

Jacobs Institute of Women's Health

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MEDICATION ABORTION

Overview of Research & Policy in the United States

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INTRODUCTION

September 2015 marked the 15th anniversary of the US Food & Drug Administration (FDA) approval of the drug Mifeprex© (generic: mifepristone) for use in medication abortions. Mifeprex approval came with requirements that affect both patients and providers and that are far more specific than typical requirements for prescription drugs. The package insert (also known as the product label) indicates procedures for mifepristone prescribers to follow, based on the regimen used during the drug's pre-approval clinical trials. FDA has not approved any other abortion drugs besides Mifeprex.

In the last 15 years, researchers have studied the safety and efficacy of Mifeprex, as well as the medication abortion process as a whole. Their findings reveal that the protocol set out in the Mifeprex label does not reflect current practice for safe and effective medication abortion and is in need of revision.

Medication abortion (also called medical abortion) is a safe method of abortion available for the past 15 years in the US. This paper summarizes the scientific evidence related to the current medication abortion process and potential changes to the process that could make it even safer and more accessible for patients, as well as policy considerations and directions for future research.

OVERVIEW OF MEDICATION ABORTION

Medication abortion is an alternative to vacuum aspiration, which also called surgical abortion, the most common procedure for early termination of pregnancy (Weitz et al., 2004). It is sometimes called medical abortion, or referred to as RU-486, mifepristone's early chemical designation. In 2011, nearly 240,000 medication abortions were performed in the US, out of 1.06 million total abortions (Jones & Jerman, 2014). Since Mifeprex was approved in 2000, medication abortion has accounted for a growing share of US abortions, increasing from 14% of non-hospital procedures in 2005 to 23% in 2011. Ninety percent of clinics that provide abortions offered medication abortions in 2011, and 17% of all non-hospital abortion providers offered only medication abortions (Jones & Jerman, 2014). The cost of medication abortion is generally similar to the cost for a surgical abortion, at comparable gestations; in 2011 and 2012, the median charge at similar gestations was \$500 for a medication abortion and \$495 for a surgical abortion (Jerman & Jones, 2014).

MECHANISM OF ACTION

In the US, the process of medication abortion generally involves taking two medications: Mifeprex, which halts the pregnancy by initiating the breakdown of the endometrium, followed by misoprostol, which leads to contractions and emptying of the uterus.

Mifepristone is a **progesterone receptor antagonist**. **Progesterone** is an endogenous steroid hormone that is necessary for the menstrual cycle and supports the endometrium during pregnancy. Steroid hormones affect cells by binding to specific **receptors** on the cell surface. A steroid **antagonist** is a substance that competitively binds to the receptor, thereby inhibiting the physiological action of the steroid.

Mifepristone competes with progesterone at progesterone-receptor sites and inhibits the activity of endogenous or exogenous progesterone, initiating the breakdown of the endometrium and implanted embryo. This activity is the first step in the abortion (FDA, 2005).

During the abortion process, mifepristone sensitizes the lining of the uterus to the contraction-inducing activity of **prostaglandins**. Prostaglandins and prostaglandin analogs stimulate uterine contractions and cause cervical dilation, both leading to emptying of the uterus. During medication abortion, the drug misoprostol is the **prostaglandin analog** that serves this function.

Box 1. Key Scientific Terms for Medication Abortion

Agonist: a molecule that combines with a receptor on a cell to trigger a reaction

Antagonist: a biological structure or chemical agent that interferes with the physiological action of another agent

Ectopic pregnancy: a gestation elsewhere than in the uterus; often occurring in the fallopian tube; presents with abdominal pain, fainting, and/or vaginal bleeding.

Endogenous: developed or originating within the body or arising from causes within the body

Exogenous: developed or originating outside the body

Receptor: a molecular structure within a cell or on the surface characterized by selective binding of a specific substance and a specific physiologic effect that accompanies the binding

