The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Society for Maternal-Fetal Medicine
High-risk pregnancy experts

April 20, 2020

Stephen M. Hahn, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue NW
Silver Spring, MD 20993

Re: Docket Number: FDA-2020-D-1106; Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency Guidance for Industry and Health Care Professionals

Dear Commissioner Hahn:

On behalf of more than 60,000 of the nation's primary care obstetrician-gynecologists and subspecialty and high-risk obstetric practitioners dedicated to advancing women's health, thank you for your recent action to suspend enforcement of Risk Evaluation and Mitigation Strategy (REMS) requirements for certain drugs with laboratory testing or imaging requirements for the duration of the COVID-19 public health emergency. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine urge the U.S. Food and Drug Administration (FDA) to immediately expand this policy to REMS and Elements to Assure Safe Use (ETASU) requirements for certain prescription drugs requiring in-person health care professional administration, where treatment could safely occur through telehealth or self-administration. In addition, physicians who provide such services in accordance with current clinical guidelines during this pandemic should not be held liable.

Obstetrician-gynecologists are serving on the front lines responding to the COVID-19 crisis. In order to provide the safest care for their patients and themselves, in-person visits are limited to emergency and essential physically necessary visits. We support the FDA's acknowledgment that REMS-required health care professional in-person dispensation is difficult because patients may need to avoid public places and patients suspected of having COVID-19 may be self-isolating and/or subject to quarantine. Under these circumstances, undergoing in-person clinic administration in order to obtain a drug subject to a REMS can put patients and others, including health care professionals and their families, at risk for COVID-19 transmission. As referenced in ACOG Committee Opinion #798, *Implementing Telehealth in Practice*, evidence suggests that telehealth provides comparable health outcomes when compared with traditional methods of health care delivery without compromising the patient–physician relationship.[1] Telehealth has quickly become integrated into nearly every aspect of obstetrics and gynecology. During this pandemic, it is essential to use telehealth services to limit COVID-19 transmission.

It is critical that the FDA promptly expand its recent policy to apply to the REMS and ETASU requirements for certain drugs requiring in-person dispensation, especially mifepristone. The current REMS and ETASU requirements for mifepristone are outdated and serve as a barrier to accessing this safe, effective medication. Further, they cause unnecessary delays in obtaining time-sensitive health care, without supporting improvements to patient safety or outcomes. During this federally declared public health emergency, these antiquated and superfluous requirements put patients and their physicians at risk, with no demonstrated benefit. As noted in the ACOG Position Statement, *Improving Access to*

Mifepristone for Reproductive Health Indications, mifepristone has been used by over 3 million women in the United States since FDA approval in 2000 and strong evidence exists regarding the safety of mifepristone for medication-induced abortion and medical management of early pregnancy loss.[2,3,4,5]

Restricting access to mifepristone interferes with the ability of obstetrician–gynecologists and other women's health clinicians to deliver the highest quality care for their patients, especially during the COVID-19 pandemic. Abortion is an essential component of comprehensive health care and is a time-sensitive service for which a delay of several weeks, or in some cases days, may increase the risks or potentially make it completely inaccessible.[6] Temporarily waiving REMS and ETASU requirements that certain drugs be dispensed in-person by certain medical professionals is particularly important for patients who suffer from other medical conditions and are at higher risk of serious complications from COVID-19, as well as those in rural areas for whom hours of travel for in-person administration would disallow social distancing recommendations and travel advisories.

In addition, we urge you to consider waiving the requirement for health care professional administration of subcutaneous depot medroxyprogesterone acetate (DMPA). Several studies have shown patient interest in self-administration and increased continuation of DMPA via subcutaneous at-home delivery.[7,8,9] In a period when limiting patient interactions with the health care system is essential to prevent COVID-19 transmission, it is in our patients' best interest to have unencumbered access to the contraceptive method of their choice, including DMPA.

Ensuring the safety of patients and physicians during the COVID-19 pandemic requires policy changes such as those already enacted by FDA to waive the REMS requirements for certain drugs with laboratory testing or imaging requirements. We strongly urge FDA to further protect patients and their health care professionals from the risk of transmission by promptly expanding the existing policy to waive REMS and ETASU requirements that certain drugs be dispensed in-person by certain medical professionals. Thank you for your consideration. We are available to answer any questions you may have regarding these issues.

Sincerely,

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ACOG
The American College of Obstetricians and Gynecologists

Improving Access to Mifepristone for Reproductive Health Indications

Position Statement

The American College of Obstetricians and Gynecologists (ACOG) supports efforts to improve access to quality women's health care and opposes regulations, restrictions, or mandates that impede access to evidence-based care. Recent evidence highlighting the potential for mifepristone to significantly improve the safe and effective medical management of early pregnancy loss, such as a missed abortion, provides incentive to facilitate improved access to mifepristone.[1,2] Early pregnancy loss is common, occurring in 10% of all clinically recognized pregnancies and affecting approximately 1 million women in the U.S. annually.[3,4] The current U.S. Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategy (REMS) and Elements to Assure Safe Use (ETASU) requirements for Mifeprex® (mifepristone, 200 mg) are outdated and substantially limit access to this safe, effective medication. Therefore, ACOG urges the removal of the REMS and ETASU for Mifeprex®.

The ETASU for Mifeprex® require that the medication be dispensed in a clinic, medical office, or hospital (precluding its availability in retail pharmacies), that clinicians obtain certification prior to prescribing the medication, and that patients sign an FDA-approved agreement before receiving the medication.

Evidence regarding the safety of mifepristone for medication-induced abortion, used by over 3 million women in the U.S. since FDA approval in 2000, supports the removal of the REMS and ETASU.[5,6] These requirements are inconsistent with those for other medications with similar or greater risks, including a 300-mg formulation of mifepristone used in treatment of Cushing's syndrome, and serve as barriers to access without supporting demonstrated improvements to patient safety or outcomes. In addition, ACOG opposes regulations or restrictions that are inappropriately unique to the provision of abortion. In line with its safety record and to improve access, ACOG recommends that mifepristone for reproductive health indications be made available in retail pharmacies like other prescription drugs and without unique provider certification or patient consent requirements.

Restricting access to mifepristone interferes with the ability of obstetrician–gynecologists and other women's health care providers to deliver the highest quality care for their patients. Removing the REMS and ETASU on Mifeprex® would allow more women the option of medical management for early pregnancy loss, and improve access for first trimester medication-induced abortion.

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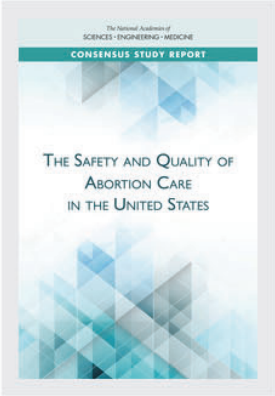

The Safety and Quality of Abortion Care in the United States (2018)

DETAILS

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CONTRIBUTORS

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

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The Safety and Quality of Abortion Care in the United States

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

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every state, clinicians and inpatient facilities (e.g., hospitals, rehabilitation centers) must be licensed by a state board or agency to provide health care services legally. When states regulate specific office-based health care procedures, the requirements are usually triggered by the level of sedation that the facility offers. Abortion services are an exception. A wide variety of state regulations affect abortion care, including the type of clinician permitted 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); health insurance coverage (e.g., Medicaid or private insurance plans may be prohibited from paying for abortions); how the informed consent process is conducted (e.g., providers may be required to inform women that abortion increases their risk of breast cancer or mental illness, despite the absence of valid scientific evidence); 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); and the physical attributes of the clinical setting (e.g., procedure room size, corridor width). In most states, the regulations apply to all abortion methods regardless of weeks' gestation, the use of sedation, or the invasiveness of the procedure.

U.S. Food and Drug Administration's (FDA's) Risk Evaluation and Mitigation Strategy (REMS) Program

The distribution and use of mifepristone has been restricted under the requirements of the FDA's REMS program since 2011. The FDA-approved protocol for medication abortion was updated in 2016 based on extensive clinical research demonstrating the safety of the revised regimen. The revised REMS continues to limit the distribution of Mifeprex (the brand name for mifepristone) to patients in clinics, hospitals, or medical offices under the supervision of a certified prescriber and cannot be sold in retail pharmacies. The committee could not find evidence on how this restriction impacts the safety or quality of abortions.

CONCLUSIONS

This report provides a comprehensive review of the state of the science on the safety and quality of abortion services in the United States. As noted earlier (see Box S-1), the committee was charged with answering eight specific research questions. The committee's conclusions regarding each question appear below. The committee was also asked to offer recommendations regarding the eight questions. However, the committee decided that its conclusions regarding the safety and quality of U.S. abortion care responded comprehensively to the scope of this study. Therefore,

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).

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

[5]An "incomplete abortion" occurs when parts of the products of conception are retained in the uterus.

abortion, patients should receive the contraceptive method of their choice or be referred elsewhere if the preferred method is unavailable (NAF, 2017; RCOG, 2015; WHO, 2012). The Centers for Disease Control and Prevention and the U.S. Office of Population Affairs recommend the following for providers offering contraceptive services, including contraceptive counseling and education (Gavin et al., 2014):

- Establish and maintain rapport with the client.
- Obtain clinical and social information from the client (medical history, pregnancy intention, and contraceptive experiences and preferences).
- Work with the client interactively to select the most effective and appropriate contraceptive method (providers should ensure that patients understand the various methods' effectiveness, correct use, noncontraceptive benefits, side effects, and potential barriers to their use).
- Conduct a physical assessment related to contraceptive use, when warranted.
- Provide the selected contraceptive method along with instructions for its correct and consistent use, help the client develop a plan for using the selected method and for follow-up, and confirm the client's understanding of this information.

Competencies Required for Abortion Methods

Medication Abortion

Medication abortion is a method commonly used to terminate a pregnancy up to 70 days' (or 10 weeks') gestation with a combination of medications—mifepristone followed by misoprostol. The skill set required for early medication abortion has been outlined by several organizations and is similar to the management of spontaneous loss of a pregnancy with medications (Goodman et al., 2016). The skills include the essential competencies outlined in the section above, plus the knowledge of medication abortion protocols, associated health effects, and contraindications. Prescribing medication abortion is no different from prescribing other medications—providers must be able to recognize who is clinically eligible; counsel the patient regarding medication risks, benefits, and side effects; and instruct the patient on how to take the medication correctly and when to seek follow-up or emergency care.

Chapter 2 describes the U.S. Food and Drug Administration's (FDA's) Risk Evaluation and Mitigation Strategy (REMS) for Mifeprex, the brand name for mifepristone, the first drug administered during a medication

U.S. FOOD & DRUG ADMINISTRATION

April 12, 2021

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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).

State of California
Office of the Attorney General
XAVIER BECERRA
ATTORNEY GENERAL

March 30, 2020

Secretary Alex M. Azar II
U.S. Department of Health & Human Services
200 Independence Ave., S.W.
Washington, DC 20201

Commissioner Stephen Hahn
U.S. Food & Drug Administration
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Dear Secretary Azar and Commissioner Hahn:

We write to request that you increase access to reproductive healthcare, including safe and legal abortion, during this pandemic. Specifically, as the U.S. Food & Drug Administration (FDA) considers policy changes in response to the Coronavirus Disease 2019 (COVID-19) public health emergency, we urge you to waive its Risk Evaluation and Mitigation Strategy (REMS), or use FDA enforcement discretion, to allow certified prescribers to use telehealth for Mifepristone, the medication abortion prescription drug.[1] The REMS create unnecessary delays for women who need access to time-sensitive healthcare and force them to travel unnecessarily.

During this unprecedented crisis, we need to ensure that women across the country have access to critical healthcare services. Steps have already been taken in many States at the behest of the federal government to increase telehealth. Yet, the current FDA REMS create unnecessary barriers between women and abortion care, not only making it harder to find—for example, by prohibiting sale by retail or mail-order pharmacies—but also making it unappealing to prescribe. By barring the use of telehealth, the REMS force women to travel at a time when many States and the federal government are urging people to stay home to curb the spread of COVID-19. Further, in some States across the country, like Texas and Ohio, politicians are using the pandemic to further restrict women's access to care by deeming abortion "nonessential" healthcare.[2] Denying women care and forcing them to travel unnecessarily is not

[1] FDA-2020-D-1106, https://www.regulations.gov/comment?D=FDA-2020-D-1106-0018.

[2] Sabrina Tavernise, *Texas and Ohio Include Abortion as Medical Procedures That Must Be Delayed*, New York Times (March 23, 2020), https://www.nytimes.com/2020/03/23/us/coronavirus-texas-ohio-abortion.html.

only shortsighted, it is putting women across the country in harm's way. Consequently, we urge you to act immediately and remove the FDA REMS designation.

Since 2000, Mifepristone has been approved by the FDA and remains the only drug approved in the United States for pregnancy termination. Since its approval, about three million women in the United States have used Mifepristone. And according to the FDA, this medication "has been increasingly used as its efficacy and safety have become well-established by both research and experience, and serious complications have proven rare."[3]

Despite Mifepristone's benefits and safety, the FDA subjects it to a REMS designation that is outdated, inconsistent with medical evidence, and limits healthcare providers' ability to use telehealth and provide this necessary drug, ultimately limiting patients' access to care. The Nation's leading reproductive healthcare specialists, the American College of Obstetricians and Gynecologists (ACOG), agree that the REMS are "outdated and substantially limit access to safe, effective medication," and have advocated for the FDA to remove the REMS.[4] Further, both the American Medical Association and American Academy of Family Physicians have also urged their removal.[5]

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[3] Mifepristone is used in a regimen with the drug misoprostol as a medical option for terminating an early pregnancy. The FDA has approved the use of this regimen through 70 days (i.e. 10 weeks of pregnancy). The patient first takes Mifepristone, in a single oral dose on day one. Then, 24-48 hours later, she takes the misoprostol. Most women experience a miscarriage within 2 to 24 hours after taking the misoprostol. The FDA label does not specify where the patient should be located when she takes either medication; however, the REMS requirements dictate that she be handed the Mifepristone (but not the misoprostol) at a clinic, medical office, or hospital under the supervision of a health care provider.

[4] Improving Access to Mifepristone for Reproductive Health Indications, ACOG (June 2018) https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications.

[5] "The AAFP seeks changes in the drug's current REMS designation to conform to current evidence. This aligns with other medical specialty organizations, such as the American College of Obstetricians and Gynecologists. Recent research also indicates the agency's safety protocols are particularly stringent for the drug. Most importantly, the current drug label creates an unnecessary health care barrier for women who need it the most." Letter to the FDA, AAFP (June 20, 2019), https://www.aafp.org/dam/AAFP/documents/advocacy/prevention/women/LT-FDA-MifepristoneREMS-062019.pdf; *Mifepristone*, AMA Policy (2018), https://policysearch.ama-assn.org/policyfinder/detail/mifepristone?uri=%2FAMADoc%2FHOD.xml-H-100.948.xml

Under the REMS, the FDA requires that (1) a patient be handed the Mifepristone at a clinic, medical office, or hospital under the supervision of a healthcare provider; (2) the healthcare provider must be registered with the drug manufacturer; and, (3) the patient must sign a "Patient Agreement" form confirming that she has received counseling on the risks associated with Mifepristone. These onerous and medically unnecessary requirements limit healthcare providers' ability to assist their female patients, particularly during this global healthcare crisis.

For example, due to the REMS, patients have to travel to a designated clinic, medical office, or hospital, as opposed to getting a prescription from their doctor using telehealth, and then obtaining Mifepristone at a local pharmacy or delivered by mail. The FDA should not mandate this medically unnecessary travel, particularly during the COVID-19 crisis where not only are women being advised to stay home, but families are faced with additional childcare and financial constraints.

The REMS also require that a prescriber must be registered with the manufacturer in order to prescribe Mifepristone, which poses additional obstacles. Once a prescriber is certified, the prescriber must set up an account with the drug distribution company, provide the distribution company with a hard copy of their U.S. DEA license and state medical license, and then sign a special resolution to become a Mifepristone dispenser. These steps create delays and obstacles to accessing care for women under even the best of circumstances. In this time of crisis, when the States are being encouraged to expand use of telehealth in order to bend the curve and contain the spread of COVID-19, these REMS barriers on Mifepristone mean that providers cannot increase access to meet demand.

Yet, the most burdensome aspect of the REMS are the "Elements to Assure Safe Use." These requirements must be "commensurate with the specific serious risk[s]" listed in the drug label, "required as part of [a] strategy to mitigate" such risks, and not be "unduly burdensome on patient access to the drug, considering in particular . . . patients in rural or medically underserved areas."[6] Mifepristone should not be subjected to these requirements when numerous medical studies have shown that Mifepristone is safe. In fact, Mifepristone is *four times* safer than Viagra and *fourteen times* safer than carrying a pregnancy to term. The FDA itself has stated that the "safety profile of Mifepristone is well-characterized and its risks well-understood after more than 15 years of marketing. Serious adverse events are rare and the safety profile of Mifepristone has not substantially changed." Furthermore, given the current pandemic, this requirement is imposing significant burdens on women in rural and medically underserved communities in accessing care, not to mention the additional burdens it imposes to all women across the country as the Centers for Disease Control and Prevention and the World Health Organization urge people to stay home.

[6] 21 U.S.C. §§ 355-1(f)(1)(A), 2(A), 2(C).

In light of the unprecedented COVID-19 crisis, we request you remove the FDA's restrictive REMS designation for Mifepristone thereby removing these unnecessary, undue burdens in accessing safe and time-sensitive, essential medical care. Alternatively, at a minimum, we request that you use your enforcement discretion to allow certified prescribers to use telehealth for mifepristone. As you know, all residents of California, Colorado, Connecticut, Delaware, Hawaii, Illinois, Maine, Minnesota, New Mexico, New York, North Carolina, Oregon, and Vermont are ordered to shelter-in-place or are under similar restrictions, as are other Americans around the country, and our economy is feeling those immediate impacts. National public health experts urge the same nationwide. However, with the FDA's REMS designation, women seeking to obtain healthcare cannot abide by such requirements. These women are putting themselves and their families at risk when they seek out the healthcare that they need, and the federal government must act to ensure that no matter where they live, they can continue to receive necessary, safe, and legal abortion care.

Sincerely,

XAVIER BECERRA
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PHIL WEISER
Colorado Attorney General

WILLIAM TONG
Connecticut Attorney General

KATHLEEN JENNINGS
Delaware Attorney General

KARL A. RACINE
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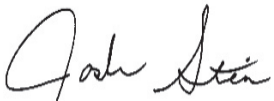
KEITH ELLISON
Minnesota Attorney General

AARON D. FORD
Nevada Attorney General

HECTOR BALDERAS
New Mexico Attorney General

LETITIA JAMES
New York Attorney General



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PETER F. NERONHA
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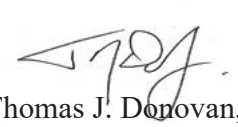

Thomas J. Donovan, Jr.
Vermont Attorney General

Mark R. Herring
Virginia Attorney General

AAFP
AMERICAN ACADEMY OF FAMILY PHYSICIANS

June 20, 2019

Norman Sharpless, M.D.
Acting Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue NW
Silver Spring, MD 20993

Dear Acting Commissioner Sharpless:

On behalf of the American Academy of Family Physicians (AAFP), which represents 134,600 family physicians and medical students across the country, I write to convey the organization's support for removing the current Risk Evaluation and Mitigation Strategy (REMS) and Element to Assure Safe Use (ETASU) status for mifepristone, the drug regime that can medically induce abortion and help provide miscarriage treatment.

The AAFP seeks changes in the drug's current REMS designation to conform to current evidence. This aligns with other medical specialty organizations, such as the American College of Obstetricians and Gynecologists. Recent research also indicates the agency's safety protocols are particularly stringent for the drug. Most importantly, the current drug label creates an unnecessary health care barrier for women who need it the most.

Section 501-1 of the *Food, Drugs, and Cosmetics Act* (21 U.S.C. 355-1) indicates that the agency must evaluate if a drug's risks outweigh benefits. Since mifepristone entered the market in 2000, nearly 3 million women have used it, along with misoprostol, for essential medical care with a high degree of effectiveness (over 97%) and minor complication risks (less than 1%), particularly when accessing it early. In addition, the drug regime poses far fewer risks than medications with similar safety standards in place such as Accutane, which is associated with risk for birth defects. For women, particularly those in rural and medically-underserved areas who typically lack health care options, current protocols may result in delays that may increase their need for surgical abortion. This also applies for those who may need miscarriage treatment where efficient mifepristone usage may be the most patient-centered option.

Again, we urge your consideration of this request. For more information, please contact Sonya Clay, Government Relations Representative, at 202-232-9033 or sclay@aafp.org.

Sincerely,

Michael L. Munger, MD, FAAFP
Board Chair

April 6, 2020

Dr. Stephen Hahn
Commissioner
Office of the Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Dear Commissioner Hahn,

We, the undersigned 80 organizations, urge you to immediately lift the medically unnecessary restrictions on medication abortion that further endanger pregnant people and strain the health care system during the global COVID-19 outbreak. As you may be aware, the United Kingdom Department of Health recently approved home use of both stages of medication abortion to limit the spread of COVID-19.[i] The U.S. FDA should similarly act quickly to protect the health of pregnant people and health care professionals.

Due to the pandemic, one in four Americans are currently under strict shelter-at-home orders to slow the virus's spread, with more closures expected as the health system copes with a growing caseload. We know that hundreds of thousands of pregnant people will need an abortion during this crisis. For many of these people, access to safe and effective mifepristone could be a lifeline, ensuring they receive prompt abortion care without having to visit a clinic, or even leave their homes.

Yet the FDA mandates that providers must be certified and registered with the drug sponsor to prescribe the drug, and pregnant people must go to a clinic, medical office or hospital to obtain it, rather than through a retail pharmacy — even though the FDA permits patients to wait until they get home to swallow the pill. Solid research and nearly 20 years of clinical experience have demonstrated that these requirements are medically unnecessary.[ii]

These requirements have long harmed patients' health by delaying or blocking access to medication abortion with no countervailing medical benefit. Now, in the midst of a public health emergency, these requirements are further endangering patients and straining the health system. Under the Risk Evaluation and Mitigation Strategies (REMS) and Elements to Assure Safe Use (ETASU) imposed by the FDA on mifepristone, both patients and clinic staff are forced to travel during a pandemic, don protective gear, and increase their exposure to potentially sick individuals — with no corresponding health benefit to justify these serious risks.

Some states have attempted to prohibit clinic-based abortion services altogether by falsely declaring that abortions are "nonessential" procedures and can be delayed during the outbreak. But even in states with robust support for abortion access, clinic services may be curtailed

by nationwide shortages of basic medical supplies and personal protective equipment, such as gloves and masks.

In every case, requiring pregnant people to travel to providers for services that could be performed remotely through telehealth consultations in order to receive FDA-approved medication that could be available at retail pharmacies through pickup or delivery, threatens both patient and provider.

Sensibly, the FDA has explicitly recognized that enforcement of REMS and ETASU restrictions during a pandemic "put[s] patients and others at risk for transmission of the coronavirus" and has suspended its enforcement of critical restrictions imposed on other drugs — even when they have a far riskier safety profile.

In guidance issued in March, the FDA noted its "critical role in protecting the United States from threats including emerging infectious diseases" and its commitment "to providing timely guidance to support response efforts to this pandemic."[iii]

The guidance states:

> FDA recognizes that during the COVID-19 PHE [public health emergency], completion of REMS-required laboratory testing or imaging studies may be difficult ***because patients may need to avoid public places and patients suspected of having COVID-19 may be self-isolating and/or subject to quarantine.*** Under these circumstances, undergoing laboratory testing or imaging studies ***in order to obtain a drug subject to a REMS can put patients and others at risk for transmission of the coronavirus*** [emphasis ours].

In light of the FDA's March guidance and explicit recognition of the dire risks, we urge you to lift the REMS and ETASU restrictions on mifepristone to ensure that pregnant people have access to this safe and effective drug even during this national public health crisis. If everyone who needs a medication abortion can safely access mifepristone through telehealth appointments and have it shipped to them, then that action alone would alleviate strain on the health system while protecting patients.

In the absence of this action, the FDA will force pregnant people to pursue alternatives. Some will turn to overseas pharmacies. While many of us believe that this can be a safe method for procuring medication abortion, *the FDA* has argued that doing so "poses an inherent risk to consumers who purchase those products."[iv] Some pregnant people will use alternative, non-medical methods of self-managed abortion — as long practiced by women — that can be safe and effective. But many others will turn to dangerous or unproven methods. Some people who travel (often over long distances) to pick up mifepristone in a clinic will be exposed to COVID-19. And, of course, many people will be forced to carry an unwanted pregnancy to term during a pandemic — with unknown but likely significant risks. **In making a risk-benefit analysis around the REMS and ETASU for mifepristone, the FDA must weigh all of these real-world considerations.**

The FDA is putting the lives of pregnant people at risk. We urge you to take steps now to ensure that mifepristone remains a safe and effective form of abortion care during the crisis.

Thank you for your prompt attention to this urgent public health matter. Please contact Cynthia A. Pearson, Executive Director at the National Women's Health Network at cpearson@nwhn.org with your response.

