James Carroll, *Healthy Communities: Housing and Women Victims of Domestic Violence (WVODV)*, 1 The Opine 3 (2023), https://www.asterhill.com/The%20Opine_WVODV%20February %202023.pdf (indicating that in some counties there are fewer family-beds than adult-only beds).
[24] Jeanne L. Alhusen, *Intimate Partner Violence During Pregnancy: Maternal and Neonatal Outcomes*, 24 J. Women's Health 100, 101 (2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4361157/pdf/jw h.2014.4872.pdf.
[25] Munira Z. Gunja et al., The Commonwealth Fund, *The U.S. Maternal Mortality Crisis Continues to Worsen: An International Comparison* (Dec. 1, 2022),

reproductive care due to systemic racism in healthcare.[26] Immigrant women are at higher risk because they tend to receive less prenatal care than non-immigrant women, in part due to exclusionary health insurance laws and policies.[27]

Not only do people in abusive relationships face increased health risks associated with pregnancy, IPV is common and often escalates during pregnancy. [28] Approximately 324,000 pregnant women are abused in the United States each year[29] and homicide is the leading cause of death among pregnant women, with Black and Native women at the highest risk.[30]

The ability to access mifepristone through telehealth services and mail delivery plays a crucial role in providing a safe and private abortion option and has been on the rise since 2022.[31] It is particularly important for survivors who cannot safely visit clinics due to the controlling nature of their partners.[32] Indeed, IPV survivors are nearly three times as likely to conceal their abortion from their partner.[33] Without these options, IPV survivors may be forced to travel long distances, an impossible burden for many facing abusive financial control or childcare responsibilities. Many IPV survivors have children and need to arrange childcare to go to medical appointments. Childcare options are limited for people who lack funds, want to keep their abortion private, or are isolated from friends and family, and leaving children alone with an abuser may not be an option. Further, the cost of travel, including gas—assuming a survivor has access to a car—and lodging, is a significant barrier. These costs will be prohibitive for many survivors of IPV, who disproportionately face economic hardship and financial control by their partners. Marginalized communities, including BIPOC people and immigrants, face additional obstacles like limited transportation, low wages, and lack of insurance, making abortion care even less accessible.[34]

Restricting Mifepristone Puts Intimate Partner Violence Survivors at Risk

The current REMS and ETASU requirements limit access to mifepristone, harming IPV survivors by making it difficult for them to access needed care. The patient agreement form is stigmatizing, and certification requirements make it more burdensome for providers to prescribe and dispense mifepristone, deterring some providers from providing medication abortion.[35] These unnecessary administrative requirements cause real harm to IPV survivors by reducing the number of providers they can go to to get care.

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[26] Cynthia Prather et al., *Racism, African American Women, and Their Sexual and Reproductive Health: A Review of Historical and Contemporary Evidence and Implications for Health Equity*, 2 Health Equity 249, 253 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6167003/pdf/he q.2017.0045.pdf.
[27] Sheela Maru et al., *Utilization of Maternal Health Care Among Immigrant Mothers in New York City, 2016–2018*, 98 J. Urban Health 711, 721–723 (2021), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8688674/pdf/11 524_2021_Article_584.pdf.
[28] Am. Coll. of Obstetricians & Gynecologists, *Committee Opinion No. 518: Intimate Partner Violence*, 119 Obstetrics & Gynecology 1, 2 (2012, reaffirmed 2022), https://www.acog.org/clinical/clinical-guidance/committee- opinion/articles/2012/02/intimate-partner-violence.
[29] *Id*.
[30] Maeve Wallace et al., *Homicide During Pregnancy and the Postpartum Period in the United States, 2018–2019*, 138 Obstetrics & Gynecology 762, 762 (2021), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9134264/pdf/ni hms-1804550.pdf.
[31] Sophia Resnick, *Telehealth Abortions on the Rise Since Dobbs, New Report Shows*, Idaho Capital Sun (Mar. 1, 2024), https://idahocapitalsun.com/2024/03/01/telehealth-abortions-on-the-rise-since-dobbs-new-report-shows/.
[32] Yvonne Lindgren, *The Doctor Requirement: Griswold, Privacy, and At-Home Reproductive Care*, 32 Const. Comment 341, 373 (2017), https://www.law.berkeley.edu/wp- content/uploads/2017/10/4-Lindgren.pdf.
[33] Hall et al., *supra* note 32, at 10.
[34] Maeve Wallace et al., *Homicide During Pregnancy and the Postpartum Period in the United States, 2018–2019*, 138 Obstetrics & Gynecology 762, 762 (2021), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9134264/pdf/ni hms-1804550.pdf.
[35] Na'amah Razon et al., *Exploring the Impact of Mifepristone's Risk Evaluation and Mitigation Strategy (REMS) on the Integration of Medication Abortion into US Family Medicine Primary Care Clinics*, 109 Contraception 19, 20–21 (2022), https://www.contraceptionjournal.org/article/S0010-7824(22)00027-0/fulltext.

Any changes that the FDA makes to reinstate previous REMS and ETASU requirements would be even more harmful. Requiring in-person dispensing of mifepristone by providers would reduce the number of providers that IPV survivors can turn to for medication abortion due to the additional burdensome administrative steps.[36] When there are fewer providers available and direct-to-patient telehealth is not an option, people who want a medication abortion will be forced to travel long distances for care, and others will need to travel farther to reach a clinic that offers procedural abortions and that has available appointments.[37] For survivors of color and immigrants, discrimination and structural oppression exacerbate the barriers to abortion when mifepristone is more difficult to access.

In 2023, medication abortion made up 63% of all abortions in the United States.[38] Medication abortion is a particularly important option for survivors of IPV because they are subject to coercive control.[39] Disrupting the distribution of mifepristone and reinstating medically unnecessary, burdensome restrictions on its dispensing would irreparably harm IPV survivors by rendering abortion care inaccessible to many and consequently exposing them to a higher likelihood of significant health risks and further violence, including homicide. Simply put, changes in the availability of mifepristone will have life and death consequences for many survivors of IPV.

We urge the Department to consider the issues raised in this comment and incorporate them when analyzing the petition. Thank you for the opportunity to submit these comments. Should you wish to discuss their contents with us further, please reach out to Kelly O'Neill at koneill@legalvoice.org and Julia Marks at jmarks@legalvoice.org.

Sincerely,

Legal Voice

Family Violence Appellate Project

Sexual Violence Law Center

Washington State Coalition Against Domestic Violence

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