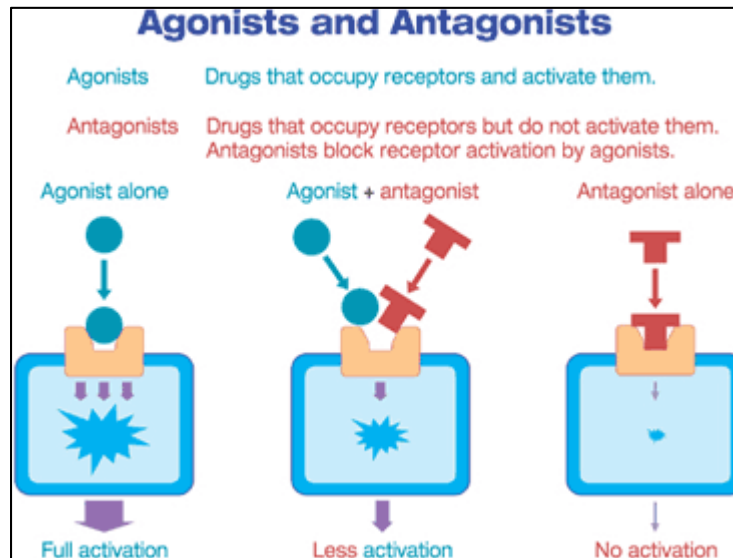
Progesterone: a steroid hormone produced in the ovary; prepares and maintains the uterus for pregnancy

Prostaglandin: mediator of physiological processes, including speeding evacuation of the uterus by stimulating contractions

Teratogenic: tending to produce anomalies of formation, the development of malformations, or serious deviations from the normal type of organism

Adapted from biology-online.org

Figure 1. How Agonists and Antagonists Work



Source: Antranik.org, 2012

SAFETY AND EFFICACY

Medication abortion is a safe and effective process. The CDC began collecting data on mortality from medication abortion in 1997 and noted no deaths among over 6,000 women using mifepristone during clinical trials (Beal, 2007). Although mifepristone's safety record has remained strong overall, in the first years after its approval, several women who had undergone medication abortion in the US died as a result of infection (see "GAO Review of FDA Approval Process for Mifeprex" section on page 8 for further discussion). When these deaths are included in the total abortion surveillance data, they bring the mortality rate to approximately 1 per 100,000, which is slightly higher than the mortality rate for surgical abortion but significantly lower than the maternal mortality rate for women bringing their pregnancies to term (9.8 per 100,000) (Beal, 2007).

Studies of medication abortion find that between 95% and 98% of cases result in complete termination. These outcomes may vary slightly depending on the exact regimen used (e.g., dosage of Mifeprex, timing of misoprostol) but are similar to success rates for surgical abortion (Bartz & Goldberg, 2009). The American College of Obstetricians and Gynecologists (ACOG) reports the success rate of medication abortion as 95%, compared to 99% for surgical abortion (Committee on Practice Bulletins – Gynecology and the Society of Family Planning, 2014).

After taking both mifepristone and misoprostol, women can expect heavy bleeding and cramping. These are both normal reactions to the medications, although women may seek medical attention if they are severe. Additional medical interventions can include antibiotics for infection and aspiration or curettage for bleeding or for ongoing pregnancies if necessary.

A study of abortion-related insurance claims from California's Medicaid program found that 5.2% of more than 11,000 women who received medication abortions sought care in an emergency department, and the vast majority of their conditions were minor and expected. The authors

report that only 0.31% of the women who received medication abortions experienced serious unexpected adverse events, such as hemorrhage, that required hospital admission, surgery, or blood transfusion, and fewer than one percent (0.87%) had incomplete abortions (Upadhyay et al., 2015). A separate study of more than 200,000 medication abortions provided between 2009 and 2010 at Planned Parenthood health centers found significant adverse events in 0.16% of cases, including one death from an undiagnosed ectopic pregnancy, and ongoing intrauterine pregnancies in 0.50% of cases. The authors noted that the count of ongoing pregnancies does not include cases in which an ongoing pregnancy was detected in a follow-up evaluation and successfully treated with a repeat dose of misoprostol (Cleland et al., 2013).

There are very few specific medical contraindications to medication abortion, which means that medication abortion can be an appropriate option for most women. Contraindications include: previous allergic reaction to one of the drugs used, chronic adrenal failure, severe anemia, having an IUD in place, and known/suspected ectopic pregnancy (Bartz & Goldberg, 2009; Committee on Practice Bulletins – Gynecology and the Society of Family Planning, 2014).

Box 2. Other Medication Abortion Drugs

While the mifepristone-misoprostol combination is widely used in the US, other medications may be used for medication abortions in other countries, or in rare circumstances, in the US. In several countries, methotrexate is often the first step in the medication abortion process. Although methotrexate is very effective (up to 97% of women successfully abort if methotrexate is followed by misoprostol), it also has significant drawbacks. Because methotrexate is teratogenic, surgical follow-up must be performed if there is an incomplete abortion procedure. Women may also have to wait up to four weeks to determine if their abortions are complete, by which point, surgical intervention may become more intensive and difficult for both patients and providers (Bartz & Goldberg, 2009). In China, ethacridine lactate (via intra-amniotic injection) is the first step in the medication abortion process and is followed by misoprostol; however, a recent study found that the mifepristone-misoprostol regimen is preferable because of fewer side effects and a higher success rate (Hou et al., 2011).