Sincerely,

500 Women Scientists
Abortion Care Network
Access Reproductive Care-Southeast
Advocates for Youth
All-Options
American Humanist Association
American Medical Student Association (AMSA)
AMPLIFY GA
Asian & Pacific Islander American Health Forum
Black Women's Health Imperative
California Latinas for Reproductive Justice
Catholics for Choice
Center for American Progress
CHOICES. Memphis Center for Reproductive Health
Civil Liberties and Public Policy
Clearinghouse on Women's Issues
Cobalt
Consumers for Affordable Health Care
Creating a Clinician Corps
DuPont Clinic
Equality California
Equity Forward
EverThrive Illinois
Feminist Majority Foundation
Feminist Women’s Health Center
Florida Access Network
Forward Together Action
Gender Justice
Gender Justice League Seattle
GLMA: Health Professionals Advancing LGBTQ Equality
Human Rights Watch
Ibis Reproductive Health
If/When/How: Lawyering for Reproductive Justice
In Our Own Voice: National Black Women’s Reproductive Justice Agenda
Indiana Religious Coalition for Reproductive Choice

International Campaign for Women's Safe Right to Abortion
International Women's Health Coalition
Ipas
Jacobs Institute of Women's Health
Jane's Due Process
Legal Voice
Medical Students for Choice
NARAL Pro-Choice America
NARAL Pro-Choice Texas
National Abortion Federation
National Advocates for Pregnant Women
National Asian Pacific American Women's Forum
National Center for Lesbian Rights
National Council of Jewish Women
National Health Law Program
National Hispanic Medical Association
National Latina Institute for Reproductive Justice
National Minority Quality Forum
National Network of Abortion Funds
National Organization for Women
National Women's Health Network
National Working Positive Coalition
New Era Colorado
Our Bodies Ourselves
PAI
Pendergast Consulting
Population Connection Action Fund
Power to Decide
Progress Florida Education Institute
Public Citizen
Religious Coalition for Reproductive Choice
Reproaction
Reproductive Health Access Project
SIECUS: Sex Ed for Social Change
SisterSong Women of Color Reproductive Justice Collective
Southwest Women's Law Center in Albuquerque, New Mexico
SPARK Reproductive Justice NOW!
Students for Choice
The Women's Centers
Union of Concerned Scientists
URGE: Unite for Reproductive & Gender Equity
Women First Digital
Women's Health Specialists
Women Have Options/Ohio
Women's Law Project, Pennsylvania
WVFREE

CC:
Dr. Janet Woodcock
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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[i] "Temporary approval of home use for both stages of early medical abortion" Department of Health and Social Care and The Rt Hon Matt Hancock MP. March 30, 2020
https://www.gov.uk/government/publications/temporary-approval-of-home-use-for-both-stages-of-early-medical-abortion--2

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https://www.nap.edu/catalog/24950/the-safety-and-quality-of-abortion-care-in-the-united-states

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https://www.fda.gov/media/136317/download

[iv] "WARNING LETTER to Aidaccess.org," U.S. Food and Drug Administration, 8 March 2019.
https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/aidaccessorg-575658-03082019

Published on *Guttmacher Institute* (https://www.guttmacher.org)
Date: 12-Nov-2019

Medication Abortion

Evidence You Can Use: Medication Abortion is designed to give advocates, service providers and policymakers the data and resources they need to engage in ongoing policy discussions in their states. It includes information on state laws and policies, a synthesis of the relevant research, information on states in which the issue has been debated in the past three years and links to state-specific data. The toolkit provides the evidence base for understanding regulations and restrictions related to medication abortion.

BACKGROUND

A safe and effective option at early gestations, medication abortion accounted for more than one-third (39%) of all abortions in the United States in 2017. Many women prefer medication abortion to surgical abortion, as it is noninvasive and can be completed in a patient's chosen setting, such as at home.

Medication abortion using a combination of mifepristone and misoprostol was first approved by the U.S. Food and Drug Administration (FDA) in 2000. In 2016, on the basis of scientific studies, the FDA updated its protocol to a regimen that is just as effective but uses less medication, has fewer side effects, has a longer time span for use (up to 70 days after a patient's last menstrual period) and requires fewer visits to the provider. By the time the protocol was updated, this evidence-based regimen was already in widespread use among providers.

Since 2004, states have enacted several types of restrictions targeting medication abortion. Most of the laws take one of two approaches: limiting provision to the FDA protocol or requiring in-person administration. By limiting providers to the current FDA protocol, states may preclude providers from taking advantage of future evidence-based changes in the administration of medication abortion. And by requiring in-person administration, states prevent providers from using telemedicine to administer medication abortion. In doing so, they reduce access to abortion in rural areas. In addition, a few states require providers to share with patients the medically unsupported claim that the medication abortion process can be reversed.

STATE LAWS AND POLICIES

For a chart of current laws and policies in each state related to medication abortion, see Medication Abortion.

For information on state laws and policies related to other sexual and reproductive health and rights issues, see State Laws and Policies, issue-by-issue fact sheets updated monthly by the Guttmacher Institute's policy analysts to reflect the most recent legislative, administrative and judicial actions.

RELEVANT DATA AND ANALYSIS

Administration of Medication Abortion

The protocol for administering medication abortion is based on decades of research showing that it is safe and effective.

- The current protocol for administering medication abortion, updated by the FDA in March 2016, is widely tested and evidence-based. This regimen is supported by the American College of Obstetrics and Gynecologists (ACOG), National Abortion Federation and Planned Parenthood Federation of America.
  - The protocol is approved for use up to 70 days after a patient's last menstrual period.[1]
  - Under the protocol, only one visit is required for a patient to obtain medication abortion pills, and the patient may take the second medication in the regimen (misoprostol) at home or another chosen location. Follow-up with the provider can be done over the phone 7–14 days later.[2,3]
- Evidence shows that medication abortion is safe.[2,3] Serious complications requiring hospitalization for infection treatment or transfusion occur in fewer than 0.4% of patients under the updated protocol.[4]
- Medication abortion is highly effective, with a success rate of more than 95% using the standard protocol.[5]

The administration of medication abortion is more heavily regulated than necessary. The medication abortion regimen is low-risk and easy to follow, and the process can be safely managed by patients and providers. Despite this, the FDA imposes restrictions on medication abortion that hinder access for potential patients and do not reflect its long record of safe use.

- Mifepristone, the medication licensed for medication abortion in the United States, is available as both a brand-name pill (Mifeprex) and as a generic (approved in 2019).[3] Both are subject to a Risk Evaluation and Mitigation Strategy (REMS) that limits dispensing to certified providers and specified settings, which do not include retail pharmacies.[6]
- The FDA's limitations on mifepristone can discourage providers from offering medication abortion because they have to preorder and stock the medication ahead of time and, due to the history of violence and harassment against abortion providers, may be reluctant to be added to the manufacturer's record of certified providers.[7,8]
- This dispensing requirement prevents patients from obtaining the medication from a pharmacy (whether online or in-person) like most other safe and effective medications.[7,8]
- A 2017 expert panel suggested that the REMS is inconsistent with mifepristone's safety record and simplicity of use, and places an unfair burden on those seeking access to medication abortion.[7]

Expanding Abortion Access Using Medication Abortion

Medication abortion can be safely offered in diverse settings and by a range of health care providers.

- An expert panel convened by the National Academies of Science, Engineering and Medicine in 2018 concluded that requiring medication abortion to be provided at a particular type of facility, solely by a physician or in the physical presence of a health care provider yields no improvement in safety or quality of care.[9]
- The use of medication abortion has increased, even as overall abortion rates decline. In 2017, medication abortion accounted for 39% of all abortions—an increase of 25% since 2014.[10]
  - The majority of medication abortions are provided at specialized abortion clinics, where more than half of patient visits are for abortion services. However, in 2017, nearly half (47%) were provided at nonspecialized clinics offering a broader range of health care services or at physicians' offices.[10]
  - The number of abortion providers offering only medication abortion increased slightly between 2014 and 2017 (from 23% to 26%). A higher proportion of nonspecialized clinics (41%) offered medication abortion as their sole abortion service, compared with 4% of specialized abortion clinics.[10]
- Practically speaking, medication abortion does not need to be administered by physicians. It can be safely provided by other trained health care providers, including physician assistants, nurse practitioners and certified nurse midwives. State laws that restrict provision only to physicians limit patient access.[9]
  - The World Health Organization recommends that general practice physicians, nurses, midwives and other advanced practice clinicians be allowed to provide medication abortion.[11] Training in surgical abortion is not necessary to administer medication abortion.
  - The 2016 FDA protocol update expanded provider eligibility to include advanced practice clinicians.[3]
- The recent growth in the use of telemedicine in diverse health care settings has proven that it is an effective and important tool for expanding access to care, improving health outcomes and reducing health care costs.[12]
  - The use of telemedicine has increased substantially in the last decade. For instance, a study of private health insurance claims showed the proportion of claims using telehealth increased by 1,200% between

ANSIRH
ADVANCING NEW STANDARDS IN REPRODUCTIVE HEALTH

Mifepristone safety

ISSUE BRIEF, APRIL 2019

Analysis of Medication Abortion Risk and the FDA report "Mifepristone U.S. Post-Marketing Adverse Events Summary through 12/31/2018"

Summary

The FDA report "Mifepristone U.S. Post-Marketing Adverse Events Summary through 12/31/2018" includes adverse events associated with the use of mifepristone, regardless of their likelihood of being causally linked to the abortion.[1] Over 3.7 million US women have used medication abortion with mifepristone and misoprostol since Mifeprex (mifepristone 200 mg) was first approved by the US Food and Drug Administration (FDA) in 2000. Since then, the safety of the treatment has been reaffirmed by rigorous research that supplements monitoring data from the FDA.

Understanding medication abortion complications as published by the FDA

As of December 2018, the FDA reports that 24 women, out of approximately 3.7 million, have died after taking mifepristone for medication abortion. However, as the FDA notes, "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." Among these 24 deaths:

- 13 cases are probably or possibly related to the abortion, including:
  - 8 cases of Clostridium-related sepsis
  - 1 case of delayed onset toxic shock-like syndrome
  - 1 case of hemorrhage
  - 2 cases of ruptured ectopic pregnancy
  - 1 case where the cause of death was unclear
- 11 cases appear to be unrelated to the abortion, including:
  - 6 cases of drug or substance use, intoxication and/or overdose
  - 3 cases of confirmed or suspected homicide
  - 1 case of suicide
  - 1 natural death due to severe pulmonary emphysema

Based on this, the overall mortality rate associated with medication abortion is 0.65 deaths per 100,000 medication abortions (24 deaths/3.7 million medication abortion cases). This mortality rate is similar to that reported for abortion overall (0.7 deaths per 100,000 procedures).[2] If only the cases that appear to be related to the abortion are included, the mortality rate is 0.35 deaths per 100,000 medication abortions (13 deaths/3.7 million medication abortion cases).

Because it is mandatory to report any death among someone who used mifepristone and because the US Centers for Disease Control and Prevention has an active surveillance program to monitor abortion-related deaths,[2] these reports capture information about all possible deaths related to medication abortion.

The FDA also published the number of cases of hospitalization and other complications (some already counted in the hospitalization cases) reported to them among women using medication abortion. However, unlike for deaths, there is no active surveillance program, so this report should not be considered as conclusive. We do know that serious complications are rare with medication

abortion. The most rigorous study of medication abortion safety included data from 11,319 Medi-Cal patients in California.[3] In this study, only 35 (0.31%) had a major complication, defined as hospitalization, blood transfusion, or surgery.

Other reports and FDA approvals highlighting the safety of medication abortion

The FDA conducted a rigorous review of research from the United States and other countries to assess the safety profile before it approved mifepristone in 2000. The safety of medication abortion has been highlighted repeatedly since then:

- In 2016, the FDA approved an updated label for mifepristone that allowed for using medication abortion later in pregnancy (up to 10 weeks from last menstrual period) and simplified the drug regimen. It also removed the requirement that all serious adverse events be reported to the agency and now only requires that deaths be reported.[4]
- In 2018, the US Government Accountability Office published a report that evaluated the process that FDA used when it updated the mifepristone label. The report concluded that the agency used its standard review process to incorporate the best available evidence into the updated label. [5]
- In 2018, the National Academies of Sciences, Engineering, and Medicine released a report that highlighted the safety and effectiveness of medication abortion.[6]
- In April 2019, the FDA approved a generic form of mifepristone for medication abortion, which gave the agency another opportunity to review the safety of the treatment.[4]

Understanding risk

Unfortunately, pregnancy can be risky, and women are also at risk of dying if they choose to continue their pregnancy to term. Nationally, the pregnancy-related mortality ratio is 18 deaths per 100,000 live births, and it is even higher for Black women—40 deaths per 100,000 live births.[7] The mortality rate for women known to have had a live-born infant is 8.8 per 100,000 live births,[8] which is about 14 times higher than the mortality rate associated with medication abortion.

Other medications that are commonly prescribed or administered in outpatient settings also have risks, including a small risk of death. Penicillin causes a fatal anaphylactic reaction at a rate of 2 deaths per 100,000 patients administered the drug.[9] Phosphodiesterase type-5 inhibitors, which are used for erectile dysfunction and include Viagra, have a fatality rate of 4 deaths per 100,000 users.[10] These risks are several times higher than the risk of death with medication abortion. Acetaminophen (Tylenol) overdose is the most common cause of acute liver failure in the U.S. and accounts for over 600 deaths annually.[11]

Conclusion

Medication abortion with mifepristone and misoprostol is very safe and effective. The safety profile is similar to that of vacuum aspiration abortion, and medication abortion is safer than continuing a pregnancy to term or using other common medications.

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Time to Reevaluate U.S. Mifepristone Restrictions

Jane E. Henney, M.D., and Helene D. Gayle, M.D., M.P.H.

In September 2000, the Food and Drug Administration (FDA) — of which one of us was commissioner at the time — approved mifepristone, one of two medications used to end early unwanted pregnancies. At that time, because of limited clinical trial data from the United States, the FDA simultaneously imposed various restrictions — including a limited distribution system — to ensure that the benefits outweighed the risks of the newly approved drug. Now, after nearly two decades of actual use, additional research, and a comprehensive review conducted by the National Academies of Science, Engineering, and Medicine (NASEM) — which the other one of us cochaired — all of which clearly demonstrate that mifepristone is extremely safe and effective, we believe that the distribution restrictions may no longer be appropriate.

Mifepristone is a antagonist that blocks progesterone, a hormone that is essential to pregnancy, and along with another medication (misoprostol) enables the body to terminate pregnancy. When the FDA approved mifepristone, data from its use in Europe — primarily, but not limited to, France, where it had been used for more than a decade — were used to support the approval. There were questions about its use, however, such as whether the rate and severity of adverse events would be similar or greater with mifepristone than with surgical abortions in the United States. Furthermore, the health care delivery systems in France and other European countries differ greatly from that in the United States. In recognition of these issues, the FDA restricted the distribution of mifepristone to certified health care providers and limited dispensing to patients, who could receive it only at qualified clinics and hospitals. In addition, extensive record keeping by these health care providers was required. Thus, a pregnant person would not be able to be treated by her own physician unless her doctor was among those certified. Given the available scientific evidence at the time, we believe that the decision to approve mifepristone was the right one, as was the FDA's judgment with regard to initially limiting its distribution system.

Since its approval in 2000, more than 3.7 million women have used mifepristone to end an early pregnancy in the United States — it is approved for use up to 70 days into a pregnancy.[1] Nearly two decades of data on its use and effects on patients provide significant new insights into its safety and efficacy.[2] Mifepristone is more than 97% effective. Most adverse effects are mild, such as cramping or abdominal pain, and the rate of severe adverse events is very low: such events occur in less than 0.5% of patients, according to the FDA. Many drugs marketed in the United States have higher adverse event rates and are not subject to restricted distribution. A 2018 review conducted for the NASEM by a committee of leading medical and research experts (which one of us cochaired) concluded that both surgical and medication abortion in the United States are extremely safe.[3]

The accumulated knowledge about mifepristone strongly suggests that the current restricted distribution system is not aligned with the limited risks that are now known to be posed by the drug. A recent study of mifepristone in Ireland and Northern Ireland showed that medication abortions can be done at home as safely as treatments can be administered in a clinic, confirming that there is no advantage to special dispensing restrictions.[4] Countries with regulatory bodies similar to the FDA have minimal restrictions on mifepristone. For example, Australia and Canada allow it to be dispensed in pharmacies, and Canada recently removed restrictions that require that an ultrasound be performed to determine gestational age before medication for an abortion is provided.

Removing access barriers to this medication has a significant effect on the ability to obtain safe abortion care. In fact, the World Health Organization has included mifepristone on its List of Essential Medicines, noting that it "has revolutionized access to safe and effective abortion care globally."[5] The NASEM report notes that state restrictions that require multiple visits or impose waiting periods may delay access to care and "by doing so, may increase the clinical risks and costs of care." To mitigate inequities in access, NASEM experts recommended that the FDA reconsider the distribution restrictions placed on mifepristone, given "the extensive

body of research demonstrating its safety and effectiveness." In fact, the FDA has approved clinical trials for alternative distribution models for mifepristone in the United States.

Recent media reports indicate that, as access to clinics that satisfy the FDA restrictions shrinks, people are increasingly turning to the Internet to source mifepristone on their own from foreign manufacturers. The FDA cannot effectively control Internet sales, which are likely to grow further, nor can the safety of these foreign-sourced products be ensured.

Women should have access to FDA-approved products whose safety and effectiveness are confirmed. Since the evidence available today indicates that the current restrictions are overly prescriptive, we urge the FDA to reevaluate whether they are still necessary.

Disclosure forms provided by the authors are available at NEJM.org.

From the National Academy of Medicine, Washington, DC (J.E.H.); and the Chicago Community Trust, Chicago (H.D.G.).

This article was published on June 26, 2019, at NEJM.org.

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DOI: 10.1056/NEJMp1908305

A Most Reckless Proposal — A Plan to Continue Asbestos Use in the United States

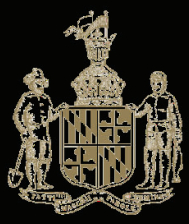
Philip J. Landrigan, M.D., and Richard A. Lemen, Ph.D.

Each year, nearly 40,000 Americans die often painful, protracted deaths from diseases caused by asbestos. These deaths occur in firefighters, police officers, construction workers, miners, military veterans, shipyard workers, and maintenance workers whose exposures to asbestos are primarily occupational. Death also occurs in partners and children of such workers, whose only exposures to asbestos were from dust on clothing brought home from work by a family member. In the United States, treatment of asbestos-related diseases — including malignant mesothelioma, asbestosis, lung cancer, laryngeal cancer, and ovarian cancer[1] — costs hundreds of millions of dollars each year.

The health hazards of asbestos were recognized in the early 20th century, but this information did not become widespread until a landmark 1964 publication documented the association between asbestos exposure and cancer.[2] In the years after that report, the amount of asbestos used in the United States fell by more than 99% — from more than 650,000 metric tons in 1963[3] to roughly 750 metric tons in 2018, according to data from the U.S. Geological Survey. The main drivers of this decline have been federal regulations that banned and restricted many uses of asbestos and aggressive litigation on behalf of injured workers against companies that produced and used asbestos with full knowledge of its dangers.

Most asbestos-related deaths in the United States today are caused either by cancers of long latency that resulted from exposures decades ago or by more recent exposures to asbestos installed long ago in the form of insulation, pipe wrapping, roofing tiles, and siding in thousands of office buildings, schools, and homes. The populations at greatest risk for exposure to legacy asbestos are firefighters, maintenance workers, and people employed in the construction and demolition industries. Great diligence is required of employers and federal regulators to protect these high-risk workers against occupational asbestos exposures.

But contrary to common belief among health professionals and the public, asbestos has never been permanently banned in the United States. The dominant legally permitted use of asbestos today is by the chemical-manu-



THE MARYLAND GENERAL ASSEMBLY
ANNAPOLIS, MARYLAND 21401

October 6, 2020

Dr. Stephen Hahn
Commissioner
Office of the Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20093-0002

Dear Commissioner:

We write you as Members of the Maryland General Assembly who want to ensure Marylanders have access to the full range of evidenced-based clinical services to manage their reproductive health. We are concerned that the Food and Drug Administration's (FDA's) restrictions on Mifepristone have created a significant and unnecessary barrier to individuals in obtaining medical abortions. The American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Family Physicians (AAFP) have recommended that these restrictions, known as the Risk Evaluation and Mitigation Strategies (REMS), be eliminated[1,2]. We ask the FDA to consider the position of these leading medical organizations and repeal REMS both immediately and permanently.

The REMS has limited access to medical abortion in Maryland, just as it has in other states. We are particularly concerned about the REMS' impact on individuals and communities already struggling to access health care services. Black and brown communities are disproportionately impacted by access issues, as reflected in health disparities across health outcome measures.

- **Medically At-Risk Individuals in Pandemic and Beyond:** The REMS places more risk on individuals susceptible to airborne infections, such as COVID-19, when seeking medical care. Individuals must go to their clinician's office or facility to obtain Mifepristone. They cannot obtain Mifepristone at a pharmacy; either in person or through mail order, as the REMS requires clinicians to dispense Mifepristone directly to patients.

[1] American College of Obstetricians and Gynecologists, "Improving Access to Mifepristone for Reproductive Health Indications: Position Statement," June 2018. https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications

[2] American Academy of Family Practitioners, "Letter to FDA on REMS Requirements for Mifepristone," June 2019. https://www.aafp.org/dam/AAFP/documents/advocacy/prevention/women/LT-FDA-MifepristoneREMS-062019.pdf

This restriction means telehealth is not an option for medical abortions. The REMS requirements create risk for individuals who are self-isolating to protect themselves and household members;

- **Rural Communities:** The REMS restrictions have contributed to the shortage of abortion providers. This shortage is particularly pronounced in rural communities. In Maryland, almost three-fourth of counties do not have a clinic that provides abortion services[3]. To address this issue, we need to expand the number of clinicians who provide medical abortion services in-person and through telehealth. While the FDA lifted the outdated restrictions on advanced practice clinicians in the provision of Mifepristone in 2016, other restrictions remain. Clinicians must enter into a written FDA-approved agreement with the manufacturer of Mifepristone. This is not the usual practice for other drugs. These agreements make some clinicians uneasy because they fear they will be identified publicly. With the history of violence against abortion providers, clinicians have a heightened need for confidentiality;

- **Lower-Income/Working Communities:** The REMS restrictions profoundly impact access to medical abortion in communities with lower-income and working households. These communities may face challenges with transportation and inflexible work schedule in getting to health care appointments. To improve access for medical abortion, it is imperative to increase the number of providers in these communities and provide the flexibility of in-person or telehealth services. However, the REMS restricts the ability of the health care community and policy makers to support their communities.

Mifepristone is not a new drug. The FDA approved Mifepristone twenty years ago on September 28, 2000. With a long track record of safety and efficacy, we support the conclusions of ACOG and AAFP. The FDA should repeal the REMS.

In Maryland, we have endeavored to protect and expand access to reproductive health care for all residents. However, our efforts have been hampered by the REMS. **By singling-out Mifepristone for unnecessary restrictions, the REMS marginalize abortion care. Abortion is a part, not separate from, the health care continuum.**

Thank you for your attention to this matter. We would appreciate a response on the FDA's plans regarding the REMS issue.

Sincerely,

President Bill Ferguson Speaker Adrienne A. Jones

Senator Shelly Hettleman Delegate Ariana Kelly

[3] Jones RK, Witwer E and Jerman J, Abortion Incidence and Service Availability in the United States, 2017, New York: Guttmacher Institute, 2019.

Senator Pam Beidle
Senator Jill Carter
Senator Sarah Elfreth
Senator Brian Feldman
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Delegate Courtney Watson
Delegate Melissa Wells
Delegate Jheanelle Wilkins
Delegate Nicole Williams
Delegate Karen Lewis Young
Delegate Patrick Young, Jr.

INTERIM UPDATE

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 200 *(Replaces Practice Bulletin Number 150, May 2015)*

Committee on Practice Bulletins—Gynecology. This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins Gynecology in collaboration with Sarah Prager, MD; Vanessa K. Dalton, MD, MPH; and Rebecca H. Allen, MD, MPH.

INTERIM UPDATE: This Practice Bulletin is updated as highlighted to reflect recent evidence regarding the use of mifepristone combined with misoprostol for medical management of early pregnancy loss. This Practice Bulletin also includes limited, focused updates to align with Practice Bulletin No. 181, *Prevention of Rh D Alloimmunization*.

Early Pregnancy Loss

Early pregnancy loss, or loss of an intrauterine pregnancy within the first trimester, is encountered commonly in clinical practice. Obstetricians and gynecologists should understand the use of various diagnostic tools to differentiate between viable and nonviable pregnancies and offer the full range of therapeutic options to patients, including expectant, medical, and surgical management. The purpose of this Practice Bulletin is to review diagnostic approaches and describe options for the management of early pregnancy loss.

Background

Definition

Early pregnancy loss is defined as a nonviable, intrauterine pregnancy with either an empty gestational sac or a gestational sac containing an embryo or fetus without fetal heart activity within the first 12 6/7 weeks of gestation (1). In the first trimester, the terms miscarriage, spontaneous abortion, and early pregnancy loss are used interchangeably, and there is no consensus on terminology in the literature. However, early pregnancy loss is the term that will be used in this Practice Bulletin.

Incidence

Early pregnancy loss is common, occurring in 10% of all clinically recognized pregnancies (2 4). Approximately 80% of all cases of pregnancy loss occur within the first trimester (2, 3).

Etiology and Risk Factors

Approximately 50% of all cases of early pregnancy loss are due to fetal chromosomal abnormalities (5, 6). The most common risk factors identified among women who have experienced early pregnancy loss are advanced maternal age and a prior early pregnancy loss (7, 8). The frequency of clinically recognized early pregnancy loss for women aged 20 30 years is 9 17%, and this rate increases sharply from 20% at age 35 years to 40% at age 40 years and 80% at age 45 years (7). Discussion of the many risk factors thought to be associated with early pregnancy loss is beyond the scope of this document and is covered in more detail in other publications (6, 7).

Clinical Considerations and Recommendations

▶ ***What findings can be used to confirm a diagnosis of early pregnancy loss?***

Common symptoms of early pregnancy loss, such as vaginal bleeding and uterine cramping, also are common in normal gestation, ectopic pregnancy, and molar pregnancy. Before initiating treatment, it is important to distinguish early pregnancy loss from other early pregnancy complications. Treatment of an early pregnancy loss before confirmed diagnosis can have detrimental consequences, including interruption of a normal pregnancy, pregnancy complications, or birth defects (9). Therefore, a thorough

serial quantitative serum β-hCG measurements, may be useful, especially for women with limited access to follow-up ultrasound examination (25). However, these approaches have not been studied sufficiently among women with early pregnancy loss to provide meaningful guidance.

Medical Management

Medical management for early pregnancy loss can be considered in women without infection, hemorrhage, severe anemia, or bleeding disorders who want to shorten the time to complete expulsion but prefer to avoid surgical evacuation. Compared with expectant management, medical management of early pregnancy loss decreases the time to expulsion and increases the rate of complete expulsion without the need for surgical intervention (26).

Misoprostol-based regimens have been extensively studied for the medical management of early pregnancy loss (26). Most studies suggest that a larger dose of misoprostol is more effective than a smaller dose, and vaginal or sublingual administration is more effective than oral administration, although the sublingual route is associated with more cases of diarrhea (26). The largest randomized controlled trial conducted in the United States demonstrated complete expulsion by day 3 in 71% of women with first-trimester pregnancy loss after one dose of 800 micrograms of vaginal misoprostol (23). The success rate was increased to 84% after a second dose of 800 micrograms of vaginal misoprostol was administered if needed. Therefore, in patients for whom medical management of early pregnancy loss is indicated, initial treatment using 800 micrograms of vaginal misoprostol is recommended, with a repeat dose as needed (Box 1).

The addition of a dose of mifepristone (200 mg orally) 24 hours before misoprostol administration may significantly improve treatment efficacy and should be considered when mifepristone is available (Box 1). Although initial studies were unclear about the benefit of mifepristone for the management of early pregnancy loss (27), a 2018 randomized controlled trial showed that a combined mifepristone misoprostol regimen was superior to misoprostol alone for the management of early pregnancy loss (28). Among 300 women undergoing medical management for early pregnancy loss, those who received mifepristone (200 mg orally) followed by misoprostol (800 micrograms vaginally) 24 hours later had significantly increased rates of complete expulsion (relative risk [RR], 1.25; 95% CI, 1.09 1.43) compared with women who received misoprostol alone (800 micrograms vaginally) (28). The mifepristone misoprostol regimen also was associated with a decreased risk of surgical intervention with uterine aspiration to complete treatment (RR, 0.37; 95% CI, 0.21 0.68). Reports of bleeding intensity and pain as well as other adverse effects were generally similar for the two treatment groups, and the occurrence of serious adverse events was rare among all participants. These results are consistent with the demonstrated efficacy and safety of the mifepristone misoprostol combined regimen for medication-induced abortion (29, 30). Currently, the availability of mifepristone is limited by U.S. Food and Drug Administration Risk Evaluation and Mitigation Strategy restrictions (31). The American College of Obstetricians and Gynecologists supports improving access to mifepristone for reproductive health indications (32).

A 2013 Cochrane review of limited evidence concluded that among women with incomplete pregnancy loss (ie, incomplete tissue passage), the addition of

Box 1. Protocol for the Medical Management of Early Pregnancy Loss

- Misoprostol 800 micrograms vaginally, with one repeat dose as needed, no earlier than 3 hours after the first dose and typically within 7 days if there is no response to the first dose*
- A dose of mifepristone (200 mg orally) 24 hours before misoprostol administration should be considered when mifepristone is available.†
- Prescriptions for pain medications should be provided to the patient.
- Women who are Rh(D) negative and unsensitized should receive Rh(D)-immune globulin within 72 hours of the first misoprostol administration.
- Follow-up to document the complete passage of tissue can be accomplished by ultrasound examination, typically within 7–14 days. Serial serum β-hCG measurements may be used instead in settings where ultrasonography is unavailable. Patient-reported symptoms also should be considered when determining whether complete expulsion has occurred.
- If medical management fails, the patient may opt for expectant management, for a time determined by the woman and her obstetrician–gynecologist or other gynecologic provider, or suction curettage.

*Zhang J, Gilles JM, Barnhart K, Creinin MD, Westhoff C, Frederick MM. A comparison of medical management with misoprostol and surgical management for early pregnancy failure. National Institute of Child Health Human Development (NICHD) Management of Early Pregnancy Failure Trial. N Engl J Med 2005;353:761–9.

†Schreiber CA, Creinin MD, Atrio J, Sonalkar S, Ratcliffe SJ, Barnhart KT. Mifepristone pretreatment for the medical management of early pregnancy loss. N Engl J Med 2018;378:2161–70.

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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The authors thank Rachel K. Jones, PhD and Lawrence B. Finer, PhD of the Guttmacher Institute and Suzanne Zane, DVM, of the Division of Reproductive Health, Centers for Disease Control and Prevention, for providing essential input to develop the manuscript.

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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

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.

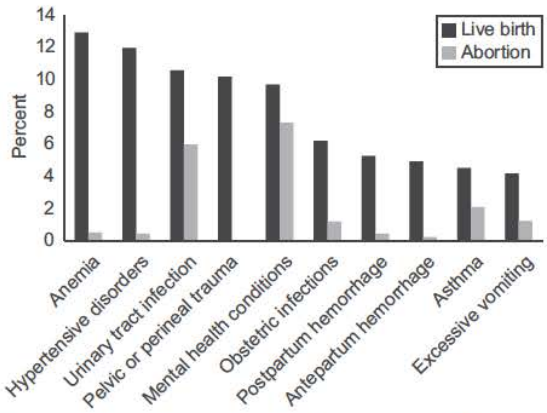

Fig. 1. Common maternal morbidities associated with live birth and abortion, 1998–2001. Common maternal morbidities defined as conditions either unique to pregnancy or potentially exacerbated by pregnancy that occurred in at least 5% of all pregnancies. Data from Bruce FC, Berg CJ, Hornbrook MC, Whitlock EP, Callaghan WM, Bachman DJ, et al. Maternal morbidity rates in a managed care population. Obstet Gynecol 2008;111:1089–95.

Raymond. Safety of Abortion Compared With Childbirth. Obstet Gynecol 2012.

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

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]

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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Morbidity and Mortality Weekly Report

Vital Signs: Pregnancy-Related Deaths, United States, 2011–2015, and Strategies for Prevention, 13 States, 2013–2017

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Abstract

Background: Approximately 700 women die from pregnancy-related complications in the United States every year.

Methods: Data from CDC's national Pregnancy Mortality Surveillance System (PMSS) for 2011–2015 were analyzed. Pregnancy-related mortality ratios (pregnancy-related deaths per 100,000 live births; PRMRs) were calculated overall and by sociodemographic characteristics. The distribution of pregnancy-related deaths by timing relative to the end of pregnancy and leading causes of death were calculated. Detailed data on pregnancy-related deaths during 2013–2017 from 13 state maternal mortality review committees (MMRCs) were analyzed for preventability, factors that contributed to pregnancy-related deaths, and MMRC-identified prevention strategies to address contributing factors.

Results: For 2011–2015, the national PRMR was 17.2 per 100,000 live births. Non-Hispanic black (black) women and American Indian/Alaska Native women had the highest PRMRs (42.8 and 32.5, respectively), 3.3 and 2.5 times as high, respectively, as the PRMR for non-Hispanic white (white) women (13.0). Timing of death was known for 87.7% (2,990) of pregnancy-related deaths. Among these deaths, 31.3% occurred during pregnancy, 16.9% on the day of delivery, 18.6% 1–6 days postpartum, 21.4% 7–42 days postpartum, and 11.7% 43–365 days postpartum. Leading causes of death included cardiovascular conditions, infection, and hemorrhage, and varied by timing. Approximately sixty percent of pregnancy-related deaths from state MMRCs were determined to be preventable and did not differ significantly by race/ethnicity or timing of death. MMRC data indicated that multiple factors contributed to pregnancy-related deaths. Contributing factors and prevention strategies can be categorized at the community, health facility, patient, provider, and system levels and include improving access to, and coordination and delivery of, quality care.

Conclusions: Pregnancy-related deaths occurred during pregnancy, around the time of delivery, and up to 1 year postpartum; leading causes varied by timing of death. Approximately three in five pregnancy-related deaths were preventable.

Implications for Public Health Practice: Strategies to address contributing factors to pregnancy-related deaths can be enacted at the community, health facility, patient, provider, and system levels.

Introduction

Approximately 700 women die annually in the United States from pregnancy-related complications (*1*). Significant racial/ethnic disparities in pregnancy-related mortality exist; black women have a pregnancy-related mortality ratio approximately three times as high as that of white women (*2*,*3*). Better understanding is needed on the circumstances surrounding pregnancy-related deaths and strategies to prevent future deaths.

This report describes the timing and characteristics of pregnancy-related deaths in the United States using 2011–2015 national CDC Pregnancy Mortality Surveillance System (PMSS) data. Data from 13 state maternal mortality review committees (MMRCs) during 2013–2017 were used to determine the percentage of pregnancy-related deaths that were preventable and factors that contributed to the deaths. MMRC-identified strategies for prevention are reported.

Methods

PMSS was established in 1986 by CDC and the American College of Obstetricians and Gynecologists (ACOG) to evaluate the causes of death and risk factors associated with pregnancy-related deaths. PMSS methodology has been described previously (*2*); CDC's Division of Reproductive Health requests that all states, the District of Columbia, and New York City send death certificates, linked live birth or fetal death certificates, and additional data when available, on deaths that occurred during

Summary

What is already known about this topic?

Approximately 700 women die annually in the United States from pregnancy-related complications.

What is added by this report?

Among pregnancy-related deaths for which timing was known, 31.3% deaths occurred during pregnancy, 16.9% on the day of delivery, 18.6% on days 1–6 postpartum, 21.4% on days 7–42 postpartum, and 11.7% on days 43–365 postpartum. Leading causes of death varied by timing relative to the end of pregnancy. Approximately three in five pregnancy-related deaths were preventable. Contributing factors can be categorized at the community, health facility, patient, provider, and system levels.

What are the implications for public health practice?

Most pregnancy-related deaths are preventable, demonstrating the need to identify and implement strategies to address the multiple contributing factors.

pregnancy or within 1 year after delivery. Information on individual deaths are reviewed by medically trained epidemiologists to determine the pregnancy-relatedness and cause (*4*). A death is determined to be pregnancy-related if the death was caused by a pregnancy complication, a chain of events initiated by pregnancy, or the aggravation of an unrelated condition by the physiologic effects of pregnancy. Cause of death coding includes the following 10 mutually exclusive categories: hemorrhage; infection; amniotic fluid embolism; thrombotic pulmonary or other embolism (i.e., air, septic, or fat); hypertensive disorders of pregnancy (i.e., preeclampsia or eclampsia)*; anesthesia complications; cerebrovascular accidents†; cardiomyopathy; other cardiovascular conditions (e.g., congenital heart disease, ischemic heart disease, cardiac valvular disease, hypertensive heart disease, and congestive heart failure); and other noncardiovascular medical conditions (e.g., endocrine, hematologic, immunologic, and renal).

Pregnancy-related death data from PMSS for 2011–2015 were analyzed. The pregnancy-related mortality ratio (PRMR) is the number of pregnancy-related deaths per 100,000 live births. PRMRs were calculated by race/ethnicity, age, marital status, education, and year. Birth data, used for determining the number of live births, were obtained from U.S. natality files from the National Center for Health Statistics (*5*). SAS (version 9.4; SAS Institute) was used for all analyses.

Cause and timing of pregnancy-related deaths were analyzed. Timing of death was identified as "during pregnancy" when keywords on the death certificate noted the death was during pregnancy or the pregnancy checkbox option "pregnant at the time of death" was checked. Otherwise, timing of death in relation to the end of pregnancy was determined by comparing date of death on the death certificate with date of live birth or fetal death on linked birth or fetal death certificates. The specific timing of postpartum deaths was classified as unknown if there was no linked birth or fetal death certificate.

Data shared by 13 state MMRCs for deaths that occurred during 2013–2017§ were analyzed. Using a standardized data collection system, each multidisciplinary MMRC reviewed available data sources (e.g., medical records, social service records, autopsy reports, and vital records) to determine preventability, factors that contributed to the death, and prevention strategies to address contributing factors. Deaths attributable to suicide, drug overdose, homicide, and unintentional injury were excluded from analyses. MMRCs used the following definition of preventability: "a death is considered preventable if the committee determines that there was some chance of the death being averted by one or more reasonable changes to patient, community, provider, health facility, and/or system factors" (*6*). Percentage of deaths determined by MMRCs to have been preventable were calculated, and chi-squared tests were used to assess whether preventability differed by race/ethnicity or by timing of death. Thematic analyses of MMRC-identified factors that might have contributed to deaths and strategies to prevent future deaths also were conducted.

Results

During 2011–2015, a total of 3,410 pregnancy-related deaths occurred in the United States; the overall PRMR was 17.2 pregnancy-related deaths per 100,000 live births. The highest PRMRs were in women who were black (42.8) and American Indian/Alaska Native (32.5); these PRMRs were 3.3 and 2.5 times as high, respectively, as were those in white women (13.0) (Table 1). The PRMR was highest among women aged ≥35 years and women who were not married. The overall PRMR fluctuated by year, ranging from 15.9 (2012) to 18.0 (2014).

When combined, cardiovascular conditions were responsible for >33% of pregnancy-related deaths; these conditions include cardiomyopathy (10.8%), other cardiovascular conditions (15.1%), and cerebrovascular accidents (7.6%). Other leading causes of pregnancy-related death included other noncardiovascular medical conditions (14.3%), infection (12.5%), and obstetric hemorrhage (11.2%). The cause of death could not be determined for 6.7% of pregnancy-related deaths.

* Deaths caused by hypertension that was not preeclampsia, eclampsia, or gestational hypertension were categorized in the "other cardiovascular conditions" category.

† Deaths caused by cerebrovascular accidents that were a result of preeclampsia or eclampsia were classified in the "hypertensive disorders of pregnancy" category; otherwise, deaths were classified in the "cerebrovascular accidents" category.

§ Arizona (2016), Colorado (2014–2015), Delaware (2013–2017), Florida (2017), Georgia (2013–2014), Hawaii (2015–2016), Illinois (2015), Mississippi (2016–2017), North Carolina (2014–2015), Ohio (2013–2016), South Carolina (2014–2017), Tennessee (2017), and Utah (2015–2016).

Timing of death was known for 2,990 (87.7%) pregnancy-related deaths. Among these deaths, 937 (31.3%) occurred during pregnancy, 506 (16.9%) on the day of delivery, 556 (18.6%) 1–6 days postpartum, 640 (21.4%) 7–42 days postpartum, and 351 (11.7%) 43–365 days postpartum (Table 2). Timing of deaths did not significantly differ between black and white women for most periods; however, a greater proportion of deaths among black women (14.9%) occurred 43–365 days postpartum compared to the proportion of deaths among white women (10.2%) that occurred during the same period (p<0.01).

Distribution of timing of death varied by cause of death (Table 2). Most deaths caused by amniotic fluid embolism occurred on the day of delivery or within 6 days postpartum. Approximately 60% of deaths caused by hypertensive disorders of pregnancy occurred 0–6 days postpartum, whereas those caused by cerebrovascular accidents occurred most frequently 1–42 days postpartum. Deaths caused by cardiomyopathy most commonly occurred 43–365 days postpartum; deaths caused by other cardiovascular conditions occurred most commonly during pregnancy and within 42 days postpartum.

The leading causes of death also varied by time relative to the end of pregnancy. During pregnancy, other noncardiovascular and other cardiovascular conditions were the leading causes of death (Figure); on the day of delivery, hemorrhage and amniotic fluid embolism were the major causes of death. Hemorrhage, hypertensive disorders of pregnancy, and infection were leading causes of death during the first 6 days postpartum. From 6 weeks postpartum (43 days) through the end of the first year (365 days), cardiomyopathy was the leading cause of death.

Among 251 pregnancy-related deaths evaluated for preventability by the 13 MMRCs, a determination was made for 232 (92.4%). Among these, 139 (60.0%) were determined to be preventable deaths. Preventability did not significantly differ between black and white women (p = 0.4), or between Hispanic and white women (p = 0.7), with 57.4% of deaths among black women, 62.7% among white women, and 58.3% among Hispanic women determined to be preventable. Preventability was also similar by timing of pregnancy-related death (59.0% during pregnancy, 53.3% during delivery, 57.1% 1–6 days postpartum, 66.7% 7–42 days postpartum, and 61.9% 43–365 days postpartum; [p = 0.8]).

MMRCs identified an average of three to four contributing factors and two to three prevention strategies per pregnancy-related death. Contributing factors were thematically coded as community factors (e.g., unstable housing and limited access to transportation); health facility factors (e.g., limited experience with obstetric emergencies and lack of appropriate personnel or services); patient factors (e.g., lack of knowledge of warning signs and nonadherence to medical regimens); provider factors (e.g., missed or delayed diagnosis and lack of continuity of care); and system-level factors (e.g., inadequate access to care and poor case coordination) (Table 3). MMRC-identified prevention strategies addressing community factors included expanding clinical office hours and the number of providers who accept Medicaid, prioritizing pregnant and postpartum women for temporary housing programs, and improving access to transportation. Actions addressing health facility factors included implementing obstetric emergency protocols and simulation training, providing telemedicine for facilities without on-site obstetric expertise, and implementing systems to foster communication among multiple providers. Although patient-level contributing factors were commonly identified, prevention strategies to mitigate these factors are often reliant upon providers and health systems. For example, prevention strategies to address patient-level factors included improving patient education materials and providing home health and patient support services. Provider-level prevention strategies included offering provider education to reduce missed or delayed diagnoses, implementing a maternal early warning system (*7*), and improving hand-off communication between obstetricians

TABLE 1. Pregnancy-related deaths, by sociodemographic characteristics — Pregnancy Mortality Surveillance System, United States, 2011–2015

Characteristic	No. of pregnancy-related deaths	Pregnancy-related mortality ratio*
Total	**3,410**	**17.2**
Race/Ethnicity† (N = 3,400)		
White	1,385	13.0
Black	1,252	42.8
American Indian/Alaska Native	62	32.5
Asian/Pacific Islander	182	14.2
Hispanic	519	11.4
Age group (yrs) (N = 3,409)		
<20	158	11.3
20–24	543	12.1
25–29	751	13.2
30–34	799	15.3
35–39	706	28.7
≥40	452	76.5
Highest level of education (N = 2,938)		
Less than high school	572	19.8
High school graduate	1,090	24.2
Some college	775	14.8
College graduate or higher	501	9.4
Marital status (N = 3,371)		
Married	1,543	13.1
Not married	1,828	22.8
Year		
2011	702	17.8
2012	627	15.9
2013	679	17.3
2014	718	18.0
2015	684	17.2

* Number of pregnancy-related deaths per 100,000 live births.
† Women identified as white, black, American Indian/Alaska Natives, or Asian/Pacific Islanders were not Hispanic. Hispanic women could be of any race.

TABLE 2. Pregnancy-related deaths, by cause of death and time of death relative to the end of pregnancy — Pregnancy Mortality Surveillance System, United States, 2011–2015*

	Time of death relative to the end of pregnancy§					
	No. (%) attributed to each cause (row %)					
Cause of death†	During pregnancy	Day of delivery	1–6 days postpartum	7–42 days postpartum	43–365 days postpartum	Total no. of deaths
Hemorrhage	72 (21.9)	123 (37.4)	105 (31.9)	27 (8.2)	2 (0.6)	**329**
Infection	117 (32.5)	17 (4.7)	83 (23.1)	121 (33.6)	22 (6.1)	**360**
Amniotic fluid embolism	12 (6.9)	114 (65.9)	42 (24.3)	4 (2.3)	1 (0.6)	**173**
Thrombotic pulmonary or other embolism	115 (40.9)	24 (8.5)	41 (14.6)	69 (24.6)	32 (11.4)	**281**
Hypertensive disorders of pregnancy	23 (10.8)	41 (19.3)	94 (44.3)	44 (20.8)	10 (4.7)	**212**
Anesthesia complications	2 (20.0)	3 (30.0)	3 (30.0)	2 (20.0)	0	**10**
Cerebrovascular accidents	68 (29.8)	9 (3.9)	49 (21.5)	79 (34.6)	23 (10.1)	**228**
Cardiomyopathy	48 (15.6)	21 (6.8)	25 (8.1)	75 (24.4)	138 (45.0)	**307**
Other cardiovascular conditions	173 (37.6)	65 (14.1)	61 (13.3)	110 (23.9)	51 (11.1)	**460**
Other noncardiovascular medical conditions	225 (52.7)	61 (14.3)	27 (6.3)	59 (13.8)	55 (12.9)	**427**
Unknown	82 (40.4)	28 (13.8)	26 (12.8)	50 (24.6)	17 (8.4)	**203**
Total	**937 (31.3)**	**506 (16.9)**	**556 (18.6)**	**640 (21.4)**	**351 (11.7)**	**2,990**

* Deaths in which timing of death was unknown were excluded (n = 420).
† Cause of death categories are mutually exclusive.
§ Time of death might be distant from onset of disease or initial event leading to death.

and other providers. MMRC-identified prevention strategies addressing system-level factors included developing policies to ensure that women deliver at a health facility with an appropriate level of maternal care and extending Medicaid coverage for pregnant women to include 1 year of postpartum care.

Discussion

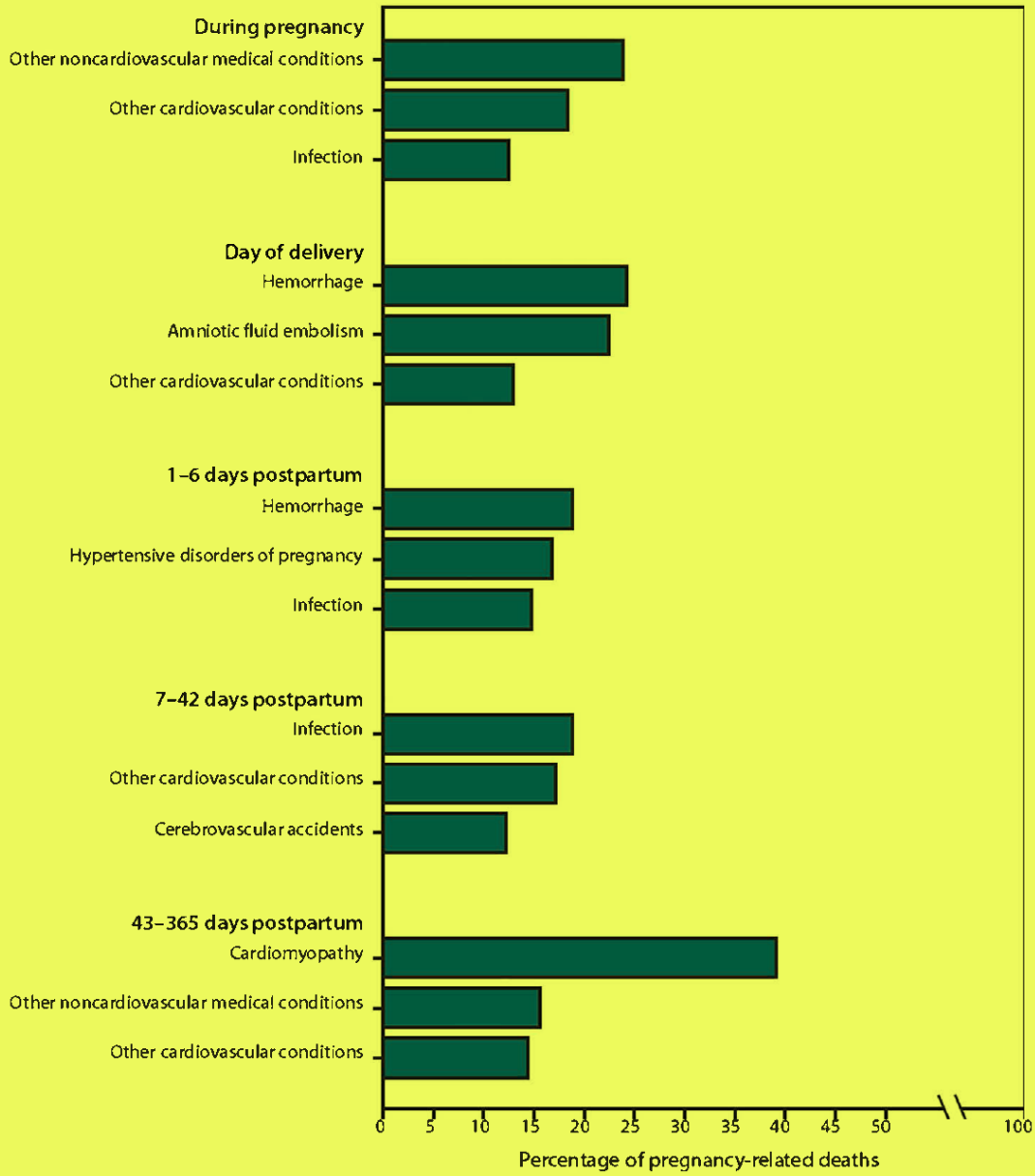
Pregnancy-related deaths occur not only during delivery but also during pregnancy and up to 1 year postpartum. The leading causes of pregnancy-related deaths varied by timing of death. Acute obstetric emergencies such as hemorrhage and amniotic fluid embolism most commonly occurred on the day of delivery, whereas deaths caused by hypertensive disorders of pregnancy and thrombotic pulmonary embolism most commonly occurred 0–6 days postpartum, and during pregnancy and 1–42 days postpartum, respectively. Cardiomyopathy was the most common cause of death in the late postpartum period (43–365 days postpartum). The higher proportion of pregnancy-related deaths in the late postpartum period among black women is likely attributable to higher proportion of pregnancy-related deaths due to cardiomyopathy among these women (*8*). Approximately three in five pregnancy-related deaths were determined by MMRCs to be preventable, and preventability did not differ significantly by race/ethnicity or timing of death. Recognizing the major causes of death by timing can help identify opportunities for intervention.

These data demonstrate the need to address the multiple factors that contribute to pregnancy-related deaths during pregnancy, labor and delivery, and postpartum. No single intervention is sufficient; reducing pregnancy-related deaths requires reviewing and learning from each death, improving women's health, and reducing social inequities across the life span, as well as ensuring quality care for pregnant and postpartum women (*9*). Throughout the preconception, pregnancy, and postpartum periods, providers and patients can work together to optimally manage chronic health conditions (*10*). Standardized approaches to addressing obstetric emergencies can be implemented in all hospitals that provide delivery services. The Alliance for Innovation on Maternal Health (AIM) has provided sets of bundled guidance to provide for such standardization.¶ Implementation of this guidance is often supported by perinatal quality collaboratives, state-based initiatives that aim to improve the quality of care for mothers and infants (*11*). Ensuring that pregnant women at high risk for complications receive care in facilities prepared to provide the required level of specialized care also can improve outcomes; professional organizations have developed criteria for recommended levels of maternal care (*12*). CDC has created the Levels of Care Assessment Tool (LOCATe) for public health decision makers to evaluate risk-appropriate care (*13*). In the postpartum period, follow-up care is critical for all women, particularly those with chronic medical conditions and complications of pregnancy (e.g., hypertensive disorders of pregnancy). ACOG recommends that postpartum women have contact with obstetric providers within the first 3 weeks postpartum and recognizes postpartum care as an ongoing process tailored to each woman's individual needs (*14*).

The findings in this report are subject to at least four limitations. First, errors in reported pregnancy status on the death certificates have been described, potentially leading to overestimation or underestimation of the number of pregnancy-related deaths (*15*). Second, data for specified race or Hispanic-origin groups other than non-Hispanic white and non-Hispanic black

¶ https://safehealthcareforeverywoman.org/aim-supported-patient-safety-bundles.