In addition to misoprostol, several other prostaglandin analogs can be used for the second step in the process. The most commonly studied include cervagem, gemeprost, carboprost, and sulprostone (Lalithkumar, Bygdeman, & Gemzell-Danielsson, 2007). A Danish study comparing gemeprost and misoprostol found both to be equally effective, with a 99% complete abortion rate (Lipp, 2008). Another study comparing cervagem – which was widely used in the UK before misoprostol became available – with misoprostol found no significant differences in the efficacy of the two drugs (Dodd & Crowther, 2006). See “Misoprostol-Only Abortions” (page 25) for further discussion.

FDA DRUG APPROVAL PROCESS

In general, it takes approximately eight to nine years to bring a drug to market, from the first experimental animal tests to the final approved product. The drug manufacturer writes (and owns) the product label, but FDA must approve the exact language used on the label; this process often involves negotiation between the manufacturer and FDA. Once approved by FDA, the label governs the information that can be distributed by the sponsor, including materials distributed by industry and sales representatives.

Once a drug has been developed and tested in clinical trials, the drug manufacturer must submit the drug for approval by FDA. In general, the process for approval of a new drug is as follows:

“Before a drug can be marketed in the United States, the drug sponsor must submit a new drug application (NDA) to FDA containing data demonstrating the safety and efficacy of the drug. FDA reviews the NDA to determine whether the drug’s benefits outweigh its risks. Once FDA completes its review, the agency issues an action letter¹ in which it either approves the drug as safe and effective for its intended use (approval letter), informs the sponsor that the drug is likely to be approved once the deficiencies FDA has identified are resolved (approvable letter), or indicates that approval cannot be obtained without substantial additional information (not approvable letter). If FDA issues an approvable or not approvable letter, a subsequent review cycle can begin once the sponsor has addressed the issues FDA identified.” (GAO, 2008)

All information distributed by drug manufacturers must be “on-label” – consistent with the drug label. However, providers may prescribe a drug “off-label” after it is approved for use in the US. Off-label prescribing is a common phenomenon across many types of care, and different protocols or uses often arise after a drug is approved for a specific condition. For example, albuterol is a rescue medicine prescribed for asthma but is often prescribed off-label for chronic obstructive pulmonary disease (COPD) (Radley, Finkelstein, & Stafford, 2006). In the US, between 10% and 21% of prescriptions are given off-label (Fitzgerald & O’Malley, 2014; Radley, Finkelstein, & Stafford, 2006).

FDA APPROVAL OF MIFEPREX

Mifepristone was first approved for use in France in 1988 (Jones & Henshaw, 2002). In the US, Danco Laboratories, LLC first submitted Mifeprex for FDA approval in 1996, after a long delay and opposition by anti-abortion advocates and policy-makers. The approval process took approximately four years, from the submission of the initial new drug application (NDA) in 1996 through three review cycles and ultimate approval (see Table 1) (GAO, 2008). Bringing this

¹ FDA no longer uses the format of the approval/approvable/not approvable letter. Instead, applicants receive a complete response letter, the process for which is outlined here: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.110>.

product to the US required a collaborative effort between researchers, industry, and pro-choice advocates.

Table 1: Timeline of Key Events in FDA's Approval of Mifeprex

Date	Event
First Review Cycle	
March 1996	The sponsor submitted a new drug application (NDA) for the use of Mifeprex in combination with the drug misoprostol for the medical termination of intrauterine pregnancy.
July 1996	FDA Reproductive Health Drugs Advisory Committee meeting.
September 1996	FDA issued an approvable letter listing issues that the sponsor needed to address before the application could be approved.
Second Review Cycle	
August 1999	After delays securing a manufacturer, the sponsor completed its responses to FDA's 1996 approvable letter.
February 2000	FDA issued a second approvable letter, listing issues that the sponsor needed to address prior to approval.
Third Review Cycle	
March 2000	The sponsor completed its responses to FDA's second approvable letter.
September 2000	FDA approved Mifeprex under the restricted distribution provision of Subpart H.
November 2000	Distribution of Mifeprex began in the United States.