FIGURE. Three most frequent causes of pregnancy-related deaths, by time relative to the end of pregnancy — Pregnancy Mortality Surveillance System, United States, 2011–2015



should be interpreted with caution because of inconsistencies in reporting these data on death certificates and surveys. Third, generally the pregnancy-relatedness cannot be determined in PMSS for injury deaths such as drug overdoses, suicides, or homicides, or for cancer-related deaths, because of limited information concerning death circumstances. As such, these types of death are often not included in the PRMR. For consistency among data sources, these conditions were not investigated in MMRC data, although MMRC data have found suicides and drug overdoses to be a leading underlying cause of pregnancy-related mortality (*6*). Most (75.0%) of these deaths occur in the late postpartum period. Finally, not all preventable deaths reported by MMRCs had a prevention strategy to address contributing factors; improving quality, completeness, and

TABLE 3. Maternal Mortality Review Committee–identified contributing factors and strategies to prevent future pregnancy-related deaths — Maternal Mortality Review Committees, 13 states, 2013–2017

Level	Contributing factor	Strategies to address contributing factor
Community	Access to clinical care	Expand office hours, increase number of providers who accept Medicaid, increase availability and use of group prenatal care programs
	Unstable housing	Prioritize pregnant and postpartum women for temporary housing programs
	Lack of, or inadequate, transportation options	Strengthen or build systems to link persons to affordable transportation, or provide vouchers for transport to medical appointments
		Improve availability of transportation services covered by Medicaid
	Obesity and associated chronic disease complications	Improve access to healthy foods and enhance efforts to educate and promote healthy eating habits and weight management strategies
Health facility	Limited experience with obstetric emergencies	Implement obstetric emergency simulation training for emergency department and obstetric staff members
		Ensure emergency department staff members ask about recent pregnancy history and consult with obstetrician on call if patient is pregnant or has recently been pregnant
	Lack of appropriate personnel or services	Provide telemedicine for facilities with no obstetric provider on-site
		Ensure Medicaid managed care organizations' contracts include sufficient access to specialists for patients at high risk
	Lack of guiding protocols or tools to help ensure quality care provision	Ensure sepsis, hemorrhage, and massive transfusion protocols are in place and followed by staff members
		Implement applicable patient safety bundles
		Implement systems to foster communication among multiple providers to ensure proper case coordination
		Implement protocols for using patient navigators
Patient/Family	Lack of knowledge of warning signs or need to seek care	Improve counseling and use of patient education materials on warning signs and when to seek care, such as AWHONN Save Your Life discharge instructions
		Implement a public education campaign to increase awareness of signs and symptoms of common complications
	Nonadherence to medical regimens or advice	Standardize patient education to ensure providers relay consistent messages and implement techniques for ensuring patient understanding, such as patient "teaching back" to the provider
		Make education materials available in the clinic and online
		Strengthen and expand access to patient navigators, case managers, and peer support
		Ensure access to interpreter services when needed
		Offer home health or social work follow-up services
Provider	Missed or delayed diagnosis	Repeat blood pressure measurement in a timely (and possibly manual) manner when initial blood pressure result is unexpected
		Offer provider education on cardiac conditions in pregnant and postpartum women
		Perform thorough evaluation of patients reporting pain and shortness of breath
	Inappropriate or delayed treatment	Only perform cesarean deliveries when medically indicated
		Implement a maternal early warning system
	Lack of continuity of care	Improve care transition communication among obstetrician-gynecologists and other primary and specialty care physicians
System	Inadequate receipt of care	Develop policies to ensure pregnant women are transported to a hospital with an appropriate level of maternal care
		Enlist state perinatal quality collaboratives to identify quality improvement procedures and periodic drills/simulation training for birth facilities, including obstetric emergency drills
		Design education initiatives for emergency department staff members on the care of pregnant and postpartum women
	Case coordination or management	Extend expanded Medicaid coverage eligibility for pregnant women to include 1 year of postpartum care
		Create quality improvement entity to manage outpatient care gaps and improve care coordination
		Implement a postpartum care transition bundle for better integration of services for women at high risk
		Develop procedures for all hospitals to improve documentation of abnormal test results, plan for follow-up care, and management of conditions
		Develop universal health record system that allows for sharing of medical records among hospitals
	Guiding policies, procedures, or standards not in place	Develop protocol for timely referrals and consults
		Ensure all hospitals within a health care system follow the same protocols and policies

Abbreviation: AWHONN = Association of Women's Health, Obstetric and Neonatal Nurses.

timeliness of MMRC data can translate into opportunities for prevention. MMRC-identified prevention strategies are based on comprehensive case review by a multidisciplinary group of clinical and nonclinical experts and might not always be drawn from published evidence-based interventions, in part because of a lack of programmatic and policy-based evidence. MMRCs' access to comprehensive medical and social service records highlights their unique and critical role in understanding all factors contributing to pregnancy-related deaths and using those data to identify strategies to potentially prevent future deaths and contribute to the evidence base.

Pregnancy-related deaths occur during pregnancy, around the time of delivery, and within 1 year postpartum; leading causes of death vary by timing of death. Most pregnancy-related deaths can be prevented. Comprehensive review of pregnancy-related deaths can identify contributing factors and opportunities to implement strategies for preventing future deaths.

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Medication Abortion Up to 70 Days of Gestation

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

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

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 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?*

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).

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.

▶ *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 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).

(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 (123 125), 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?*

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,

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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Dr. Grossman has served as a consultant to Planned Parenthood Federation of America and the Center for Reproductive Rights. Dr. Creinin and Dr. Meckstroth are consultants for Danco, Inc., the manufacturer of Mifeprex (mifepristone 200 mg). Dr. Rafie is a consultant for GenBioPro, the manufacturer of generic mifepristone. The other authors did not report any potential conflicts of interest.

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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.
* $P<.05$.

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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Abortion Provision Among Practicing Obstetrician–Gynecologists

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Abstract

Objective—To estimate prevalence and correlates of abortion provision among practicing obstetrician–gynecologists in the United States.

Methods—We conducted a national probability sample mail survey of 1,800 practicing obstetrician–gynecologists. Key variables included whether respondents ever encountered patients seeking abortion in their practice, and whether they provided abortion services. Correlates of providing abortion included physician demographic characteristics, religious affiliation, religiosity, and the religious affiliation of the facility in which a physician primarily practices.

Results—Among practicing obstetrician–gynecologists, 97% encountered patients seeking abortions, while 14% performed them. Young female physicians were the most likely to provide abortions (18.6% vs. 10.6%, adjusted OR = 2.54, 95% CI = 1.57–4.08), as were those in the Northeast or West, those in highly urban zip codes, and those who identify as Jewish. Catholics, Evangelical Protestants, non–Evangelical Protestants, and physicians with high religious motivation were less likely to provide abortions.

Conclusion—The proportion of U.S. obstetrician–gynecologists who provide abortion may be lower than estimated in previous research. Access to abortion remains limited by the willingness of physicians to provide abortion services, particularly in rural communities and in the South and Midwest.

INTRODUCTION

The demand for abortion services in the United States is high. Approximately half of all pregnancies in the United States are unintended, and about half of unintended pregnancies end in abortion (1). Abortion is one of the most common outpatient surgical procedures for women of reproductive age (2), yet many women have trouble accessing abortion services, and access has become more limited over the past few decades (1,3). A recent study found that while the abortion rate among U.S. women increased slightly from 2005 to 2008, 87%

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performing abortions, Roman Catholic teaching is reflected in directives that govern Catholic hospitals, which probably accounts for the fact that obstetrician–gynecologists who work primarily in Catholic hospitals are also less likely to perform abortions. Of note, the association between religious characteristics and provision of abortion was not absolute: a few physicians who reported high religious importance still performed abortions. Furthermore, providers of abortion came from every religious affiliation, including some Catholics and Evangelical Protestants. A small proportion of physicians who reported working in Catholic facilities did provide abortions, which may be due to incomplete enforcement of Catholic hospital policy or may reflect physicians who work in multiple facilities since the survey question on religious hospital affiliation only asked about a physician's primary place of practice.

This study did not assess whether obstetrician–gynecologists who do not perform abortions routinely refer their patients seeking abortions to colleagues who do perform them. Consistent referral would facilitate access to abortions for at least some of these patients. In 2010, the Ethics Committee of the American College of Obstetricians and Gynecologists issued a paper in which they argued that obstetrician–gynecologists are obligated to refer their patients for all legal reproductive health services, including abortions (16). Nonetheless, that paper proved controversial, and previous research has shown that substantial minorities of physicians do not believe they are obligated to refer patients for, or provide information about how to obtain, procedures to which the physician has a religious or moral objection (17). Furthermore, the fact that so few obstetrician-gynecologists provide abortions may limit access to abortion even for patients whose obstetrician–gynecologists are willing to refer. In the end, patients should know the large majority of physicians give information about how to obtain an abortion, and most refer for abortion, but only 1 in 7 perform abortion. Those who perform abortion tend to be female, less religious, to live in urban areas, and to live in the Northeast or West.

Because obstetrician–gynecologists in general, and abortion providers in particular, are concentrated in urbanized areas, access to abortion might be particularly limited for women in rural areas, and especially in the South and the Midwest, where physicians were less likely to perform abortions. It is possible that obstetrician–gynecologists who have religious or other moral objections to abortion are also more likely to live in rural areas. Yet, previous surveys indicate that providers living in rural areas are less likely to perform abortions even if they do not personally object to abortion. Such physicians often face opposition from the surrounding community, especially as facilities for surgical abortions are often targeted for protests by anti–abortion activists (18). Recent research indicates that harassment of abortion providers is especially common in the South and in the Midwest (4).

There are several limitations to this study. First, we only surveyed obstetrician–gynecologists, and thus do not include information on other clinicians such as family physicians, who provide a significant minority of abortions (19). Second, survey nonrespondents might differ from respondents in terms of abortion provision or other characteristics in ways that would bias the findings we report. Unfortunately no information on non-respondents was available for comparison. Third, information on religious affiliation, religiosity, and abortion provision is self–reported, and thus is subject to measurement error. Although respondents were guaranteed confidentiality and names were removed from responses for analysis, the survey was not anonymous so respondents might have been hesitant to report abortion provision. Fourth, our assessment of abortion provision is categorical in nature and thus might classify as abortion providers obstetricians–gynecologists who only rarely perform abortions, and perhaps only under very specific circumstances such as fetal anomaly. This might yield a skewed perception of how many physicians are actually available to provide broader abortion services. The existing census of

August 11, 2021

Food and Drug Administration
Center for Drug Evaluation and Research
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5901-B Ammendale Road
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Re: US Food and Drug Administration's review of the risk evaluation and mitigation strategy for mifepristone

Dear (b)(6)/PPI :

On May 7, 2021, the US Food and Drug Administration (FDA) announced a review of the risk evaluation and mitigation strategy for the drug mifepristone (hereafter, the mifepristone REMS). On behalf of the Society of Family Planning, the academic society for Complex Family Planning subspecialists and over 1,000 academicians, scientists, and partners focused on abortion and contraception research and clinical care, we write to share relevant evidence to support your review of the mifepristone REMS. We appreciate the opportunity to lend the expertise of the Society and its members to this process and applaud your efforts, as a science-based agency, to center sound medical evidence in the decision-making process related to mifepristone and its distribution and use.

As the organization representing Complex Family Planning Fellowship-trained obstetrician-gynecologists—the leaders in clinical care and medical education related to complex abortion and contraception—we conclude the additional controls provided by the REMS are not medically necessary to ensure patient safety. Our 30 years of experience within the Fellowship providing abortion and pregnancy loss care in complex cases, as well as the existing evidence on this topic described in detail below, does not support requiring provider certification and registration to prescribe mifepristone or restricting the healthcare professionals that can prescribe mifepristone. Mifepristone is extremely safe and highly effective when provided via a health center, pharmacy, or home delivery, and does not require a clinician to oversee dispensing.

On behalf of our expert membership, we offer the following summary of peer-reviewed scientific evidence related to the mifepristone REMS, with a focus on research published since the most recent FDA-approved labeling change in 2016. **We conclude that the current REMS, specifically the provisions that require provider certification and registration and restrict where mifepristone may be dispensed, confers no benefit in terms of safety, efficacy, or acceptability of the drug mifepristone and instead creates barriers to use that negatively impact public health and equity in access to care.**

Requiring provider certification and registration to prescribe mifepristone is unnecessary because it does not increase patient safety and constrains abortion provision.

- **The mifepristone REMS currently requires that providers are specially certified to prescribe the drug and must register as prescribers directly with the manufacturer(s); however, there is no evidence this requirement increases abortion safety**. In Canada, mifepristone-specific requirements for provider certification were lifted in November 2017. According to a comprehensive analysis of linked medical and financial records in Ontario, medication abortion remained extremely safe after deregulation, with a major complication rate of 0.33% compared to a rate of 0.31% in an analysis of a similar administrative dataset from California under the REMS, and consistent with a clinical review finding major complication rates <1% across multiple studies of mifepristone use for early abortion.[1–3]

- **Requiring provider certification and registration prevents many providers from incorporating mifepristone into their scope of practice**. In a representative national population-based survey of obstetrician-gynecologists, Grossman and colleagues found that 28% of obstetrician-gynecologists who did not currently provide care using mifepristone would do so if they could prescribe it similarly to other drugs.[4] Several recent, rigorous qualitative studies with diverse groups of clinicians have also demonstrated how the REMS creates barriers to incorporation of mifepristone into practice by creating administrative burdens that clinical champions are unable to overcome.[5,6]

The current restrictions on where mifepristone may be dispensed are unnecessary because mifepristone dispensing in clinical care settings is not associated with higher efficacy, greater safety, or greater acceptability compared to dispensing in brick-and-mortar pharmacies or via postal mail or delivery service.

- **The requirement for in-person dispensing of mifepristone in certain health care settings confers no safety benefit**. Through the mifepristone labeling change approved in 2016, the FDA recognized that requiring misoprostol be administered in clinical settings as part of early abortion care is unnecessary. As the summary of the peer-reviewed literature below suggests, patient self-administration of mifepristone at home is effective, safe, and acceptable. However, the current mifepristone REMS further require that mifepristone be distributed “only in…clinics, medical offices, and hospitals.”

- **Mifepristone can be safely dispensed in brick-and-mortar pharmacies**. Pharmacists are well qualified to assure safe dispensing of medications with a comparable safety profile to the 200 mg mifepristone tablet, including the 300 mg formulation of mifepristone for Cushing’s syndrome, which is not subject to a REMS. Evidence from high-income countries with health care infrastructure comparable to the US has demonstrated the acceptability of pharmacy dispensing of mifepristone. For example, mifepristone is currently distributed by pharmacists in Canada, a practice that Canadian physicians report facilitates the provision of medication abortion with mifepristone.[7] In the

US, physicians support pharmacy dispensing of mifepristone. In a qualitative study of primary care providers' perceptions of and experiences with mifepristone, Rasmussen and colleagues found that primary care providers in Illinois support pharmacy dispensing of mifepristone, describing it as a more patient-centered approach to administration of this drug.[8] Further, a recent US study demonstrated that pharmacy dispensing of mifepristone is safe and effective. In a study that included eight pharmacies in California and Washington state, Grossman and colleagues demonstrated that mifepristone dispensing by pharmacists in the pharmacy setting after the patient received counseling from a clinician is as effective (93.5% abortion completion with medication alone) as in-clinic dispensing efficacy reported by Winikoff and colleagues in a large multi-site national trial.[9,10] In Grossman and colleagues' study, only three (1.3%) participants visited an emergency department during the study follow up period, a lower proportion than most clinical trials of medication abortion using in-clinic mifepristone administration (range 2.9-4.1%).[10,11]

- **Mifepristone can also be safely dispensed by mail**. In a large (N=1,157 abortions) national US-based clinical trial of mifepristone dispensing by mail (the Teleabortion study), Chong and colleagues also found that mifepristone dispensing by direct mail to consumers is effective (95% abortion completion with medication alone), with only 0.9% experiencing any serious adverse event compared to an adverse event rate of 0.65% in a large (N=233,805 medication abortions) retrospective cohort study of in-clinic mifepristone administration.[12,13]

- **Retrospective analyses of rapid practice adaptations in the context of the COVID-19 pandemic further demonstrate the safety, efficacy, and acceptability of mifepristone dispensing by mail**. In a large (N=52,218) retrospective cohort study, Aiken and colleagues reported on the safety, efficacy, and acceptability of telemedicine abortion at Britain's largest abortion providers, which rapidly adapted to provide medication abortion using telemedicine during the spring and summer of 2020.[14] Following a telehealth consultation, individuals with a last menstrual period dating the pregnancy up to 69 days and without symptoms of ectopic pregnancy were able to receive both mifepristone and misoprostol for home administration. Investigators found that while medication abortion was equally effective in the telemedicine model (98.8%) vs the traditional in-clinic mifepristone administration model (98.2%, p=1.0), individuals using telemedicine had a shorter wait time between first contact and initiating the medication abortion (6.5 days vs. 10.7 days, p<0.001).

- **Whether patients receive mifepristone at a pharmacy or by mail, they report high acceptability**. In their pharmacy dispensing study, Grossman and colleagues report that 74.3% of patients would recommend pharmacy dispensing of mifepristone to a friend in a similar situation, and 65.4% were highly satisfied with their abortion experience.[9] Hyland and colleagues report that 97% of women cared for by an Australian telemedicine medication abortion service report high satisfaction, and Chong and colleagues report that 85% of participants in the Teleabortion study found their abortion experience "very satisfactory".[12,15]

Requiring provider certification and registration to prescribe mifepristone and mifepristone dispensing restrictions may lead to abortions happening later in pregnancy. Unfortunately, abortions become more socially and clinically complicated the further along in a pregnancy the abortion occurs.[2,16–18] Thus, restrictions such as the mifepristone REMS that limit people's ability to access abortion as soon as they discover they are pregnant negatively impact public health. Delays are particularly problematic for people with low incomes as abortions after the first trimester are more expensive and often result in even further delays in obtaining a desired abortion.[19–21] In Canada, where abortions are covered as part of universal health care, the proportion of abortions in the second trimester decreased by approximately 12% after mifepristone deregulation.[1] In the US, where limited access and cost are major contributors to delays in abortion, lifting the REMS may result in an even greater shift in abortions to earlier gestational ages.

The National Academies of Science, Engineering, and Medicine defines quality abortion care as safe, effective, patient-centered, timely, efficient, and equitable.[16] **By unnecessarily limiting the number of mifepristone providers in the US, the mifepristone REMS adversely impacts timeliness and equity in access to care.** As the academic society representing Complex Family Planning subspecialists, scientists, and partners focused on abortion and contraception research and clinical care, we hope this sound medical evidence is held central in your review of the mifepristone REMS. We appreciate your commitment to centering science and ensuring that policy decisions are based on the latest evidence.

Sincerely,

The Society of Family Planning Board of Directors

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remaining 6, 3 were PUL treated with methotrexate and 3 were ectopic (salpingectomy=2, methotrexate=1). However, in 2 of these 6 cases, ultrasound falsely indicated an intrauterine pregnancy.

Conclusions Ectopic pregnancies are uncommon amongst women presenting for abortion. The value of routine ultra sound in excluding ectopic pregnancy in symptom free women without significant risk factors is questionable as it may aid detection of some cases but may give false reassurance that a pregnancy is intrauterine.

3 ACCEPTABILITY OF EARLY MEDICAL ABORTION DELIVERED BY TELEMEDICINE – PRELIMINARY DATA FROM AN NHS COMMUNITY ABORTION SERVICE

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Introduction In response to the COVID 19 outbreak, the NHS Lothian abortion service (based at the Chalmers Centre for Sexual and Reproductive Health, Edinburgh) transferred wholly to telemedicine delivery of abortion care. The need for ultrasound scan was assessed as per Royal College of Obstetricians and Gynaecologists (RCOG) guidance based on symptoms and/or significant risk factors for ectopic, uncertain gestation or last menstrual period (LMP) of more than 12 weeks ago. Those with a gestation of less than 12 weeks, and medically eligible could choose early medical abortion (EMA) at home with collection of medication or delivery by courier. We sought to evaluate the experience of these women.

Methods Between 1 April and 9 July 2020, an interviewer administered survey was conducted of women who had received EMA, at 4 days and 14 days following their teleme dicine consultation. Questions included preparedness for the EMA, acceptability of telemedicine and preferred future type of consultation, importance of ultrasound and result of the day 14 low sensitivity pregnancy test (LSPT).

Results Our preliminary analysis includes 322 women with complete follow up at day 4 and day 14. 281 (87%) of women rated their telephone abortion care as 'very accept able' or 'somewhat acceptable', and 275 (85%) rated them selves as 'very prepared' or 'somewhat prepared for the procedure'. 236 (73%) had a negative LSPT at day 14. Of the remaining women, less than 1% had an ongoing preg nancy after further investigation. 231 (72%) of respondents would select a telephone consultation again if they needed a further abortion. Only 70 (22%) women considered ultra sound as being 'very important' or 'somewhat important' to them.

Conclusions The move to telemedicine has been positively received by the majority of women in our cohort. Continu ing to provide the majority of EMA care via telemedicine would appear to be an effective approach, appreciated by patients.

4 DO MEDICATION ABORTION COMPLICATIONS INCREASE WHEN MIFEPRISTONE IS AVAILABLE WITHOUT REGULATIONS RESTRICTING PRACTICE? A POPULATION-BASED STUDY USING LINKED HEALTH ADMINISTRATIVE DATA FROM CANADA

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Objective In January 2017, mifepristone became available in Canada, where abortion has been fully decriminalised since 1988. By November 2017, all drug label restrictions on pre scribing and dispensing were removed. Canada's globally unique policies allow any physician or nurse practitioner to prescribe mifepristone physically or via telemedicine, any phar macist to directly dispense mifepristone to patients, and patients to swallow their mifepristone when and where they choose. In this study, we examined the association of this deregulated medication abortion approach with abortion uti lisation and complications including ongoing pregnancy.

Methods We used linked administrative data (billing, hospital, ambulatory care, and prescription records) from Ontario, Can ada to examine the 308 344 surgical and medication abortions from January 2012 to December 2019. We examined abortion utilisation, abortion after 14 weeks' gestation, abortion related complications (infection, haemorrhage, embolism, shock, renal failure, damage to pelvic organs, other venous complications) and severe adverse events (overnight hospitalisation, blood transfusion, or death), surgical follow up (laparotomy, laparo scopy, hysterectomy), aspiration/re aspiration, and ongoing pregnancy (ectopic, intrauterine) within 6 weeks of the abor tion. We compared incidences before and after mifepristone deregulation (2012 2016 vs 2018 2019).

Results Medication abortion utilisation increased substantially from 2.9% of all abortions from 2012 2016 to 31.0% in 2018 2019. Abortion after 14 weeks' gestation decreased from 5.8% (95% CI 5.7 5.9) before to 5.3% (95% CI 5.2 5.5) after mifepristone deregulation. Among the 255 642 first trimester abortions, complications were similar before and after deregulation: abortion related complication inci dence was 0.66% (95% CI 0.62 0.69) before and 0.61% (95% CI 0.55 0.67) after, while severe adverse event inci dence was 0.26% (95% CI 0.24 0.28) before and 0.33% (95% CI 0.28 0.37) after (Figure 1). Surgical follow up was similar in both periods, occurring in 0.05% (95% CI 0.04 0.06) before and 0.06% (95% CI 0.04 0.08) after deregula tion. Aspiration/re aspiration increased modestly from 0.05% (95% CI 0.04 0.06) to 0.13% (95% CI 0.10 0.16), as did ectopic pregnancy diagnosed after the abortion, from 0.15% (95% CI 0.14 0.17) to 0.22% (95% CI 0.19 0.26). Ongoing intrauterine pregnancy continuing to delivery increased from 0.07% (95% CI 0.06 0.08) to 0.31% (95% CI 0.27 0.35) after, while ongoing pregnancy leading to subsequent abor tion increased from 0.54% (95% CI 0.50 0.57) to 0.96% (95% CI 0.89 1.03).

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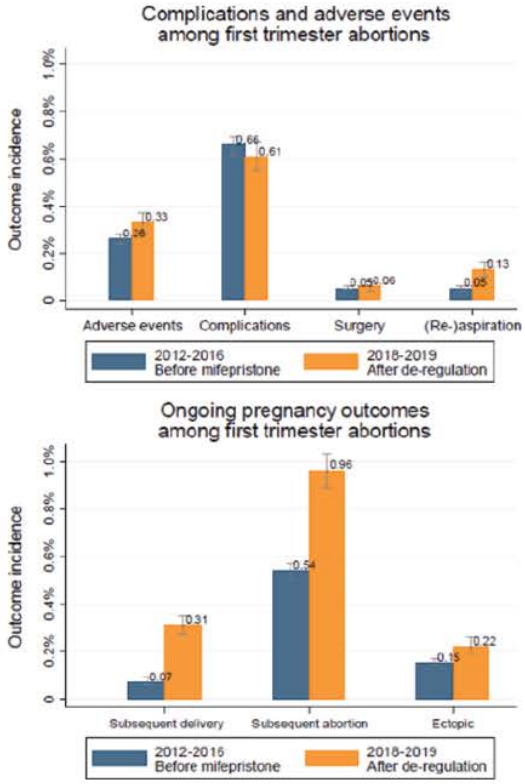

Abstract 4 Figure 1 Incidence of adverse events, abortion-related complications, and ongoing pregnancy outcomes before (2012–2016) and after (2018–2019) mifepristone deregulation in Ontario, Canada among all first-trimester abortions

Impact Canada's globally unique deregulation of mifepristone medication abortion, which enabled patients to self manage their care with their primary care provider's support available, substantially increased medication abortion utilisation and was not associated with a clinically significant increase in abortion complications, ongoing pregnancy, or adverse events.

5 DEMAND FOR SELF-MANAGED ONLINE TELEMEDICINE ABORTION IN EUROPE DURING THE COVID-19 PANDEMIC

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Objectives In most European countries, patients seeking medication abortion during the COVID 19 pandemic are still required to attend healthcare settings in person. We assessed whether demand for self managed medication abortion provided by a fully remote online telemedicine service increased following the emergence of COVID 19.

Methods We examined 3915 requests for self managed abortion to Women on Web (WoW), an online telemedicine abortion service, between 1 January 2019 and 1 June 2020. We used regression discontinuity to compare request rates in 10 European countries before and after they implemented lockdown measures to slow COVID 19 transmission. We examined the prevalence of COVID 19 infection, the degree of government provided economic support, the severity of lockdown travel restrictions, and the medication abortion service provision model in countries with and without significant changes in requests.

Results Five countries showed significant increases in requests to WoW, ranging from 28% in Northern Ireland (p=0.001) to 139% in Portugal (p<0.001) (Table 1). Two countries showed no significant change in requests, and one country, Great Britain, showed an 88% decrease in requests (p<0.001). Countries with significant increases in requests were either countries where abortion services are mainly provided in hospitals or where no abortion services are available and international travel was prohibited during lockdown. By contrast, Great Britain authorised teleconsultation for medication abortion during the pandemic, and remote provision of medications.

Abstract 5 Table 1 Actual versus expected numbers of self-managed abortion requests in the 'after' period for each country included in the study.

Country	Actual requests (n)	Expected requests (n)	Percentage (%) change over baseline trend (95% CI)	P value
Portugal	34	14.2	139.0 (54.5, 385.7)	<0.001
Italy	53	31.6	67.9 (23.3, 152.4)	<0.001
Hungary	113	83.2	35.8 (11.9, 71.2)	<0.001
Malta	69	52.3	31.9 (3.0, 76.9)	<0.001
Northern Ireland (UK)	97	75.8	28.0 (4.3, 64.4)	0.001
Germany	465	467.1	0.5 (9.0, 9.2)	0.798
Netherlands	47	50.9	7.7 (28.8, 27.0)	0.458
Great Britain	1	8.1	87.6 (92.9, 66.7)	<0.001

Conclusion These marked changes in requests for self managed medication abortion during COVID 19 demonstrate demand for remote models of care, and an urgent need to expand access to medication abortion by telemedicine.

Abortion: *Original Research*

Induced Abortion Provision Among a National Sample of Obstetrician–Gynecologists

Daniel Grossman, MD, Kate Grindlay, MSPH, Anna L. Altshuler, MD, MPH, and Jay Schulkin, PhD

OBJECTIVE: To estimate the proportion of obstetrician–gynecologists (ob-gyns) who provided induced abortion in the prior year, disaggregated by surgical and medication methods, and document barriers to provision of medication abortion.

METHODS: In 2016–2017, we conducted a cross-sectional survey of a national sample of American College of Obstetricians and Gynecologists Fellows and Junior Fellows who were part of the Collaborative Ambulatory Research Network. We sent the survey by email, and mailed nonresponders paper surveys. We performed descriptive statistics, χ^2 tests, and logistic regression analyses.

RESULTS: Sixty-seven percent (655/980) of Collaborative Ambulatory Research Network members responded. Ninety-nine percent reported seeing patients of reproductive age, and 72% reported having a patient in the prior year who needed or wanted an abortion. Among those seeing patients of reproductive age, 23.8% (95% CI 20.5%–27.4%) reported performing an induced abortion in the prior year; 10.4% provided surgical and medication abortion, 9.4% surgical only, and 4.0% medication only. In multivariable analysis, physicians practicing in the Midwest (adjusted odds ratio [AOR] 0.31, 95% CI 0.16–0.60) or South (AOR 0.22, 95% CI 0.11–0.42) had lower odds of provision compared with those practicing in the Northeast, whereas those practicing in an urban inner city (AOR 2.71, 95% CI 1.31–5.60) or urban non–inner-city area (AOR 2.89, 95% CI 1.48–5.64 vs midsize towns, rural areas, or military settings) had higher odds of provision. The most common reasons for not providing medication abortion were personal beliefs (34%) and practice restrictions (19%). Among those not providing medication abortion, 28% said they would if they could write a prescription for mifepristone.

CONCLUSION: Compared with the previous national survey in 2008–2009, abortion provision may be increasing among practicing ob-gyns, although important geographic disparities persist. Few provide medication abortion, but uptake might increase if mifepristone could be prescribed.

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In a 2018 analysis of induced abortion care in the United States, the National Academies of Sciences, Engineering, and Medicine concluded that legal induced abortion is safe and effective, yet the quality of care varies geographically owing to state-level regulations.[1] Timeliness and equity, two dimensions of quality, greatly depend on the distribution of services, requiring care to be readily available locally to all women when needed. Obstetrician–gynecologists

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Presented as a poster at the North American Forum on Family Planning, October 14–16, 2017, Atlanta, Georgia.

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Each author has confirmed compliance with the journal's requirements for authorship.

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Table 2. Abortion Methods Provided by Obstetrician–Gynecologists in the Prior Year (N=597)

Method	n (%)
Provided any induced abortion	142 (23.8)
Provided only surgical induced abortion	56 (9.4)
Provided only medication abortion	24 (4.0)
Provided surgical and medication abortion	62 (10.4)
Provided any surgical induced abortion	118 (19.8)
Dilation and sharp curettage	31 (5.2)
Electrical vacuum aspiration	57 (9.5)
Manual vacuum aspiration	31 (5.2)
Provided any medication abortion	86 (14.4)
Treatment with misoprostol alone	36 (6.0)
Treatment with mifepristone and misoprostol	50 (8.4)
Treatment with methotrexate and misoprostol	9 (1.5)

abortion (n=120). A total of 32.5% reported providing abortion only in an ambulatory surgical center or hospital setting, 47.5% reported providing in an outpatient office but not at a specialized clinic or Planned Parenthood, and 10.8% reported providing at least some abortions at a specialized clinic or Planned Parenthood. However, the number of abortions performed by participants varied by site. The median number of abortions performed in the past year by those who only provided at an ambulatory surgical center or hospital was 5.5, and the median was 8.0 for those who provided in their office but not at a specialized clinic. Among those who provided any abortion at a specialized clinic, the median number of procedures was 112.0 in the prior year (Table 3).

Respondents who reported having patients seeking abortion but did not provide medication abortion in the prior year were asked about reasons why they did not provide (n=368). About one third (34%) cited personal, religious, or moral beliefs against abortion, 19% pointed to practice setting restrictions against abortion provision, and 16% mentioned office staff attitudes. Ten percent said there was no perceived need, and 8% said their patients had access to another provider or they referred out (Table 4). Eleven percent cited a lack of training as the reason for not providing medication abortion, and a similar proportion cited the requirement to stock the medications in their clinic. Nine percent cited the requirement to sign the provider agreement with the manufacturer of mifepristone. Some of the responses in the "other" category, each of which was cited by less than 4% of participants, included community attitudes, not having an ultrasound scanner in the office, lack of surgical backup, and laws and regulations.

When those who did not provide medication abortion but reported having patients seeking abortion were asked whether they would offer the service if they could write prescriptions for the medications, 28% said they would offer medication abortion, 47% said they would not, and 22% said they were not sure (Table 4). The number of respondents who said they would offer medication abortion by prescription (n=102) is more than the number in the survey who reported providing medication abortion in the prior year (n=86). This suggests that the proportion of ob-gyns offering induced medication abortion might increase from 14% currently to as much as 31% if it were not required to stock the medication in one's office.

DISCUSSION

This study aimed to describe induced abortion provision among practicing ob-gyns in the United States and found that 24% of them had performed abortion in the prior year. Factors associated with provision included practicing in the Northeast or West rather than the South or Midwest and practicing in an urban setting. This inequitable geographic distribution is similar to findings in previous research, which may be related to more restrictions on abortion provision in Southern and Midwestern states.[2,7,8]

The proportion of ob-gyns who reported providing induced abortion in our survey was higher than the 14% reported in a national survey conducted in 2008–2009.[2] Our results were similar to a survey of ob-gyns who became board certified between 1998 and 2001, which found that 22% performed an induced abortion in the prior year.[9] The Accreditation Council for Graduate Medical Education has required training in induced abortion in obstetrics and gynecology residency programs since 1996, which may have contributed to an increase in provision.

Among those providing induced abortion in the prior year, approximately one third reported providing the service only in an ambulatory surgical center or hospital setting. Given the safety of providing abortion in an outpatient setting,[10] more research is needed to understand the reasons why ob-gyns choose to provide the service in a hospital. These physicians provided a small number of procedures in the prior year (median of 5.5), which is consistent with national data.[3]

Desai et al recently reported on a survey of ob-gyns in private practice, which found that 7% reported performing an induced abortion in 2013 or 2014.[7] That survey focused on provision of abortions at the physician's office and excluded specialized clinics

Table 3. Site Where Induced Abortion was Provided and Annual Number of Abortions Performed Among Obstetrician–Gynecologists Providing Any Abortions (n=120)*

Site	n (%)	Annual No. of Abortions Performed	
		Median	IQR
Induced abortion provided only in ambulatory surgical center or hospital setting	39 (32.5)	5.5	3 12
Any abortion provided in outpatient office but not at a Planned Parenthood or specialized clinic	57 (47.5)	8.0	3 15
Any abortion provided at a Planned Parenthood or specialized clinic	13 (10.8)	112.0	75 251

IQR, interquartile range.
Columns may not tally to 100% owing to missing values.
* Among respondents who answered long survey.

providing abortion care. About half of the ob-gyns in our survey who provided abortion reported doing so in an outpatient setting, which makes our findings comparable with those of Desai.

Among ob-gyns who reported seeing patients who needed or requested an abortion, the most commonly cited reasons for not providing medication abortion were personal reasons or practice restrictions. These results are similar to a survey of ob-gyns in New Mexico in 2008.[11] Qualitative research has also highlighted how practice restrictions prevent trained physicians from providing the service.[12]

Beyond these personal and practice explanations, some of the reasons for not providing medication abortion could be addressed through training and policy changes. Eleven percent cited a lack of training, suggesting medication abortion teaching in residencies and continuing education might increase uptake of the method. A similar proportion reported that the requirement to stock mifepristone in their clinics was a reason they did not provide the method, and our findings suggest that the number of ob-gyns providing medication abortion might at least double if they could write a prescription for mifepristone. Pharmacy dispensing of Mifeprex by prescription is currently prohibited by the drug's Risk Evaluation and Mitigation Strategy imposed by the U.S. Food and Drug Administration.[6] A recent analysis found that the mifepristone Risk Evaluation and Mitigation Strategy is not justified given the positive safety record of the drug, and the authors argued for its withdrawal.[13] Our survey suggests that the Risk Evaluation and Mitigation Strategy is a barrier to provision of medication abortion, which should add new urgency to the push to remove this medically unnecessary restriction.

Table 4. Perspectives of Obstetrician–Gynecologists Who Do Not Provide Medication Abortion, Among Those Who Had Patients Seeking Abortion (n=368)

	n (%)
Reasons for not providing medication abortion (multiple responses allowed)	
Personal, religious, or moral beliefs against abortion	126 (34.2)
Practice setting restrictions against abortion provision	69 (18.8)
Office staff attitudes	58 (15.8)
Lack of training	41 (11.1)
Requirement to stock medications in clinic	40 (10.9)
No perceived need	36 (9.8)
Requirement to sign agreement with manufacturer of Mifeprex	33 (9.0)
Patients have access to someone else or provider refers out	28 (7.6)
Other	64 (17.4)
Would offer medication abortion to patients if they could write a prescription for mifepristone and misoprostol and patients could obtain both medications at a pharmacy, among those who had not provided induced medication abortion in past year and who had patients seeking abortion	
Would offer medication abortion	102 (27.7)
No	173 (47.0)
Not sure	79 (21.5)

Columns may not tally to 100% owing to missing values.

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Original Research Article

US clinicians' perspectives on how mifepristone regulations affect access to medication abortion and early pregnancy loss care in primary care

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ABSTRACT

Objective: Protocols including mifepristone are the most effective medication regimens for medication abortion and early pregnancy loss (EPL) management. Both can be safely and effectively offered in primary care settings. Despite mifepristone's excellent safety record, the United States (US) Food and Drug Administration (FDA) heavily regulates provision. This exploratory study examines US primary care clinicians' perspectives on the effects of mifepristone restrictions, including FDA regulations, on access to medication abortion and EPL management in primary care.

Study Design: In 2019, we conducted an online qualitative survey of US primary care clinicians recruited from six reproductive health-focused listservs. Open-ended questions queried about barriers to providing mifepristone and effects on patients when unable to access mifepristone in primary care. We iteratively coded and analyzed qualitative data using inductive thematic analysis.

Results: Of our analytic sample of 113 respondents, one-third had mifepristone available in their current primary practice setting. Key barriers to provision stemmed from the FDA rule to stock and dispense mifepristone onsite, including logistical difficulties and resistance from health center leadership. Clinicians believed that lack of mifepristone in primary care resulted in negative patient experiences, including disrupted continuity of care, medically-unnecessary appointments, and undesired aspiration procedures.

Conclusions: FDA regulations that inhibit mifepristone provision in primary care create structural barriers to provision. This may result in physical, emotional, and financial burdens for patients.

Implications: When mifepristone is unavailable in primary care, some patients in need of abortion or EPL care may experience physical, emotional, and financial harms. Removing FDA restrictions is a critical step in reducing primary care barriers to mifepristone provision and improving access to timely, patient-centered medication abortion and EPL care.

1. Introduction

Abortion and early pregnancy loss (EPL) are very common. In the United States (US), one in four women will have an abortion in their lifetime; one in five will have a clinically-recognized EPL [1-2]. Using mifepristone with misoprostol for medication abortion is safe and effective [3-5]. Mifepristone with misoprostol is recommended by professional medical organizations to treat EPL off-label, as it is the most effective medication regimen (83.8% vs 67.1% misoprostol-only) [5-7]. To date, abortion is the only US Food and Drug Administration (FDA)-approved indication for mifepristone.

The FDA has long restricted mifepristone under a Risk Evaluation and Mitigation Strategy (REMS), a drug safety program designed to regulate medications suspected to cause serious adverse effects [8]. Yet, among 3.7 million US people who have taken mifepristone since 2000, the FDA reported 24 deaths, of which several were unrelated to the drug. Between 2012 and 2018, the FDA reported 1,455 adverse events, including 274 people requiring hospitalization and 12 severe infections [9]. The mifepristone REMS includes three Elements to Assure Safe Use (ETASU): (1) mifepristone cannot be mailed or dispensed in pharmacies, only stocked

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and provided to patients in medical offices; (2) a clinician with prescriptive authority must become certified through a prescriber agreement; and (3) patients must sign an FDA-approved agreement. All elements apply even for off-label indications, like EPL [10].

Providing abortion and EPL care in primary care settings is feasible and acceptable to patients, and enhances continuity of care [4,11]. Some patients report a preference for getting this care from their primary care practice, while others prefer receiving abortion care at freestanding clinics [12,13]. Providing mifepristone in primary care may also increase access to abortion care [14]. Despite feasibility, acceptability, and need, only about 25% of primary care physicians trained in reproductive health provide medication abortion and/or comprehensive EPL care. Of these, about half offer medication abortion and medication management of EPL in specialized settings, respectively, rather than in primary care [15-18].

Barriers to integrating mifepristone into primary care include staffing, limited time, training, stigma, malpractice insurance, and federal and state laws [15-19]. The Hyde Amendment, for example, prohibits using federal funds for abortion except in cases of rape, incest, and serious health consequences for or life endangerment of the pregnant person [20]. Additionally, states continue to enact laws imposing non-evidence-based conditions on patients and clinicians, like mandatory ultrasounds, waiting periods, and "physician-only" care, which contribute to delays, stigma, and medically-unnecessary visits and procedures [21,22]. While research has explored the effects of these laws on abortion access and outcomes, none to date have studied the effect of mifepristone ETASU on the delivery of medication abortion and EPL management in primary care. This exploratory study examines primary care clinicians' perspectives on the ways that regulations, specifically the REMS, affect access to medication abortion and EPL care in primary care settings.

2. Material and methods

From September to December 2019, we conducted a qualitative survey with open- and closed-ended questions with a convenience sample of US primary care clinicians. To recruit participants, we identified primary care reproductive health-focused listservs managed by professional medical and/or reproductive health organizations. From an initial list of 10 listservs, we selected 6 based on the following criteria: supports abortion care, moderator accepts postings for research, and represents a predominantly primary care clinician audience. The 6 listservs represented family medicine (n = 1), advanced practice nurses (APRNs) [nurse practitioners (NPs) and midwives, n = 3], adolescent medicine (n = 1), and internal medicine (n = 1). Five listservs ranged from 180 to 275 members; one had 3,200 members. Listserv membership was not mutually exclusive.

The Institutional Review Board of the Institute for Family Health deemed the study exempt from full board review.

2.1. Data collection

Moderators (n = 5) or the study team (n = 1) shared survey invitations and reminders to listservs. We invited primary care clinicians to share thoughts about whether and how restrictions on mifepristone affected their abilities to provide medication abortion and/or EPL care. We sent up to 3 reminders every 2 to 3 weeks. Each listserv received a unique URL for response tracking. As an incentive, respondents could enter a raffle for one free registration to a conference on family planning and abortion care.

Additionally, we employed early participant referral. Within each invitation and reminder, and upon survey completion, respondents could share a unique link to colleagues they felt would be interested in participating. We closed the survey 2 weeks after the last reminder.

2.2. Survey instrument and sample

Prior studies and discussions with experts informed survey development [23]. We pretested the survey with family physicians and NPs. The final version included closed-ended questions on demographic and practice characteristics, and knowledge and perceptions of mifepristone and hypothetical pharmacy dispensing. We paired the latter with open-ended questions asking for respondents to elaborate on their perceptions of effects of mifepristone stocking and dispensing ETASU; attitudes toward mifepristone pharmacy-dispensing; and willingness to complete the prescriber agreement. We also asked participants the following: "tell us about the challenges you have perceived, observed, or faced when thinking about or actually trying to provide mifepristone in clinical practice." We prompted respondents to share how challenges affected patients. This question did not explicitly mention the REMS to allow respondents to share any challenges that arose.

The survey included two screener questions to assess eligibility: respondents had to identify as primary care clinicians and have seen reproductive-aged female patients within the last 5 years in the US. We included participants who answered at least one open-ended question. We excluded those who primarily provided in abortion clinics and those with missing data. We de-identified and stored data in a password-protected Dropbox folder.

2.3. Analysis

We used summary statistics to describe the sample and perceptions of mifepristone regulations. We employed inductive thematic analysis to analyze barriers to providing mifepristone in primary care and respondents' perspectives of patient experiences [24]. The analysis team consisted of five women with experience in qualitative data analysis: a public health researcher (SS), a family physician and reproductive health services researcher (SR), a family physician receiving advanced training in reproductive healthcare and advocacy (JM), and 2 family medicine residents (RY, LB).

Initially, the team independently read responses and used open coding to identify emerging themes and constructs. After discussion, we adapted Bronfenbrenner's socioecological model to develop codes based on emerging barriers and patient experiences [25]. SS and SR developed an initial codebook with 14 codes and definitions. After re-reading 20 respondents' survey text, we reviewed coding for concordance and refined the codebook accordingly. Then, 2 team members independently read every respondents' survey text and applied the final codebook, which contained 19 codes. SS coded all text; one of four clinicians each employed axial coding to 25 to 32 respondents' text to make connections between constructs and to begin developing an integrated theory. We reconciled discordance through discussion. The analysis team then discussed the coded excerpts and their intersections to identify themes and organized them into matrices for in-depth analysis. Throughout, we wrote memos to practice reflexivity, acknowledging our biases as reproductive health professionals and/or clinicians [26]. We utilized Dedoose version 8.3.10 (Los Angeles, CA: SocioCultural Research Consultants, LLC) to manage data.

3. Results

Of the 172 people who took the survey, 16 screened ineligible, 12 left the survey incomplete, 5 primarily practiced in abortion

Table 1
Primary care clinician respondents' demographic and practice characteristics, and knowledge and perceptions around mifepristone regulations (N = 113).

Demographic characteristics	n (%)
Professional background	
Family physician	67 (59%)
Midwife	17 (15%)
Nurse practitioner or physician assistant	12 (11%)
Other physician type*	9 (8%)
No response	8 (7%)
Gender	
Female	95 (84%)
Male	8 (7%)
Non-binary	1 (0.9%)
No rresponse	9 (8%)
Abortion rights hostility of respondent's state**	
Very supportive	15 (13%)
Supportive	24 (21%)
Leans supportive	19 (17%)
Middle ground	20 (18%)
Leans hostile	6 (5%)
Hostile or very hostile	19 (17%)
No response	10 (9%)
Practice characteristics	
Ever provided...	
Medication abortion	75 (66%)
EPL with misoprostol	82 (73%)
EPL with mifepristone & misoprostol	40 (35%)
Never provided abortion or medication management of EPL	13 (12%)
Self-reported competence to provide	
Medication abortion	101 (89%)
EPL with misoprostol	104 (92%)
EPL with mifepristone & misoprostol	95 (84%)
Practice setting characteristics	
Mifepristone available onsite at current main practice setting	36 (32%)
Main practice setting	
Federally qualified health center	36 (32%)
Hospital-affiliated outpatient clinic	23 (20%)
University faculty practice	17 (15%)
Community health center	7 (6%)
Group private practice	8 (7%)
Other practice settings***	11 (10%)
No response	11 (10%)
Urbanicity of main practice setting	
Urban	65 (58%)
Midsize town/suburb	24 (21%)
Rural	14 (12%)
No response	10 (9%)
Knowledge and perceptions around mifepristone regulations	
Knew prior to survey that mifepristone and misoprostol for EPL is more effective than misoprostol alone	101 (89%)
If allowed to prescribe mifepristone, would prescribe for...	
Medication abortion	85 (75%)
Medication management of EPL	103 (91%)
Strongly agree patients should be able to fill a mifepristone prescription at their pharmacy	106 (94%)
Believes rule to stock and dispense in-clinic interferes with mifepristone provision	83 (74%)

*Other physician types include adolescent medicine pediatricians, internal medicine physicians, obstetrician-gynecologists who work in primary care settings.
**Abortion rights hostility level of respondents' primary practice state refers to the 2019 data presented by the Alan Guttmacher Institute that categorizes states on a scale of very supportive to very hostile based on the number of state-level abortion restrictions in place (very hostile, hostile, leans hostile, middle-ground, leans supportive, supportive, very supportive). [27] Few respondent states were considered "very hostile" so we collapsed them with "hostile." We selected 2019 data to convey the abortion rights hostility of respondents' states at the time data were collected.
***Respondents classified into "other" primary practice settings provided care in health maintenance organizations, solo private practices, urgent care, public health departments, and the Indian Health Service.

clinics, and 26 did not complete any open-ended questions, leaving an analytic sample of 113 respondents (66%). Table 1 illustrates participants' demographic characteristics and knowledge and perceptions around mifepristone regulations. Most respondents were family physicians, women, practiced in federally qualified health centers (FQHCs) and urban areas, and supported pharmacy dispensing of prescription mifepristone.

3.1. Barriers to provide mifepristone in primary care

Obstacles to providing mifepristone centered on the REMS-related organizational barriers to stock and dispense and the intersection of the REMS with other abortion policy issues.

For organizational barriers, two REMS-related obstacles emerged regarding stocking and dispensing mifepristone: bu-

reaucratic hurdles and leadership resistance. Bureaucratic hurdles involved logistical challenges, like "upfront cost[s]... training staff… [and] extra time," to establish supply, clinic, and patient care systems (NP, hospital-affiliated outpatient clinic). Some found the process more complicated than obtaining equipment for uterine aspiration. They remarked that often primary care settings "do not have the infrastructure or space" to routinely stock and dispense prescription medications (Physician, FQHC).

Additionally, various clinic and department managers, administrators, and others in positions of power demonstrated misperceptions, resistance, and discomfort to integrate medication abortion and/or mifepristone for EPL management. This administrative resistance inhibited respondents from pursuing efforts to change practice and provide mifepristone. One respondent described:

> We have tried to get mifepristone available at all of our clinic sites, and the pharmacy department has been very resistant and difficult to work with on this due to the REMS classification. They state that they are scared about being out of compliance and risking shutting down the entire institution. They demonstrate many false ideas about what the REMS classification does and does not mean, but are unwilling to change their opinions or practices about this. (Physician, FQHC).

Overall, respondents believed that bureaucratic barriers would be minimized if mifepristone was available by prescription, rather than stocked onsite.

Some shared how the REMS intersects with federal and state abortion restrictions, like the Hyde Amendment and physician-only laws. Many FQHC respondents said their organizations barred abortion care, including stocking and dispensing mifepristone, due to administrators' risk aversion and misinterpretation of the law. One explained:

> Our directors and managers believe that it's illegal for us to provide pregnancy terminations. The reality is we would have to separate out federal funding from other funding sources. Our financial department is not that savvy, nor are they interested in setting up a parallel system of funds. (Physician, FQHC).

Even for EPL care, FQHC leadership prevented clinicians from using mifepristone due to its association with abortion and perceived similarities between abortion and EPL care: "They [administration] feel it could jeopardize funding even though we would only use it for EPL" (Physician, FQHC).

In many states, physician-only laws prohibit APRNs and physician assistants from providing abortion care. One respondent described:

> I was able to provide mifepristone in my practice…until the state laws changed and restricted provision of abortion services to physicians only… We had to wait for a physician to travel 3.5 hours to our clinic twice a month. So, all patients who needed abortion services had to come on specific days, when they were previously able to come any day. (Midwife, community health center).

Though these laws were designed to impact abortion, respondents shared that they affected EPL care too.

3.2. Effects of restricted mifepristone access on patients

Respondents perceived three kinds of patient harms when mifepristone was inaccessible in primary care: disrupted continuity of care, additional medically-unnecessary appointments, and undesired aspiration procedures for EPL.

Respondents felt that not having mifepristone accessible in primary care disrupted patients' continuity of care. They described having close relationships with patients who preferred not to go to unfamiliar providers for abortion or EPL, as this may increase anxiety. One explained:

> Patients have come to me wanting medical management of miscarriage or medical abortion, and I have had to turn them away and send them to other practices... stigmatizing their experience, and sending the message that management of their pregnancy and fertility is not part of primary care... I remember a patient sitting in my office, wanting a medical abortion from her trusted midwives and saying, *how is it possible you can't provide me with this service?* (Midwife, hospital-affiliated outpatient clinic).

Additionally, patients referred to outside facilities experienced added wait times and logistical issues, leading to delays in care and disproportionate financial burdens. A respondent said:

> My patient was Spanish-speaking only and lived...45 minutes [from] the closest [abortion clinic]. I am a Spanish-speaking provider in her neighborhood. The patient had to pay for a second visit with [the abortion clinic] for a service I could have provided myself, and had to wait an additional two weeks for this appointment… It is anxiety-provoking for patients to go to an unfamiliar clinic at a distance from their home to see an unfamiliar provider who may not speak their native language. (Physician, FQHC).

Respondents also felt the ETASU to dispense mifepristone in-office created medically-unnecessary appointment-related obstacles for patients to navigate, delaying care and/or influencing decision-making. One shared:

> Sometimes, I diagnose miscarriage when a patient is not in the office. If she wants to be treated with the mifepristone/misoprostol combination, then she must come into the clinic and wait until I (or another provider who feels comfortable dispensing mife[pristone]) is in session at the clinic. (Physician, FQHC).

In some cases, patients wanted medication management for their EPL but ultimately had undesired aspiration procedures due to lack of mifepristone in primary care:

> I had a recent patient who chose aspiration due to greater effectiveness compared to misoprostol alone, but I think otherwise would have chosen medication management. She ultimately had a traumatic and painful procedure due to difficult anatomy...and I think would have been much better served with evidence-based medication management. (Physician, university practice).

In other situations, patients took the misoprostol-only regimen and needed follow-up aspirations, which may have been avoided had mifepristone been accessible in primary care:

> I had two patients with EPL who wanted to pass the pregnancy at home, in private. Both felt this would help them process the [miscarriage] in a way that was best for them. Both failed protocols with misoprostol alone, and both required referral out to another clinic for manual vacuum aspiration. This took more time, was more expensive, and involved...meeting a provider with whom they were less comfortable. (Physician, FQHC).

Overall, respondents felt that primary care access to mifepristone could have prevented negative patient experiences.

4. Discussion

Even for clinicians committed to reproductive healthcare access, the FDA REMS rule mandating in-office mifepristone stocking

and dispensing inhibited many from integrating medication abortion and/or EPL management into primary care. Respondents reported concerns that this resulted in negative physical, emotional, and financial experiences for patients. Studies exploring abortion restrictions find similar consequences: delays in care leading to large expenses, appointment and travel logistics to navigate, and emotional frustrations [22,28]. For EPL, respondents cited an inability to honor patients' preferences for treatment, which minimized decision-making autonomy and exacerbated potential harms to health and wellbeing. This is a significant public health concern, as evidence shows quality of life outcomes improve when patients have comprehensive EPL options available and they actively participate in treatment decisions [29].

These barriers to primary care access and negative patient experiences underscore the importance of removing mifepristone from the REMS. Delays due to the REMS do not enhance safety, timely care does. In fact, Canada has made pharmacy dispensing of mifepristone available, with positive experiences and improved access to care [30]. Expert opinion and safety data demonstrate that mifepristone no longer meets requirements to be regulated under a REMS [4,8]. Our findings suggest that amending the stocking and dispensing ETASU may ameliorate barriers to providing mifepristone in primary care.

However, expanding primary care provision of mifepristone is complex. Even if the mifepristone REMS were removed, policies like the Hyde Amendment and physician-only laws will continue to restrict funding for and access to medication abortion. Some healthcare organizations may continue inhibiting mifepristone for EPL, due to associations with abortion [19]. Though mifepristone may not be fully accessible to all without repealing harmful federal and state laws, removing the mifepristone REMS is a crucial evidence-based step to increase access [31]. While the mifepristone REMS persists, reproductive health and rights organizations should support interested primary care clinicians and health centers to obtain and provide mifepristone. Technical assistance and interprofessional training have shown to be effective in supporting committed primary care clinicians engage with leaders and colleagues to overcome logistical barriers and leadership resistance to offer abortion and EPL care [15,18,19,32,33].

Our study has several limitations. While we approximated potential respondents from the chosen listservs, the true size and representativeness of the eligible source population is unknown due to lack of non-respondent eligibility information, possibility that emails were never opened, and potential overlap of membership across listservs. Additionally, this sample was not representative of the US primary care clinician workforce as most respondents have provided medication abortion at some point, are knowledgeable about medication abortion and EPL care, and have demonstrated interest in providing this care. As such, barriers may be different for clinicians less actively involved. As an exploratory qualitative study, we cannot make claims about representativeness or generalizability. We hoped early participant referral would increase our reach, but few respondents were sourced this way ($n = 3$). Patient experiences are described from clinicians' perspectives, rather than patients themselves. We chose to collect qualitative data through open-ended survey questions, rather than in-depth interviews or focus group discussions. This allowed for a larger sample, which increased geographic, practice setting, and clinician diversity, though interviews and focus group discussions may have given us more insight and context. Finally, the study predated the COVID-19 pandemic, so we did not document practice changes or additional barriers.

Our exploratory study suggests that amending the mifepristone REMS may reduce barriers for clinicians interested in offering medication abortion and EPL management in primary care. Decades of prior research demonstrating mifepristone's safety combined with further studies on primary care barriers to access and patient outcomes can inform evidence-based FDA policy changes. The mifepristone REMS, intended to promote safety, should not concurrently inhibit patients from accessing standard of care treatment and must be reevaluated.

Declaration of Competing Interest

None.

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Mifepristone restrictions and primary care: Breaking the cycle of stigma through a learning collaborative model in the United States

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ABSTRACT

Despite its safety record, mifepristone is subject to a highly restrictive set of regulatory measures through the Risk Evaluation and Mitigation Strategy (REMS) by the US Food and Drug Administration. We argue that these restrictions both reflect and perpetuate a cycle of abortion stigma, creating particular barriers to mifepristone use in primary care settings where communities that historically experience barriers to care can most easily access reproductive health services. Through qualitative interviews with Illinois primary care clinicians, we discovered how the REMS heightens institutional anxiety over implementation of mifepristone use. To address this, we created *ExPAND Mifepristone*, a learning collaborative targeting institutional anxiety and logistical barriers to mifepristone use. The learning collaborative model holds high potential to mitigate institutional barriers to mifepristone use by increasing providers' self-efficacy to identify, address, and overcome institutional fears. Until the REMS is fully repealed, learning collaboratives constitute a promising tool to combat the practical and psychological barriers to mifepristone use that these restrictions currently pose.

Introduction

Abortion with mifepristone is safe and effective [1–4]. This treatment falls well within the scope of primary care in the United States, as it involves patient assessment and health education for which primary care providers are extensively trained [5–8]. Nonetheless, many clinicians trained to provide medication abortion do not currently do so, and only an estimated 1% of medication abortions occur in primary care offices [9,10]. The potential for primary care providers to help improve abortion access is particularly high in the Midwest, which experienced the largest regional decline in abortion clinics over the past decade [11]. Given this context, our team set out to develop an evidence-based intervention to support mifepristone use in primary care in Illinois, resulting in the learning collaborative *Excellence in Providing Access to New Directions in Mifepristone Use* (*ExPAND Mifepristone*). This commentary describes how *ExPAND Mifepristone* seeks to disrupt a cycle of abortion stigmatization in primary care that is anchored by the US Food and Drug Administration's inclusion of mifepristone in the Risk Evaluation and Mitigation Strategy (REMS) program. We argue that the REMS serves as the linchpin of a cycle of medication abortion stigmatization in primary care, encouraging institutional anxiety over abortion provision which leads to logistical barriers to mifepristone use. This cycle successfully excludes mifepristone from many primary care settings, reinforcing the perception that abortion is a tainted and undesirable service that should remain marginalized in specialty settings. The learning collaborative model serves as a potentially valuable framework for primary care physicians to address, understand, and overcome the institutional fears that the REMS program encourages.

1. The mifepristone REMS and the ripple effect of logistical barriers

The fascinating thing is, there are a lot of other things I've managed to implement [since joining this primary care practice], and when the perception is that your organization does not care, or prioritize providing abortion care, the barriers can be great, and other [services] the organization does prioritize, the resources, the people, the organization gets behind them. So it's very frustrating to me that abortion care again occupies this separate space. – Illinois primary care provider

The REMS for mifepristone requires that (1) the drug be dispensed in healthcare settings by or under the supervision of a cer-

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Fig. 1. Taxonomy of barriers to medication abortion care in primary care settings.

tified prescriber; (2) dispensing clinicians register with the drug manufacturer; and (3) patients sign a specific form stating the drug will be used for a medication abortion, despite the evidence base that it is also effective for both early pregnancy loss treatment and cervical ripening for dilation and evacuation procedures [12–14]. While the REMS program aims to reduce risks from drugs with high potential of serious adverse health effects [15], mifepristone has been shown to have an excellent safety profile [16]. As a result, mifepristone access has expanded globally through evidence-based deregulation. Mifepristone is fully incorporated in abortion services in Canada, as the federal regulatory system permits dispensing through a pharmacy with a prescription from a clinician and no longer requires an ultrasound prior to prescribing [17,18]. Mifepristone distribution via postal mail following a telemedicine appointment is also approved in the United Kingdom [19]. In light of these regulatory frameworks, the REMS stands out as exceptionally restrictive.

To gain a more comprehensive understanding of the institutional barriers primary care providers face to evidence-based mifepristone use, we conducted a qualitative study of providers in Illinois and assessed their opinions of the REMS restrictions and other barriers to medication abortion provision. As part of this larger study on barriers to abortion provision in primary care, 19 primary care providers and clinical administrators participated in semi-structured interviews exploring barriers to and facilitators of mifepristone use at the individual, institutional, and policy levels. We sampled clinicians based on their current abortion provision status (providing in primary care or not), type of health care facility (community health center, hospital, group or private practice), and geographic location (within vs. outside of Chicago). For full study methodology, see Rasmussen and colleagues, this issue.

Overall, interviewees expressed widespread support of removal of the mifepristone REMS and reported that removing the REMS would help them or their colleagues integrate medication abortion into primary care. We noted that providers named two types of barriers posed by the REMS: direct infrastructure requirements for dispensing mifepristone; and requirements self-imposed in response to the REMS (Fig. 1). On a practical level, some clinicians expressed that if the REMS was eliminated and they could prescribe mifepristone through a pharmacy, that would remove logistical barriers around medication stocking [20]. Participants also expressed that the REMS impedes mifepristone use in primary care by perpetuating fear and mystery around the drug that is not supported by clinical evidence of its risks, resulting in the desire for excessive clinical training, unnecessary bureaucratic infrastructure-building, and fear of extremely rare complications with mifepristone use. The resulting institutional anxiety around abortion provision drives a process of stigmatization of which the REMS forms an integral part.

2. Logistical barriers within a cycle of stigmatization

Interviewer: Your practice has implemented quite a few new services. How do you feel implementing these services is analogous or different to implementing abortion?

Clinician: I want to say it's just the stigma that surrounds it is the only real difference. When there's money…and operations stand behind it, it's much easier, but then we are also now faced with the…stigma of it. – Illinois primary care provider

The REMS program imposes medically unnecessary restrictions on mifepristone access, and these restrictions create specific logistical hurdles, as well as generating an impression that provision of mifepristone is difficult and requires extensive training, ultimately creating a hesitancy among primary care clinicians to administer it. As illustrated in Figure 2, the REMS are the linchpin of a cycle of stigmatization that continues to keep mifepristone out of primary care practice and other non-specialty settings over time. Similarly to stigma among abortion patients and providers, institutional stigma around abortion care functions as a cycle [21,22]. Because regulations such as the REMS are imposed, institutions perceive abortion care to be excessively complex, and fear abortion provision. Out of fear, leadership blocks qualified clinicians from integrating abortion into their primary care practice. Thus, abortion remains siloed from mainstream medicine, reinforcing the perception that it is a tainted medical practice [23].

We heard this hesitancy in our interviews, as clinicians expressed concern over their own competency to administer mifepristone to their patients. When asked about their personal barriers to administering medication abortion, one clinician responded: "I totally believe that it can be done, but I also feel like I didn't have that preparation… But I've heard that some people do it in primary care settings…I'm like, 'How do I do this? Can I do it?'" Other clinicians expressed feeling a sense of hypervigilance when it came to providing medication abortion services because of the seemingly specialized nature of mifepristone protocols. One clinician noted their heightened sense of alertness stems from their desire to distribute mifepristone perfectly. They commented: "I think there's a piece of perfectionism…it may lead us to stumble across smaller roadblocks, because we're looking for a perfect outcome, rather than a safe and acceptable outcome." As a result of the perceived need for extensive training in medication abortion provision, primary care institutions lean towards not administering mifepristone in fear of incorrectly distributing the medication or not knowing how to proceed with potential adverse side effects. While primary care institutions see training as necessary to overcome institutional anxiety about abortion provision, this anxiety can also prevent individuals from accessing additional training: "Even just talking about wanting abortion training or having that be a conversation that felt normal was a barrier because of the stigma around abortions."

Fig. 2. Cycle of abortion stigmatization in primary care.

This institutional anxiety directly feeds into implementation challenges, as some interview participants expressed a desire to implement medication abortion in their clinics but an unwillingness among institutional leadership to allow this service. One respondent commented, "We've been unable to get... even though there are pathways for doing medication abortion…sadly, our board…doesn't feel comfortable. They're afraid." Many interviewees named budget constraints as a main reason for not providing medication abortion services, as clinicians working in federally qualified health centers (FQHCs) have very limited funding that they cannot afford to waste. Because the REMS requires onsite drug stocking rather than pharmacy prescription, providers expressed that clinical leadership hesitated to invest funds in the medication given their very limited resources. One clinician commented: "So it's kind of, yeah, we want to, but is that a necessary thing to do to take time and money and resources away from the rest of…what the FQHC is doing." These implementation barriers, combined with institutional anxiety, create a cycle of abortion stigmatization that isolates medication abortion from mainstream medicine. Removal of the REMS would disrupt this cycle significantly by alleviating the need for infrastructure-building within clinics and signaling leadership that the drug is safe enough to be prescribed without excessive training. However, in the current context of having the REMS in place, we identified a structured, multi-institutional learning collaborative as a promising strategy to disrupt the stigma cycle and help clinics overcome both the logistical and the psychological barriers at play.

3. Opportunity for action within the learning collaborative model

*I wish that [*abortion implementation*] would have been the same way that I participated in other quality collaboratives, whether it's to improve depression care, hypertension care, implement new screening, protocols…A big part of my career now has become working in quality improvement. There are best practices out there for how to do this, for how to help organizations across the country, who are trying to do the same thing.* -Illinois primary care clinician

In our formative research, clinicians described how mifepristone distribution is seen as a complex process that requires extensive training and experience to dispense. These findings highlight the need for evidence-based interventions in primary care, leading us to create *ExPAND Mifepristone*, a learning collaborative geared towards disrupting the stigma around mifepristone use for both abortion and miscarriage management in primary care settings. *ExPAND Mifepristone* launched in spring 2020 and aims to demystify mifepristone use in clinical care by building self-efficacy and knowledge not only around clinical applications of the drug, but also regarding billing, stocking, scheduling, and other logistical barriers. This program is largely based on the learning collaborative model developed by the Institute for Healthcare Improvement's Breakthrough Series. The learning collaborative model is defined as a 6-to-15-month intervention that provides a structure for organizations to learn from each other in multidisciplinary teams on a certain issue [24]. In addition to creating collaborative teams within organizations, learning collaboratives generally include highly skilled experts to educate and train the teams to incorporate changes within their settings. This training is then followed by an action period where the teams implement the changes and report back to the learning collaborative, allowing experts to weigh in on their progress and for other teams to learn from each other. The learning collaborative approach is proven to be successful in fostering implementation of evidence-based practices across a wide range of clinical settings serving both children and adults [25,26]. In the field of reproductive health care in particular, the learning collaborative model has improved care and ed-

Fig. 3. Cycle of stigmatization of abortion in primary care—Hypothesized impact of a learning collaborative intervention.

ucation for individuals with preeclampsia and for individuals with postpartum gestational diabetes [27,28].

Drawing on the literature of best practices for learning collaboratives more broadly, we designed the *ExPAND Mifepristone* collaborative specifically to target the cycle of stigma while helping clinics build infrastructure for full-spectrum evidence-based mifepristone use (Fig. 3). The program is designed to provide clinicians with concrete tools to incorporate mifepristone in primary care settings in Illinois through monthly group meetings, on-site and distance consultation, self-assessment, and tailored evaluation. The *Expand Mifepristone* learning collaborative includes expert coaches who advise physicians and administrators on how to combat institutional hurdles and competing priorities to incorporate mifepristone in their clinics. Trainings in our pilot year shared new evidence-based guidelines for early pregnancy loss and no-test medication abortion [29,30] and provided guidance on how primary care clinicians can bill for mifepristone. Illinois law provides for public and private insurance coverage of abortion [31,32], and the collaborative clarified the funding component of abortion provision through trainings on Medicaid reimbursement policies and procedures. The collaborative also provided expert, step-by-step support in understanding and navigating the process of registering with the manufacturer(s) to dispense mifepristone, as well as understanding how to use required patient consent forms and how to enable in-office dispensing of mifepristone. This implementation-based training was designed to debunk the misconceptions associated with mifepristone.

Based on our conceptual model of how abortion stigma inhibits abortion provision in primary care (Fig. 2), we hypothesize that by the end of the program, clinicians should be equipped with enhanced self-efficacy around mifepristone use, as well as the concrete logistical tools needed to provide mifepristone for abortion and miscarriage management in primary care. We are testing these hypotheses through a mixed-methods evaluation with qualitative interviews and review of electronic medical record data from *ExPAND Mifepristone*'s pilot clinics. We will apply an implementation science framework to our analyses, to refine the program's design for future cohorts.

4. Moving forward: Deregulate, educate, and empower primary care clinicians

The *ExPAND Mifepristone* learning collaborative constitutes a potential model for mitigating medication abortion stigma specifically and mifepristone stigma more broadly in primary care settings by addressing both logistical and psychological barriers. The existence of the REMS diffuses stigma within primary care settings and encourages hesitation and fear amongst clinicians and administrators to provide abortion. While the learning collaborative model addresses the stigmatization that is driven by the REMS, removal of mifepristone from the REMS program would likely have a far greater impact on abortion stigma. Nonetheless, as stigma operates at multiple levels across medical training, institutions, and the broader social context, even in the absence of the REMS, additional work will be needed to normalize abortion in primary care [21–23,32–35].

ExPAND Mifepristone represents just one potential approach to supporting clinical champions of mifepristone use in primary care in taking on institutional barriers to evidence-based use. To complement the existing robust infrastructure to train primary care providers in pregnancy diagnosis and management, including abortion care [8,36–37], additional programs to support implementation of medication abortion in primary care should be created and evaluated over time. As the largest and most geographically well distributed provider group in the United States, primary care providers hold immense untapped potential to expand abortion access. Unless and until the US health care system joins the global trend of mifepristone deregulation, learning collaboratives and other systems of practical support can empower clinicians

to overcome logistical barriers to providing the holistic, patient-centered pregnancy care their patients deserve.

Declaration of competing interest

None.

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Perspectives Among Canadian Physicians on Factors Influencing Implementation of Mifepristone Medical Abortion: A National Qualitative Study

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ABSTRACT

PURPOSE Access to family planning health services in Canada has been historically inadequate and inequitable. A potential solution appeared when Health Canada approved mifepristone, the gold standard for medical abortion, in July 2015. We sought to investigate the factors that influence successful initiation and ongoing provision of medical abortion services among Canadian health professionals and how these factors relate to abortion policies, systems, and service access throughout Canada.

METHODS We conducted 1-on-1 semistructured interviews with a national sample of abortion-providing and nonproviding physicians and health system stakeholders in Canadian health care settings. Our data collection, thematic analysis, and interpretation were guided by Diffusion of Innovation theory.

RESULTS We conducted interviews with 90 participants including rural practitioners and those with no previous abortion experience. In the course of our study, Health Canada removed mifepristone restrictions. Our results suggest that Health Canada's initial restrictions discouraged physicians from providing mifepristone and were inconsistent with provincial licensing standards, thereby limiting patient access. Once deregulated, remaining factors were primarily related to local and regional implementation processes. Participants held strong perceptions that mifepristone was the new standard of care for medical abortion in Canada and within the scope of primary care practice.

CONCLUSION Health Canada's removal of mifepristone restrictions facilitated the implementation of abortion care in the primary care setting. Our results are unique because Canada is the first country to facilitate provision of medical abortion in primary care via evidence-based deregulation of mifepristone.

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INTRODUCTION

Approximately 40% of pregnancies in Canada are unplanned, and 1 in 3 Canadian women will have at least 1 abortion in their lifetime.[1-4] Access to health services in Canada that enable patients to plan and space their pregnancies has been historically inadequate and inequitable.[5] Before 2017 in Canada, abortion services were surgical and provided by fewer than 300 doctors at roughly 100 facilities in urban cities close to the Canada-US border.[4] In this context, patients who lived outside large cities had to travel significant distances to access abortion care.[6,7] Concern about these inequities was expressed in the November 2016 report of the Committee on Elimination of Discrimination Against Women, in which the United Nations Human Rights Commissioner called on the government of Canada to improve access.[5]

The approval of mifepristone medical abortion in July 2015 by Health Canada (the equivalent of the US Food and Drug Administration) appeared to be a potential solution to improve abortion access in the primary care setting.[8-10] Mifepristone became available for prescription

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study. In future research, our team will explore their perspectives, as well as those of midwives, patients, and pharmacists. We investigated mifepristone implementation in its early phase, during which Health Canada made significant changes to the regulation of this drug. As use and familiarity with mifepristone increase, the barriers and facilitators will likely change.

Conclusion

In the first 2 years since mifepristone has been made available in Canada, rapid regulatory revisions greatly assisted primary care practitioners to implement abortion care, particularly in rural communities. These changes have led to health care professional perceptions that there are minimal regulatory barriers to medical abortion practice. Our results are unique internationally given that Canada is the first nation to facilitate provision of medical abortion in the primary care setting via evidence-based deregulation of mifepristone.

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Original Research Article

Expanding access to medication abortion through pharmacy dispensing of mifepristone: Primary care perspectives from Illinois

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ABSTRACT

Objective: Medication abortion is safe and effective, yet access is limited by a strict Risk Evaluation and Mitigation Strategy (REMS) that prohibits pharmacy dispensing of mifepristone. Given the ability of primary care providers (PCPs) to expand medication abortion access, we assessed PCP perspectives on how lifting the mifepristone REMS would affect the provision of medication abortion in primary care.

Study design: We conducted a qualitative study of PCPs and administrators in Illinois with experience or interest in providing medication abortion care at their practice. The final sample (N=19) consisted of seven family medicine physicians, three nurse practitioners, four certified nurse midwives, and five administrators. We queried participants on how removing the REMS to allow pharmacy dispensing of mifepristone would affect their ability to provide medication abortion. We conducted interviews via telephone and used ATLAS.ti to manage our transcripts; we analyzed these data for major themes regarding pharmacy dispensing.

Results: Primary care providers expressed support for pharmacy dispensing due to its ability to help normalize medication abortion, reduce implementation barriers in primary care, and expand abortion access. Further challenges to address if the REMS restrictions are lifted include federal funding restrictions on abortion, concerns about unsupervised mifepristone use, and pharmacy cooperation.

Conclusion: Removing the mifepristone REMS to allow pharmacy dispensing could help normalize medication abortion care, facilitate provision in primary care, and address disparities in abortion access.

Implications: Our findings illuminate novel benefits of removing the mifepristone REMS and highlight methods to promote successful implementation of pharmacy dispensing. Combined with prior literature, these results support prompt reevaluation and removal of the REMS to align medication abortion care with evidence-based practices.

1. Introduction

The number of abortion facilities in the US is declining, further exacerbating disparities in abortion access. Between 2011-2014, the number of abortion clinics nationwide declined 6%, with the greatest decline occurring in the Midwest at 22% [1]. As the number of abortion clinics in the Midwest and South continues to decline [2], healthcare providers need strategies to overcome these geographic barriers and expand equitable access to care. Medication abortion offers several potential strategies to address these needs.

Medication abortion, using mifepristone and misoprostol, has become increasingly popular, making up 39% of all abortions in 2017 [2]. Patients report high rates of satisfaction [3], citing the ability to choose an alternative to procedural abortion that they perceive as safer and more natural [4]. The combination of mifepristone and misoprostol is also used to manage early pregnancy loss, yielding superior efficacy than misoprostol alone [5]. Importantly, medication abortion can be safely provided in primary care by family medicine physicians (FMPs), nurse practitioners (NPs), physician assistants (PAs), and certified nurse midwives (CNMs) [6,7]. These primary care providers (PCPs) have the potential to greatly expand access to abortion services, especially in rural and medically underserved areas. Combined with the ability to offer safe, convenient abortion care via telemedicine [8–10], medication abortion has immense potential to improve reproductive health equity in the US.

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However, current laws and policies place medically unnecessary restrictions on medication abortion care, effectively limiting this potential. Since the approval of mifepristone in 2000, the Food and Drug Administration (FDA) has imposed a set of restrictions on the medication, later deemed a Risk Evaluation and Mitigation Strategy (REMS). The purpose of the REMS is to help ensure the benefits of a medication outweigh its risks. Mifepristone has one of the most restrictive REMS: providers must be certified with the manufacturer and complete a Prescriber Agreement Form, patients must sign a Patient Agreement Form, and the medication can only be dispensed in a clinic, medical office, or hospital [11]. Thus, in contrast to most other medications, pharmacists cannot dispense mifepristone.

While there is no evidence that the mifepristone REMS protects patient safety, it does impede the availability and accessibility of mifepristone [12]. Rather than access the medication from their pharmacy via pick-up or mail-order, patients must travel to a clinic that stocks mifepristone. Likewise, the burden of stocking the drug can be a barrier to providers. A national survey of obstetrician-gynecologists found that 28% of those not providing medication abortion said they would if they could write a prescription for it [13]. In Australia, pharmacist dispensing drastically increased the number of providers and availability of abortion, especially in rural areas [14]. In Canada, pharmacy dispensing of mifepristone has contributed to its successful incorporation into abortion services [15,16].

In the US, medical and drug experts continue to call upon the FDA to lift the REMS given mifepristone's excellent safety profile and its ability to expand access to reproductive healthcare [12,17,18]. The American College of Obstetricians and Gynecologists, American Academy of Family Physicians, and American Medical Association support the removal of the mifepristone REMS [19–21], noting how these restrictions are inappropriately unique to abortion provision [19].

Given the ability of primary care providers to expand access to abortion, especially in underserved areas, it is important to understand how the REMS affects their ability to provide. We conducted a qualitative study of Illinois PCPs and assessed their perspectives on how lifting the REMS to allow pharmacy dispensing of mifepristone would affect the provision of medication abortion in primary care.

2. Methods

2.1. Recruitment

As part of a larger exploration of medication abortion in primary care, we interviewed 19 PCPs and clinical administrators in Illinois (Table 1). We obtained ethical approval from the University of Chicago Institutional Review Board. After recruiting known professional contacts with experience or interest in providing medication abortion, we used snowball sampling to recruit additional clinicians and administrators. We classified interviewees as administrators if their primary perspective for the purpose of the interview was their administrative role, even if they also had clinical training or experience. We sampled for maximum diversity on provider type, current ability to provide medication abortion, practice setting, and practice location [22]. To gain insight from NPs and CNMs who provide medication abortion, we included a few clinicians who practice at specialty clinics. Our final interview sample represented eight different healthcare organizations in Illinois. Study participants received $50 in remuneration.

Table 1
Characteristics of Illinois primary care clinicians and administrators interviewed regarding abortion provision in primary care (N=19)

Characteristic	Number of participants
Participant type	
Family medicine physician	7
Nurse practitioner	3
Certified nurse midwife	4
Administrator[a]	5
Medication abortion provision	
Site currently providing	6
Site not currently providing	13
Practice setting	
Hospital-based	4
Community-based	12
Specialty clinic	3
Practice location	
Chicago	15
Other location in Illinois	4

[a] Types of administrators interviewed include Administrative Director, Clinical Director, and Chief Operating Officer.

2.2. Interviews

We conducted in-depth telephone interviews in March 2019 – Jan 2020. Interviews lasted approximately an hour and were done by a qualitative researcher with doctoral training in sociology and public health (EJ) or one of two trained members of the research team (KR and AC). Interviewers used a semi-structured interview guide with open-ended questions, allowing participants to partially guide the conversation. Interviewees could mention pharmacy dispensing any time throughout the interview as they found relevant. In addition, toward the conclusion of each interview we asked, "If the law allowed clinicians to prescribe mifepristone for pick up at a pharmacy, how would that affect your ability to provide medication abortion, if at all?" We probed interviewees for thoughts on potential benefits or challenges of this model. We used a third party to transcribe the interviews from our audio recordings. The research team verified transcripts for accuracy.

2.3. Analysis

Analysis followed an exploratory approach grounded in a multilevel conceptual framework informed by the prior literature on factors affecting clinicians' decisions surrounding abortion provision [13,23,24]. The three researchers serving as primary coders (EJ, KR, AC) developed and validated the preliminary codebook using a combination of *a priori* and emergent codes with the assistance of a fourth researcher with clinical experience with abortion provision in primary care (DS). Two of the three primary coders analyzed each transcript. We used ATLAS.ti for coding and performed manual reconciliation of coding discrepancies through iterative discussions among the study team. We analyzed discussions of pharmacy dispensing to identify major and minor themes. Because this was a subtopic of a larger analysis, we did not prospectively assess for thematic saturation on pharmacy dispensing during data collection.

3. Results

Overall, participants expressed wide support for removing the REMS to allow pharmacy dispensing of mifepristone. We identified four major themes regarding the benefits and challenges of removing the mifepristone REMS: reducing abortion stigma by normalizing mifepristone; decreasing implementation barriers in primary

care; increasing access to safe, legal abortion; and addressing further challenges to medication abortion care.

3.1. Reducing abortion stigma by normalizing mifepristone

Participants described how stigma around abortion can be a barrier to provision. While explicit opposition to abortion from colleagues was referenced occasionally, the more common manifestation of stigma was the perception that abortion is risky and requires specialization distinct from other healthcare. Participants described how allowing pharmacists to dispense mifepristone, like any other medication, would help reduce abortion stigma, normalize its integration into primary care, and align with evidence-based practice.

Providers described how prohibiting pharmacy dispensing of mifepristone leads to heightened concern about the risks of the medication. This in turn contributes to the specialization of abortion and perpetuates the perceived need for regulations. As one provider explained: "So I feel like if it was something that could be prescribed, I think that more people would feel it was easier to do. It wouldn't feel so restricted and specialized…But I mean, if you have this drug that only you can prescribe if you are a special someone, then it makes it seem like it's this mysterious thing" (CNM, not currently providing abortion care, Chicago).

Overcoming this perception that abortion is a specialty service can be challenging for PCPs who wish to offer comprehensive sexual and reproductive health services. Removal of the REMS would align with current evidence that supports the provision of medication abortion in primary care rather than as a specialty referral. As one participant said: "There's that primary care model which people see their PCP, but then for certain services they have to go to other people. Our model historically has been that your PCP is your PCP and we're trying to have them do as many things as possible…I think [pharmacy dispensing] would help with that for sure" (administrator, site not currently providing abortion care, Chicago).

Participants expressed frustration with non-evidence-based abortion restrictions that prohibit healthcare professionals from working at their full scope of practice. Regarding pharmacist ability to dispense mifepristone, one participant said: "One, I absolutely think it should be available at pharmacies so that people can get it. I think pharmacists are well qualified to give people [mifepristone and misoprostol]. I think that would be great." They went on to express hope that lifting the REMS would shift perceptions of abortion risk and lead policymakers to reevaluate the basis of "physician-only" laws that prohibit other clinicians from prescribing mifepristone on the grounds of safety concerns: "But if the conversation gets to the point where pharmacists can hand it out, then absolutely nurse practitioners, nurse midwives and PAs should be able to also" (CNM, not currently providing abortion care, Chicago).

3.2. Decreasing implementation barriers in primary care

Not only would lifting the REMS help normalize abortion, many participants described how removing these restrictions would make it more feasible for them to provide medication abortion care in their practice. Removing the REMS would address implementation barriers including unsupportive peers, stocking mifepristone, and disruptions in clinic flow.

Treating mifepristone like any other medication would help address discomfort peers have about providing abortion in primary care. However, some providers still expressed concern about peers who object to abortion on moral grounds. In these cases, allowing providers to prescribe mifepristone for pick-up at a pharmacy would help providers work around unsupportive peers. As one participant explained: "Let's say you work in a small practice, and your one nurse or staff member does not support abortion care, then certainly as a physician you can do it yourself, but you need the staff to check the meds, and do a count and make sure things are expiring. [Pharmacy dispensing] removes that potential barrier" (FMP, not currently providing abortion care, Chicago).

Even for clinics whose providers and staff all share similar values regarding abortion, the hassle of purchasing and stocking mifepristone in the clinic can be a barrier. A NP currently providing abortion care outside of Chicago said: "I think for other places that can't financially carry a large stock of it, it could be very helpful because it's very expensive. So of course, you have to balance carrying the amount that you need with what you're using."

Although the FDA approved a generic version of mifepristone during our study, thereby reducing the cost per pill, this interviewee's concern about clinics purchasing and stocking mifepristone remains valid. Addressing this barrier is particularly important in primary care settings that expect to see a low volume of patients seeking abortion, especially when first implementing the service. As a Chicago FMP currently providing abortion care explained: "[Pharmacy dispensing] would be more helpful for a clinic that has trouble keeping mifepristone in stock or that it's expiring because they're so low volume."

While participants believed pharmacy dispensing would reduce financial barriers of providing mifepristone in clinic, one participant questioned whether this would transfer more financial burden on to patients: "Or it might get just a lot harder for patients to access if it's no longer in the office. As an FQHC, we might be able to provide that $50 tablet and eat the cost, right? We do that all the time. You can't pay today? All right, well, we're never going to take you to collections. So I can see it being possibly more damaging to patients, but I don't know" (CNM, not currently providing abortion care, Chicago).

Multiple participants noted that there is existing infrastructure at their clinics for dispensing medications through on-site pharmacies. Participants explained how routing mifepristone through their pharmacy, like all other medications, would be more efficient for both the clinic and their patients. As one said: "I would imagine that if it would just help ease the flow, and it would make it a much easier thing to implement if that was the case. We have pharmacies within most of our clinics, and so to be able just to have that at the pharmacy would help reduce patient wait times, and help increase flow and all of that" (administrator, site not currently providing abortion care, Chicago).

3.3. Increasing access to safe, legal abortion

In addition to facilitating implementation in primary care, participants described other ways in which removing the REMS to allow pharmacy dispensing would help address disparities in abortion access. These delivery models, including pharmacy pick-up and telemedicine provision, would increase patient access while maintaining the safety and efficacy of mifepristone.

Many participants believed that having access to mifepristone via pharmacies would expand medication abortion accessibility for patients. As a Chicago administrator whose site is not currently providing abortion care stated: "From just like a state policy, that would be magical. Again, it would also just help reduce stigma. It would help reduce, or help increase accessibility. So I think that it would be amazing. Huge shift."

While it would be beneficial for most patients, one Chicago FMP who is not currently providing abortion care expressed concern over how pharmacy pick-up may affect patient privacy, specifically in small towns: "And then certainly if you're in a small town, really uncomfortable potentially for patients to pick up that medication

at a pharmacy, and so I'm not entirely sure that from a patient perspective it makes the most sense." Other participants noted a solution to privacy concerns via direct-to-patient telemedicine provision of medication abortion.

Many participants supported the use of telemedicine for medication abortion care and noted how pharmacy dispensing of mifepristone would synergistically expand access to abortion. The REMS constrains providers to the site-to-site model of telemedicine provision, which requires patients to visit a clinic to pick up mifepristone. Without this requirement, providers in Illinois could utilize the direct-to-patient model in which the medication is mailed directly to the patient. When asked about the use of telemedicine to expand abortion access, one participant replied: "I mean that kind of crossed my mind when you talked about the shift in mife and if it could be prescribed by a pharmacist, because it would help increase access, and help potentially with the ability to offer telemedicine. So I think that yes, it would absolutely help benefit everybody if that can happen" (administrator, site not currently providing abortion care, Chicago).

While pharmacy dispensing has the potential to expand abortion access via multiple delivery models, participants emphasized that these innovations in care would not affect the safety or efficacy of mifepristone. When asked if they saw any disadvantages of pharmacy dispensing, one Chicago administrator whose site is not currently providing abortion care explained: "You know, it'll still allow the provider to provide the education surrounding the medication, what to expect and symptoms, side effects, all that kind of stuff, so I don't perceive any issues with that." Thus, participants did not perceive a correlation between dispensing location and risk of adverse effects.

3.4. Further challenges to address

While participants expressed strong support for removing the REMS to allow pharmacy dispensing of mifepristone, they also illuminated some challenges that would remain to be addressed. These include federal funding restrictions on abortion, lingering concerns about unsupervised mifepristone use, and pharmacy cooperation.

Providers who receive federal funding expressed uncertainty over whether legal restrictions would allow them to write a prescription for mifepristone. One clinician working in an FQHC said of writing a mifepristone prescription for pharmacy pick-up: "I'd sure love to put that. My gut reaction is like, Ooh, yeah, yeah, yeah, yeah. And then I'm like, oh, am I going to be allowed to do that? Oh, shoot, maybe I won't. I'd have to backtrack and really figure it out. But, if that barrier was gone then sure that would help a lot, but I'm not entirely sure if I would still be able to do that. I don't know. I could find out. I know people will know, but I don't know" (CNM, not currently providing abortion care, Chicago).

Since these federal restrictions apply specifically to abortion provision, providers also questioned whether they would be able to prescribe mifepristone for its other uses, such as the management of early pregnancy loss. As one Chicago FMP not currently providing abortion care said: "I think the challenge we have here with the federal funding though wouldn't allow us to write those prescriptions for abortion…I think we could write it for miscarriage management potentially, but not for abortion."

A couple participants expressed concern about patients misusing the medication if they are allowed to take it at home. One participant, whose experience involved patients taking mifepristone in the clinic, said: "It concerns me about who they [are] actually going to give it to. But, with any change, then you always think of stuff like that. Like, 'Oh, wait. We've always done it this way. What if they do this, or what if they do that?' Yeah, that would be my concern, is are they actually going to take it, or are they giving it to someone else? And, I don't know anything about that other person…Or, just ending up deciding, 'You know what? I don't want to take this,' and then deciding to take it two weeks later because they changed their mind again. Just not taking it appropriately" (NP, currently providing abortion care, outside Chicago).

Finally, many participants cautioned that pharmacy dispensing may introduce a new barrier to abortion access: pharmacist refusal to dispense mifepristone. As one Chicago CNM not currently providing abortion care explained: "Pharmacists still have the right of conscience to decline it, because they decline things like EC still. I can't imagine them agreeing to hand out mife if we have pharmacists that won't prescribe emergency contraception." While many participants raised this concern over pharmacist cooperation, most of them still expressed strong support for pharmacy dispensing of mifepristone. As one Chicago administrator whose site is not currently providing abortion care explained: "I could see it potentially being an issue, but I think it would be...It's like worth it in the end. I mean, it's not a big enough issue to not do it."

4. Discussion

Primary care providers interviewed in this study supported the removal of the REMS to allow pharmacy dispensing of mifepristone. Participants described how this policy change would help normalize the inclusion of abortion in primary care, reduce implementation barriers, and increase abortion access. Further challenges to address include perceived or possible federal funding restrictions, concerns about unsupervised medication handling and use, and potential pharmacist refusal to dispense mifepristone.

The use of a qualitative approach in this study allowed us to explore complex themes regarding pharmacy dispensing and its potential impacts on abortion. Additional strengths include the diverse expertise of our research team and our iterative methods for coding and analysis. We designed this study to capture perspectives from PCPs and administrators with experience or interest in providing abortion services at their practice. The themes presented here do not reflect the attitudes of all primary care providers in Illinois, as it was not our goal to query a representative sample of all PCPs. Additionally, these findings may not be transferrable outside of Illinois due to variations in the political and legal abortion landscape between states. While Illinois has expanded protections for abortion in recent years [25], other states continue to restrict abortion access. Currently 32 states, including most of the Midwest, have "physician-only" laws and 18 states prevent the use of telemedicine for abortion [26]. Thus, while our findings suggest that pharmacy dispensing of mifepristone would synergistically expand abortion access via primary care integration and telemedicine provision, different state policies would continue to impose limitations.

Our findings provide new insight into the burdens the REMS imposes on abortion access and availability. Prior literature supports removal of the REMS based on the safety of mifepristone, the potential for improved patient access, and the efficacy of direct-to-patient telemedicine abortion [8,12,17,18]. The perspectives of primary care providers and administrators presented in this study provide further support for these arguments and illuminate additional benefits of pharmacy dispensing. These novel insights include the potential for pharmacy dispensing to normalize abortion and facilitate the integration of medication abortion in primary care.

These findings have important implications for the future of abortion care. Expanding provision of medication abortion in primary care, combined with the ability to offer direct-to-patient telemedicine abortion, could reduce geographic disparities in abortion access and increase patient autonomy over where and how

to receive care. The COVID-19 pandemic has stressed the need for these innovations in abortion care. Evidence-based protocols support provision of medication abortion without in-person contact [27], yet the REMS unnecessarily requires patients to visit a clinic to pick up the medication. The American College of Obstetricians and Gynecologists and individual medical providers sued the FDA over its imposition of the REMS during the pandemic, resulting in a temporary suspension of the in-person requirements due to the "substantial obstacle" they present to people seeking a medication abortion during the pandemic [28]. Issued in July 2020, this injunction temporarily allows providers to mail mifepristone to patients, yet pharmacy dispensing is still prohibited. The current crisis has highlighted the need to reevaluate the REMS restrictions and the barriers they impose on abortion access.

For patients to gain the full benefit of pharmacy dispensing, the remaining challenges highlighted in this study must be addressed. Providers raised the concern that some pharmacists may refuse to dispense mifepristone on moral grounds. States have varying laws regarding healthcare refusal and the requirement for health professionals to refer patients elsewhere if they refuse to provide a service [29]. It is essential to raise awareness of these conscience clauses and include discussions of the professional, legal, and ethical dilemmas in pharmacy education [30]. Additional strategies to address pharmacist refusal include public education and community organizing, pharmacist outreach and training, and working with state pharmacy boards to shape policies on medication access [31]. These approaches have successfully expanded access to contraception in pharmacies and can apply to mifepristone as well.

Additionally, since 2016 the FDA label has allowed home use of mifepristone based on numerous studies detailing the efficacy, safety, and benefits for patients [32–34]. Given that this update aligns with the common practice in our medical system – to dispense medications to patients and entrust them with the responsibility and autonomy to self-administer their medications at home – we expected all providers to express support for this protocol. Instead, we found a handful of providers expressed the perception that mifepristone requires greater supervision and regulation than other medications. This finding highlights the need to address lingering concerns about abortion risk by increasing awareness of evidence-based guidelines.

This study found that primary care providers expressed support for pharmacy dispensing of mifepristone and its ability to expand access and availability of abortion. Further research is ongoing regarding the feasibility, effectiveness, and acceptability of pharmacy dispensing among patients and pharmacists [35]. If the FDA removes the REMS restrictions and the landscape of abortion care expands to include pharmacy dispensing, this will align mifepristone with other equally safe medications and help normalize abortion in clinical practice.

Declaration of competing interest

None.

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Sept. 29, 2021

BY ELECTRONIC MAIL

Janet Woodcock, M.D.
Acting Commissioner
United States Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Re: Evidence Supporting Elimination of the Mifepristone REMS

Dear Dr. Woodcock:

We are the health care providers and researchers engaged in litigation challenging the Risk Evaluation and Mitigation Strategy ("REMS") for mifepristone 200 mg for termination of early pregnancy. We are pleased that the U.S. Food and Drug Administration ("FDA") has initiated a comprehensive evaluation of the mifepristone REMS and its three elements to assure safe use ("ETASU"), and appreciate the opportunity to submit data and evidence for FDA's review.[1]

As you know, it is our position that a REMS is not medically necessary to ensure that the benefits of mifepristone outweigh its risks.[2] We note that one of the signatories to this letter (the Society of Family Planning) is the organization that represents Complex Family Planning Fellowship-trained obstetrician-gynecologists, who are the leaders in clinical care, medical education, and research relating to abortion and contraception. Other leading medical authorities—including the American Medical Association, the American College of Obstetricians and Gynecologists, and the American Academy of Family Physicians—likewise support eliminating these restrictions.[3] We hope that, following a comprehensive evaluation incorporating new data and evidence from the past five years, FDA will reach the same conclusion.

The Mifepristone REMS with ETASU Does Not Enhance Safety

As extensively detailed in the letter submitted by the Society of Family Planning on August 11, 2021, peer-reviewed scientific evidence, including research published since the most recent FDA-approved labeling change in 2016, confirms that mifepristone is extremely safe and highly effective whether dispensed at a health center, pharmacy, or by home delivery, and does not require a clinician to oversee dispensing or specially certify their ability to provide appropriate care. The evidence is clear that the mifepristone REMS and its three ETASU confer no benefit in terms of safety, efficacy, or acceptability of the medication, are not "commensurate with" the risks of mifepristone,[4] and create barriers to use that reduce patient access and negatively impact public health, causing particular harm to communities of color, people with fewer resources, and people living in rural areas.

Mifepristone's strong safety and efficacy findings hold true across a range of regulatory contexts, including international and domestic studies operating outside of the ETASU C dispensing framework. For instance, as you are aware,[5] a recent large (N=52,218) retrospective cohort study reported on the safety, efficacy, and acceptability of telemedicine abortion at Britain's

Additionally, ETASU C exacerbates these logistical burdens by enabling interference by individuals opposed to abortion. Instead of being able to simply issue a mifepristone prescription for an eligible patient to fill at a pharmacy, clinicians seeking to prescribe mifepristone must—as a direct result of ETASU C—involve numerous other health care staff in the process of procuring, stocking, dispensing, and billing for mifepristone onsite. As a practical matter, this means that even a single colleague who objects to abortion can substantially delay, or altogether derail, a clinician's ability to prescribe a safe and effective medication that their patients urgently need.

ETASU A also deters many qualified clinicians from becoming mifepristone prescribers. In light of the long history of anti-abortion violence and harassment in this country, some physicians are unwilling to register with the mifepristone sponsors—fearful of what they and their families might face if abortion opponents were ever able to access their certification agreements. While the drug manufacturers and distributors are required to maintain that information strictly confidentially, these clinician fears are not unfounded; indeed, in our litigation, FDA was unwilling to provide Plaintiffs with the names or offices of agency staff who had been involved in any Mifeprex reviews, *even subject to a protective order* requiring strict confidentiality of Plaintiffs and their counsel.[33] Prescriber certification presents a real barrier to patient access, and, as discussed above, there is no evidence showing that this ETASU advances any countervailing safety interest sufficient to outweigh these burdens.

Second, ETASU C forces patients to travel unnecessarily to a mifepristone provider for no medical reason, and in sharp contrast with the expansion of telemedicine nationwide. Across virtually all other areas of medicine, a telemedicine revolution is increasing health care access in medically under-resourced communities and reducing the need for patients to travel long distances for care. But, while medically eligible mifepristone patients already can and do obtain all evaluation and counseling via telemedicine, the REMS prohibits patients from filling their prescription by mail or at a local pharmacy. Instead, FDA requires that mifepristone patients travel to a health center for the sole purpose of picking up the pill and signing a form.

It is important to understand that abortion access is very limited in the United States—in part due to the burdens of ETASU C and A, which reduce the number of clinicians able to provide this essential health care. A nationally representative sample of 8,000 abortion patients found that patients traveled, on average, 68 miles round-trip to receive an abortion.[34] In a majority of states, at least 20% of reproductive-age women live more than 100 miles round-trip from the nearest abortion clinic.[35] And while rural areas are particularly lacking, patients in urban areas also struggle. A 2018 study found that 27 major cities have no publicly advertised abortion provider within 100 miles.[36] Requiring patients to pick up their mifepristone pill in person at a health center thus in many cases requires significant travel.

Given the mifepristone patient population, such travel can be incredibly difficult and in some cases impossible. According to a nationally representative survey, in 2014 (the most recent year for which such data are available), 75 percent of abortion patients had incomes at or below the U.S. Official Poverty Measure.[37] Sixty percent of abortion patients identify as people of color, including 53 percent of patients who identify as Black or Hispanic.[38] And 60 percent of abortion patients have at least one child.[39] Forcing patients to travel in person to pick up the mifepristone tablet at one of the (few) abortion providers in the country imposes costs and burdens relating to

AAFP

Resolution No. 506 (Co-Sponsored C) - Removing Risk Evaluation and Mitigation Strategy (REMS) Categorization on Mifepristone

CONGRESS OF DELEGATES
American Academy of Family Physicians

ACTION TAKEN BY THE 2018 CONGRESS OF DELEGATES: ADOPTED

The Board of Directors referred this resolution to the Commission on Governmental Advocacy. Please address questions regarding the resolution to Robert Hall at rhall@aafp.org (mailto:rhall@aafp.org).

RESOLUTION NO. 506 (Co-Sponsored C)

Removing Risk Evaluation and Mitigation Strategy (REMS) Categorization on Mifepristone

Introduced by the Oregon, New York State, and Washington Chapters

Referred to the Reference Committee on Advocacy

WHEREAS, The U.S. Food and Drug Administration (FDA) uses the Risk Evaluation and Mitigation Strategies (REMS) classification to impose restrictions on only the most dangerous drugs with known or suspected serious complications or contraindications, and

WHEREAS, although the current FDA label for mifepri tone wa modified in 2016 to reflect more evidenced ba ed do ing and ge tational limit , the label till include a REMS cla ification requiring three provi ion to "a ure afe u e," including that

- mifepri tone be di pen ed in a health care etting under upervi ion, and
- from a provider who i regi tered and ha igned a provider agreement with the pharmaceutical di tributor, and
- the patient ign an FDA approved patient agreement form, and

WHEREAS, the American Academy of Family Physicians (AAFP) "supports a woman's access to reproductive health services and opposes non-evidence-based restrictions on medical care and the provision of such services," and

WHEREAS, the REMS re triction on mifepri tone are not ba ed on cientific evidence and cau e ignificant barrier to acce ing abortion care, uch a landlord who e lea e don't allow abortion to be done on ite, manager who won't allow tocking of mifepri tone, colleague who object to provi ion, and

WHEREAS, stocking Mifepristone in the office causes an upfront expense and financial burden which can be difficult for small practitioners to bear, further decreasing access for patients who might prefer to go to their own physician and for rural patients who have no other access points beyond their local physician, and

WHEREAS, there are 16 years of data proving an outstanding safety record of mifepristone, including an 0.05% risk of major complications, and

WHEREAS, other drugs with higher complication rates, such as acetaminophen, aspirin, loratadine, and sildenafil, do not have REMS restrictions, and

WHEREAS, the REMS cla ification contribute to delay in care, thereby increa ing econd trime ter and urgical abortion , both of which have increa ed complication rate , and

WHEREAS, the REMS classification creates a barrier to safe and effective off-label uses of mifepristone, such as for anti-corticoid treatment of Cushing's disease, term labor induction, and miscarriage management, and

WHEREAS, the American College of Obstetricians and Gynecologists (ACOG) "believes that a Risk Evaluation and Mitigation Strategy (REMS) is no longer necessary for mifepristone, given its history of safe use. The REMS requirement is inconsistent with requirements for other drugs with similar or greater risks, especially in light of the significant benefit that mifepristone provides to patients", now, therefore be it

RESOLVED, That the American Academy of Family Physicians engage in efforts to overturn the Risk Evaluation and Mitigation Strategies (REMS) classification on mifepristone.

(Received 5/24/18)

Fiscal Impact: None

Background

Medication abortion, also known as, RU-486 or Mifepristone, is a family planning method that can be used during the first 10 weeks of pregnancy. According to a Kaiser Family Foundation repor (https://www.kff.org/womens-health-policy/fact-sheet/medication-abortion/)t, since the U.S. Food and Drug Administration (FDA) approved the drug in 2000, its use has quickly grown and now almo t one third of all abortion at 8 week ge tation or le are medication abortion In 2000, the FDA approved regimen required three office vi it by the patient one to di pen e mi opro tol, one to di pen e Mifepre , and a follow up vi it to confirm the termination had occurred Thi now outdated practice u ed a higher do e of Mifepre , which wa a ociated with more ide effect However, after exten ive re earch and with the upport of profe ional organization , the agency approved a new evidence ba ed regimen and drug label in 2016 that allow u e for up to 10 week ge tation and permit home admini tration

FDA's REMS

Despite the FDA's updates, the drug's administration remains restricted under the agency's Risk Evaluation and Management Strategy (REMS). Under the FDA's requirements, mifepristone may only be accessed under three conditions: (1) Mifeprex can only be administered in a clinic, hospital, or under the direct supervision of a certified

2021 REMS 001169

Original Paper

Identifying National Availability of Abortion Care and Distance From Major US Cities: Systematic Online Search

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Abstract

Background: Abortion is a common medical procedure, yet its availability has become more limited across the United States over the past decade. Women who do not know where to go for abortion care may use the internet to find abortion facility information, and there appears to be more online searches for abortion in states with more restrictive abortion laws. While previous studies have examined the distances women must travel to reach an abortion provider, to our knowledge no studies have used a systematic online search to document the geographic locations and services of abortion facilities.

Objective: The objective of our study was to describe abortion facilities and services available in the United States from the perspective of a potential patient searching online and to identify US cities where people must travel the farthest to obtain abortion care.

Methods: In early 2017, we conducted a systematic online search for abortion facilities in every state and the largest cities in each state. We recorded facility locations, types of abortion services available, and facility gestational limits. We then summarized the frequencies by region and state. If the online information was incomplete or unclear, we called the facility using a mystery shopper method, which simulates the perspective of patients calling for services. We also calculated distance to the closest abortion facility from all US cities with populations of 50,000 or more.

Results: We identified 780 facilities through our online search, with the fewest in the Midwest and South. Over 30% (236/780, 30.3%) of all facilities advertised the provision of medication abortion services only; this proportion was close to 40% in the Northeast (89/233, 38.2%) and West (104/262, 39.7%). The lowest gestational limit at which services were provided was 12 weeks in Wyoming; the highest was 28 weeks in New Mexico. People in 27 US cities must travel over 100 miles (160 km) to reach an abortion facility; the state with the largest number of such cities is Texas (n=10).

Conclusions: Online searches can provide detailed information about the location of abortion facilities and the types of services they provide. However, these facilities are not evenly distributed geographically, and many large US cities do not have an abortion facility. Long distances can push women to seek abortion in later gestations when care is even more limited.

(J Med Internet Res 2018;20(5):e186) doi: 10.2196/jmir.9717

KEYWORDS

abortion seekers; reproductive health; internet; access to information; information seeking; abortion patients; reproductive health services; information seeking behavior

Introduction

Women's ability to determine if and when they get pregnant and continue that pregnancy is key to their overall well-being. Women who are denied wanted abortions experience some negative outcomes compared with women who were able to obtain abortions, including increased economic insecurity [1] and continued exposure to violence from the man involved in the pregnancy [2]. While abortion rates have declined slightly in recent years, over 926,000 abortions were performed in the United States in 2014 [3]. This rate is equivalent to 1 in 4 women of reproductive age having an abortion within her lifetime [3], which underscores that abortion is common.

The explanations for the decline in abortion rates are varied, but part of this drop can likely be attributed to the decrease in facilities at which women can obtain abortion care across the United States over the past decade. Most abortions (95%) are performed in specialized abortion clinics (rather than private physicians' offices or hospitals), and the number of these clinics declined in half of US states from 2011 to 2014, with some regions experiencing up to a 22% decrease [3]. Because 90% of US counties do not have an abortion provider [3], many women seeking abortion must travel outside their home counties to obtain care. Other geographic disparities have been documented: women living in rural areas, the South and Midwest regions of the United States, and those seeking second-trimester or later abortions are more likely to travel farther for services, often 50 miles (80 km) or more one way [4-7]. These shifts in the availability of abortion-providing facilities indicate that women in underserved areas must travel increasingly far for abortion care.

Somedecline in the number of abortion facilities may be due to the more than 400 state laws regulating abortion that have been adopted between 2011 and 2017 [8], which, among other requirements, mandate that physicians have local hospital admitting privileges, facilities have formal transfer agreements with local hospitals, and facilities become ambulatory surgical centers. These laws have likely led to the closure of facilities that could not meet the financial or administrative requirements imposed by these laws. For example, after these types of laws were passed in Texas in 2013, the number of abortion facilities decreased by 54% over 15 months, requiring women whose nearest clinic had closed to travel 85 miles (137 km) one way to a facility [9]. Additional analyses of trends in abortion rates in Texas from 2012 to 2014 found a relationship between increases in distance to the nearest abortion facility and decreases in the county abortion rate [10]. Another analysis from Louisiana estimated that, if admitting privileges laws were to go into effect, 67% of women of reproductive age would live more than 150 miles (241 km) from the nearest abortion facility, thereby tripling the distance women have to travel to reach the nearest facility for care [11,12]. With distance come increased travel time, increased costs for transportation and childcare, lost wages, the need to take time off of work or school, the need to disclose the abortion to more people than desired, and overall delays in care [13-15]. Ultimately, delays in reaching and obtaining care can push women later into their pregnancies, even up to the point that they might not be able to obtain a wanted abortion, depending on the gestational limits on abortion in their state [16].

To obtain abortion care in their communities, women who do not know where to go may use the internet to find abortion facility information [15]. Almost half (45%) of women seeking abortion services at clinics in Nebraska located the abortion clinic through an online search [17], and a recent study documented an interest in information on self-abortion among people searching online using the search engine Google [18]. Online searching for abortion information appears to be more prevalent in states with restrictive abortion laws and where abortion availability is limited, suggesting that women with reduced access to abortion are more likely to seek out information on abortion online [19,20].

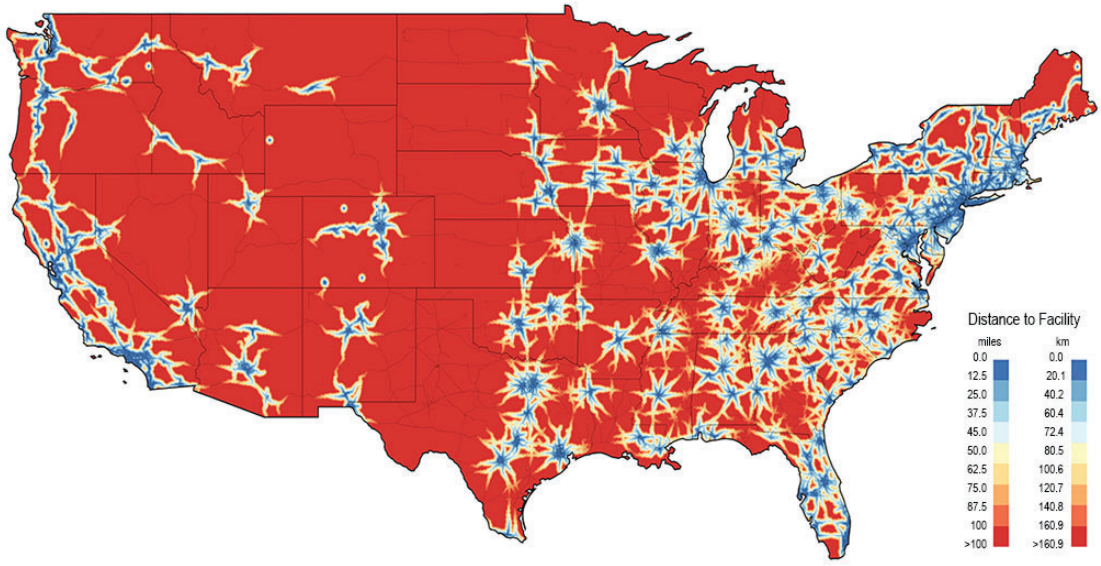
We were interested in examining the question "What does the current landscape of abortion facilities look like to women searching online for abortion services?" There are no publicly available systematically documented and comprehensive lists of US abortion facilities, which makes it difficult to determine how far women must travel to obtain these services. Considering the trends in increased restrictions and decreasing numbers of abortion-providing facilities, it is important to generate accurate estimates of the distances women must travel to obtain abortion services in order to demonstrate potential impacts of closures. This study aimed to address this question by documenting the location of and abortion services available at abortion facilities identified through a systematic online search in all 50 US states (and the District of Columbia) and then calculating travel distances to these facilities from metropolitan areas with populations of 50,000 or more.

Methods

Data Collection

We conducted a systematic online search for abortion facilities using the Google (Google LLC), Bing (Microsoft Corporation), and Yahoo (Oath Inc) search engines between February 22, 2017 and May 22, 2017. Although Google alone accounts for a substantial portion of the market share in the United States (87.5%), together the 3 search engines comprised 99.1% of the total search engine market share as of February 2017 [21]. We conducted a search with the keywords "Abortion clinic in [state]" (no quotes) for all 50 states and the District of Columbia in each of the 3 search engines. In addition, we searched all cities (n=302) with populations over 100,000 based on 2015 US Census population estimates [22] using the keywords "Abortion clinic in [city]" (no quotes). For states that had fewer than 3 cities with populations over 100,000, we used the 3 most populous cities from the same US Census source. We conducted the keyword searches in Google's Chrome browser on Incognito mode and cleared the complete browsing history, including cookies and other site data and cached images and files, prior to each search. The researcher was logged into a Google account created specifically for this study during the searches. We chose keyword searches to reflect the natural language that women would use to search for local abortion services.

Figure 1. Distance to nearest abortion facility in the contiguous United States, May 2017.



Discussion

Principal Results

Using an online search method, we identified almost 800 abortion facilities in the United States, which is consistent with other estimates of abortion clinics and nonspecialized clinics providing abortion [3]. These facilities were not distributed proportionately by state population. Through our analysis, we also found that 27 US cities, largely in the Midwest and the South, could be characterized as abortion deserts, as they did not have a publicly advertised abortion facility within 100 miles (160 km). These findings are consistent with those published by Bearak and colleagues [6], who found that the US counties where women would have to travel the farthest to reach the nearest abortion clinic were concentrated in the middle of the country, as well as several metropolitan areas in Texas. The lack of access to a common reproductive health service such as abortion is a public health concern in that more women in these cities could be forced to carry unwanted pregnancies to term if they are unable to travel long distances to obtain abortion care.

As states continue to pass, implement, and defend restrictions on abortion [8], it is possible that the number of abortion facilities will continue to decrease in those states with the most restrictions. The 6 states that have only 1 abortion facility have combined populations of almost 4 million women of reproductive age who will be forced to travel out of their home state to access abortion care if those facilities close.

For people seeking abortion services in the cities characterized as abortion deserts and in states with few facilities, reaching a facility for care could be incredibly challenging. Access to transportation is a barrier for people seeking all types of health care, in both urban and rural settings [28]. Lower-income women who are unable to access a car or money for gas may have to travel by bus, train, or other forms of transportation, which also becomes more difficult the farther they have to travel. Delays in care due to distance or transportation can push women seeking abortion to later gestations [16,29,30] and are likely to disproportionately affect low-income women, who may struggle to cover the cost of transport [11,14]. Delays to abortion care may be particularly crucial to women in Wyoming, Alaska, Indiana, South Dakota, and South Carolina, where the abortion facilities had the lowest gestational limits. We found that 26.5% of identified facilities performed abortions at 20 weeks or later, which is lower than estimates from 2011-2012 [31], perhaps due to an increased number of state restrictions on abortion after 20 weeks since those estimates were published.

It seems likely that the larger number of facilities in the Northeast and West can be attributed to the fact that 40% to 50% of identified facilities in those regions are offering medication abortion only. The high proportion of facilities offering only medication abortion reflects the opportunities provided by medication abortion: the skills required for clinicians to provide it are minimal (compared with aspiration or surgical abortion) and the large majority of abortions in the United States (80.5%) occur at or before 10 weeks' gestation (the current accepted limit by which medication abortion can be provided) [32]. While the proportion of women choosing this method of abortion now accounts for 31% of nonhospital abortions (compared with 6% in 2001) [3], it is difficult to determine what the true demand would be if both medication and aspiration abortion were equally available. However, in states such as California, where fewer barriers to access exist for both types of abortion, medication abortion is now up to 46% of abortions in some populations, such as Medicaid recipients [33]. Additionally, states in the Northeast and West are less likely to have laws that limit the provision of medication abortion to physicians [34] and more likely to have policies that allow nurse practitioners, certified nurse midwives, and physicians assistants to offer medication abortion as part of their scope of practice.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

(b)(6)/PPI

(b)(6)/PPI

(b)(6)/PPI **Memorandum**

Date:	December 16, 2021
Reviewer:	(b)(6)/PPI (b)(6)/PPI
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Product Name:	Mifepristone 200 mg
Subject:	All Adverse Events
Application Type/Number:	NDA 020687; ANDA 091178
Applicant/Sponsor:	Danco Laboratories, LLC; GenBioPro, Inc.
(b)(6)/PPI **#:**	2007-525

2.3 LITERATURE SEARCH

(b)(6)/PPI searched the medical literature with the strategy described in **Table 2**.

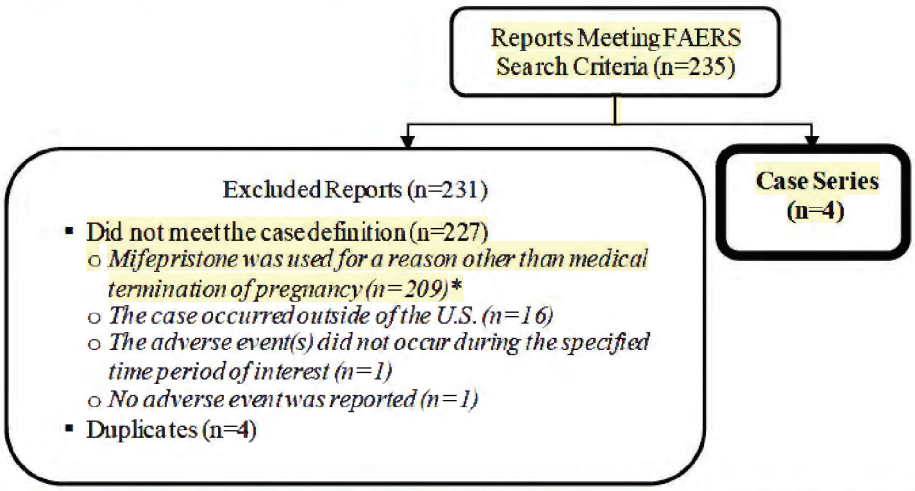
Table 2. Literature Search Strategy	
Date of search	October 16, 2021
Database	Embase and PubMed
Search terms	Embase: ('mifepristone'/exp OR mifepristone) AND (2021:py) AND 'case report'/de PubMed: (("mifepristone"[MeSH Terms] OR "mifepristone"[All Fields] OR "mifepriston"[All Fields]) AND ("case reports"[Publication Type] OR "case report"[All Fields])) AND (2021[pdat])
Years included in search	2021

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved 235 reports. After applying the case definition in **Section 2.1** and accounting for duplicate reports, four cases were identified in which an adverse event reportedly occurred from January 13, 2021 - September 30, 2021 with mifepristone use for medical termination of pregnancy in the U.S. (see **Figure 1**).

Figure 1. FAERS Case Selection



* 207 reports documented the use of mifepristone for Cushing's syndrome (or related conditions) or specified the use of Korlym®, 1 report documented the use of mifepristone for breast cancer, and 1 report documented the use of mifepristone for expulsion of an incomplete abortion.

We summarized the pertinent information from all four cases, grouped by the specified time periods of interest, below. **Appendix B** contains a line listing of these four cases.

Center for Drug Evaluation and Research (CDER)

(b) (6)

Application Type	NDA and ANDA
Application Number	020687 and 91178
Reviewer Names	(b) (6)
(b) (6)	(b) (6)
(b) (6)	(b) (6)
(b) (6)	(b) (6)
(b) (6)	(b) (6)
(b) (6)	(b) (6)
(b) (6)	(b) (6)
(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 (b) (6) 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).

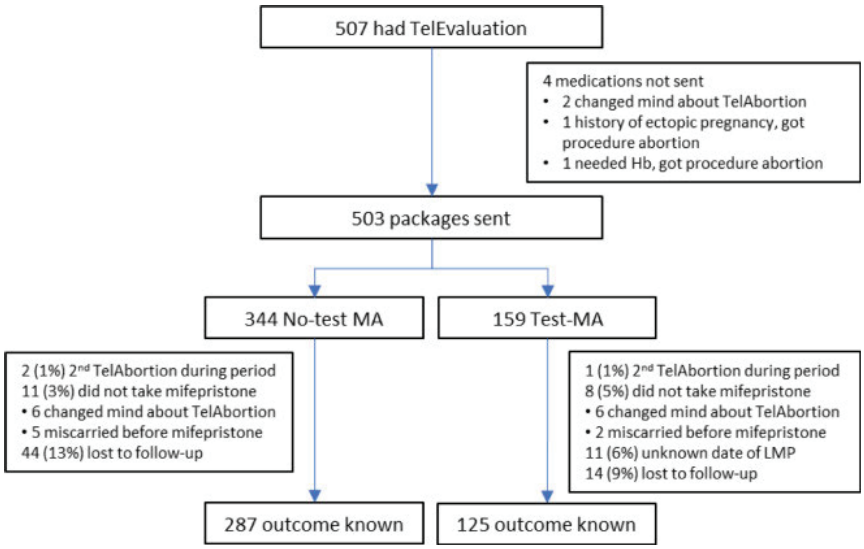
Raymond [16] (2019) reported outcomes from the Gynuity study prior to the pandemic. In the TelAbortion study, participants were not required to have an in-person clinic visit; rather, they obtained screening tests at laboratories and radiology offices and then communicated with the abortion provider 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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7. Appendix A

References Cited in Letters from Plaintiffs

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	
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

	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
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Grossman D et al. Obstet Gynecol 2021; 137 (4): 613-622.	
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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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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF HAWAI'I

GRAHAM T. CHELIUS, M.D., *et al.*,

Plaintiffs,

vs.

XAVIER BECERRA, J.D., *in his official capacity as* SECRETARY, U.S. D.H.H.S., *et al.*,

Defendants.

CIV. NO. 1:17-cv-00493-JAO-RT

[CIVIL RIGHTS ACTION]

DECLARATION OF GRAHAM T. CHELIUS, M.D., IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

Judge: Hon. Jill A. Otake
Hearing Date: Vacated per Dkt. 107
Trial Date: Vacated per Dkt. 82

to treat patients. I cannot afford these personal and professional risks.

28. To be clear, many of my colleagues and staff already know that I provide abortion referrals. I know that some staff oppose even this; some have directly expressed such views to me. But if I were to comply with the Mifeprex REMS, I would be doing more than just supporting access to abortion in my *individual* professional capacity—I would also have to involve, and win the approval of, multiple colleagues and staff members in the process of procuring, stocking, dispensing, and billing for Mifeprex within our health care facility. Asking or demanding that my colleagues who have deeply held views against abortion participate or assist in providing abortions would cause significant conflict among my staff—conflict that, as Chief of Staff, I would also be required to manage, if possible. The negative consequences for my professional standing and for carefully nurtured workplace dynamics, which benefit all of our patients, deter me from attempting to comply with the Mifeprex REMS.

29. Relatedly, I also have had serious personal safety concerns about the requirement in the REMS that I register with the drug manufacturer and drug distribution company as an abortion provider. I understand that they must keep confidential the list of clinicians registered to prescribe Mifeprex. But particularly in light of the many recent health care hacking incidents, I have been concerned about being inadvertently or maliciously exposed as an abortion provider, and the

resulting likelihood of public backlash to me and my family.

30. Of course, my name is now public in the context of this litigation, and my experience since filing this lawsuit has validated my earlier concerns. Since the lawsuit was filed, I have received numerous phone calls and letters from strangers relating to this litigation. Many of those communications were positive and supportive. But a few were negative and concerning. Based on security consultations, I now carefully examine envelopes for toxic material, and have tried to remember to only open packages that I have been expecting. We also installed a security system at our house. In a country where abortion clinic shootings are commonplace and abortion providers have been assassinated, I have feared risking my and my family's safety by following through with what the Mifeprex REMS requires.

31. I ultimately made the difficult choice to publicize my desire to provide abortion care through this lawsuit, because I believe this case has the potential to expand access to medication abortion for patients all across the country. My family and I felt that this goal was worth the risk to our safety and privacy. But we did not make that choice lightly, and I expect that I am not the only physician who has found the REMS requirement that I add my name to a list of all medication abortion providers in the country a serious deterrent to providing this care.

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Defendants.

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[CIVIL RIGHTS ACTION]

DECLARATION OF JOEY BANKS, M.D., IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

Judge: Hon. Jill A. Otake
Hearing Date: Vacated per Dkt. 107
Trial Date: Vacated per Dkt. 82

years, I have taught residents to treat patients seeking medication abortion with a regimen of 200mg of mifepristone followed by 800mg of misoprostol; and, since 2018, based on new, high-quality medical research, I also began teaching them this two-drug regimen for the medical management of miscarriages. Although both can be accomplished with misoprostol alone, evidence supports the two-drug regimen as the superior regimen.

11. On numerous occasions, I have been contacted by physicians I previously trained, telling me that the health care facility where they work does not stock mifepristone, and that they felt uncomfortable asking leadership at their health care facility to begin stocking mifepristone, or that they knew their clinic simply would not stock mifepristone. They all wanted to know whether they could still care for patients who sought a medication abortion or suffered a miscarriage, even without mifepristone. In light of these conversations, I now explain to the residents I train that if their health care facility does not stock mifepristone, they can consider prescribing misoprostol alone for either early abortion or miscarriage treatment, but that it is less effective and that the two-drug regimen, including mifepristone, is the superior regimen

12. In my experience, the mifepristone REMS is interfering with practitioners' provision of evidence-based medicine. Some clinicians fear professional repercussions if they try to persuade their colleagues to stock and dispense mifepristone onsite. And some are so concerned about the stigma and threat of violence surrounding the provision of abortion that they are unwilling to register their names and addresses with the mifepristone distributer, as required by the REMS. The prospect of this "abortion provider list" being leaked to the public is enough to prevent clinicians from providing what they deem the best medicine for their patients.

13. In sum, the mifepristone REMS prevents clinicians from providing solid evidence-based medicine due to the stigma and fear associated with having to register with the

drug manufacturer and stock the medication onsite.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct. Executed on April 12, 2021.

Joey Banks, M.D.

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XAVIER BECERRA, J.D., *in his official capacity as* SECRETARY, U.S. D.H.H.S., *et al.*,

Defendants.

CIV. NO. 1:17-cv-00493-JAO-RT

[CIVIL RIGHTS ACTION]
DECLARATION OF CHARISSE M. LODER, M.D., M.SC., IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

Judge: Hon. Jill A. Otake
Hearing Date: Vacated per Dkt. 107
Trial Date: Vacated per Dkt. 82

20. These organizational concerns related to prescriber certification stem not from any mistrust of physicians, but from concerns about compliance with the REMS.

21. I would never have been able to provide mifepristone to my patients if it were not for the tenacious advocacy and time commitment my colleagues and I invested into this effort. As it was, for more than five years, the REMS prevented me and all of my colleagues from providing that care to our patients and necessitated that we refer patients outside of the University of Michigan system. I know that many of my colleagues have had the same experience, because over the years, I have frequently been contacted by colleagues inquiring whether they were permitted to prescribe Mifeprex to their patients, and I had to tell them that—because of the REMS—the answer was no.

22. And my situation at the University of Michigan is by no means unique. I am regularly contacted by clinicians at other academic medical centers who are seeking advice on how to navigate the REMS in order to stock and dispense Mifeprex at their institutions.

23. Clinicians outside the University of Michigan have also shared with me that they have not integrated Mifeprex into their practice because they fear that completing the REMS prescriber certification requirement would place them on a registry of abortion providers and thus make them targets of anti-abortion

harassment or violence. If clinicians could simply write a prescription for Mifeprex without this obstacle and the other obstacles the REMS imposes, I believe that many more clinicians, in a wider swath of our state, would do so.

24. While abortion care is extremely safe, the risks associated with abortion increase as pregnancy advances. Therefore, delaying a patient's abortion care increases the risks she faces.

25. This delay also pushes patients past the point at which a medication abortion, or any abortion care, is available to them at all. When I worked at Planned Parenthood, I often saw patients who had been referred there by their primary provider because their provider does not provide medication abortion care. But, because of the delay caused by this referral, by the time these patients got to Planned Parenthood, they were frequently too far along in their pregnancies to be eligible for a medication abortion—even though they preferred that option and that option would have been most clinically suitable for them. Because of this delay, these patients were only eligible for aspiration or dilation and evacuation ("D&E") abortion, in-clinic procedures that are significantly more expensive than medication abortion. And some of these patients could not afford these more expensive in-clinic procedures and ultimately were unable to get an abortion at all.

26. My patients at Planned Parenthood frequently told me about the burdens they faced traveling to us for care: paying for transportation, arranging

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

October 6, 2021

Janet Woodcock, MD
Acting Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Re: U.S. Food and Drug Administration's review of the risk evaluation and mitigation strategy for mifepristone

Dear Acting Commissioner Woodcock:

On behalf of the American College of Obstetricians and Gynecologists (ACOG), representing more than 60,000 physicians and partners dedicated to advancing women's health, we write to express our strong support for the review of the risk evaluation and mitigation strategy (REMS) for mifepristone currently underway at the U.S. Food and Drug Administration (FDA). ACOG supports efforts to improve access to quality women's health care and, given the decades of research and data reinforcing the safety of this medication, urges the FDA to remove the REMS and Elements to Assure Safe Use (ETASU) requirements for mifepristone.

Mifepristone has been used by over 3 million women in the United States since FDA approval in 2000 and robust evidence exists regarding the safety of mifepristone for medication-induced abortion.[1,2,3,4*] The REMS and ETASU requirements for mifepristone are inconsistent with those for other medications with similar safety profiles, and create barriers to access without demonstrated improvements to patient safety or outcomes. These medically unnecessary requirements restricting access to mifepristone interfere with the ability of obstetrician–gynecologists and other health care professionals to deliver the highest quality care for their patients. In addition to being supported by researchers, clinicians, and more than twenty years of data, removing the REMS and ETASU requirements for mifepristone is consistent with FDA's mission to ensure the safety and efficacy of medications and help "…the public get the accurate and science-based information they need to use medical products…"[5]

ACOG is the premier professional membership organization for obstetrician-gynecologists and produces practice guidelines for women's health clinicians based on the best available science and evidence. As referenced in ACOG Practice Bulletin 225, *Medication Abortion Up to 70 Days of Gestation*, medication abortion is a safe and effective method of providing abortion. The REMS restrictions for mifepristone do not make care safer, are not based on medical evidence or need, and create barriers to patient access to medication abortion.[6, 7, 8] Abortion is an essential component of comprehensive health care and is a time-sensitive service for which a delay of several weeks, or in some cases days, may increase the risks or

[*] Recent evidence also supports the use of mifepristone to improve the safe and effective medical management of early pregnancy loss.
See Schreiber CA, Creinin MD, Atrio J, Sonalkar S, Ratcliffe SJ, Barnhart KT. Mifepristone pretreatment for the medical management of early pregnancy loss. N Engl J Med 2018;378:2161-70. Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa1715726. Retrieved July 9, 2018; and
Westhoff CL. A Better medical regimen for the management of miscarriage. N Engl J Med 2018;378:2232-3. Available at: https://www.nejm.org/doi/full/10.1056/NEJMe1803491. Retrieved July 9, 2018.

potentially make it completely inaccessible.[9] Furthermore, research conducted during the COVID-19 pandemic, when enforcement of the in-person dispensing requirement for mifepristone was suspended, demonstrates the safety of providing abortion through telehealth contact and mailed medications.[10,11] Additionally, recent data suggests that patients offered telemedicine with mailed medications had abortions earlier than those without this option.[12] Removing the REMS and ETASU on mifepristone will improve access to medication-induced abortion and enhance patient care.

ACOG is pleased that the FDA is conducting a thorough review of the REMS restrictions for mifepristone and urges the FDA to remove the medically unnecessary REMS and ETASU restrictions that hinder access to medication abortion. Thank you for your attention to this critical issue. We are available to answer any questions.

Sincerely,

Maureen G. Phipps, MD, MPH, FACOG
Chief Executive Officer
American College of Obstetricians and Gynecologists

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[1] Improving Access to Mifepristone for Reproductive Health Indications. Position Statement. American College of Obstetricians and Gynecologists. June 2018. Available at https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications.
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[11] Kerestes C, Murayama S, Tyson J, Natavio M, Seamon E, Raidoo S, et al. Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models. Contraception 2021.
[12] Aiken A, Lohr P, Lord J, Ghosh N, Starling J. Effectiveness, safety and acceptability of no-test medical abortion provided via telemedicine. British J Obstet Gynecol 2021.