Source: GAO, 2008

During the third and final review cycle for Mifeprex, FDA determined that the drug's approval process met the criteria for the process known as Subpart H, from Title 21, Part 314, Subpart H of the Code of Federal Regulations, "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (CFR - Code of Federal Regulations Title 21, 2015). Subpart H regulations for approval generally apply if a drug meets one of the following two criteria: (1) "approval with restrictions to assure safe use" or (2) "approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity" (CFR - Code of Federal

Regulations Title 21, 2015). FDA has applied the second provision mostly for cancer or HIV/AIDS drugs (GAO, 2008). In the case of Mifeprex, the first condition applied because FDA concluded that the drug could only be used safely if distribution was limited to qualified clinicians. In a review of the mifepristone approval process, the Government Accountability Office (GAO) noted that this determination is generally consistent with the approval process for other Subpart H drugs and that FDA's postmarket oversight of Mifeprex has also been consistent with oversight of other Subpart H drugs (GAO, 2008). It is important to note that Mifeprex did not undergo an expedited review process, which occurs for drugs meeting the second criterion for Subpart H.

As part of the approval conditions established in 1996, physicians who intend to offer medication abortion must sign a prescriber's agreement and must meet certain criteria, including the ability to perform surgical interventions (i.e., vacuum aspiration, also known as dilation and evacuation, or D&E) to manage complications (GAO, 2008). Patients must also sign a patient agreement before providers can give patients the medication. Both agreements are included in the appendix.

FDA no longer uses the Subpart H process. Instead, for drugs that formerly met the criteria for the Subpart H designation, FDA uses the Risk Evaluation and Mitigation Strategy (REMS) and Elements to Assure Safe Use (ETASU); further details about these mechanisms are included in "Advocacy for Label Change" on page 31.

GAO REVIEW OF FDA APPROVAL PROCESS FOR MIFEPREX

In the six years following FDA's approval of Mifeprex four women contracted fatal infections caused by a bacterium called *Clostridium sordelli* after medication abortions. (A fifth woman died of infection from a different but related bacteria, *Clostridium perfringens*, during the same time period, and an additional fatality from *C. sordelli* occurred in 2007.) Congress tasked the GAO with reviewing the approval and oversight of the drug, with particular regard to the infection deaths. The GAO report concluded that the approval process had been consistent with the general FDA approval process for similar drugs and noted that FDA itself had concluded that evidence does not indicate that Mifeprex caused the fatal infections (GAO, 2008). However, GAO did note that:

"... in the six cases of death due to infection, the women used a regimen of Mifeprex and misoprostol that has not been approved by FDA. FDA has stated that it is aware that many health care providers use modified regimens, and while some of the regimens have been described in the medical literature, FDA has not evaluated the safety and effectiveness of any other regimen than the one described in the drug's approved labeling." (GAO, 2008)

Other research studies support these findings about the clostridium deaths.

The women who died were diagnosed with toxic shock syndrome (TSS). The infection itself is not always fatal, except in cases that progress to TSS (Beal, 2007). Incidence of *C. sordelli* infection is very rare, at a rate of 1 infection per 100,000 people. Up through 2001, 10 cases of TSS from genital tract infections (unrelated to abortion) were reported in the literature, as were 28 cases of obstetric and gynecologic infections with *C. sordelli* in healthy women either postpartum, after miscarriage, or following induced abortion (Beal, 2007). Tests of the Mifeprex lots used in the fatal cases revealed no clostridium contamination. All six women who contracted fatal infections

after having a medication abortion had received the then-current regimen of 800 µg vaginal misoprostol, self-administered (Beal, 2007). The Mifeprex label now includes a boxed warning stating, “Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortion, including following Mifeprex use” (FDA, 2005).

Some researchers concluded that the administration route (vaginal) was potentially the source of the infections, despite the fact that there is little definitive evidence to support this position. However, Planned Parenthood health centers changed their practice guidelines for route of administration from vaginal to buccal and added universal antibiotic prophylaxis, and the death rate subsequently declined significantly, dropping from 1.37 per 100,000 to 0 per 100,000 (Trussell et al., 2014). There have been no reported clostridium-related deaths at Planned Parenthood in women undergoing medication abortion since the protocol change (Trussell et al., 2014), although a 2011 FDA Postmarketing Adverse Events Summary reports two sepsis deaths in addition to the original six, with one of the new cases involving vaginal misoprostol and the other buccal misoprostol (FDA, 2011). It is not possible to determine whether the death rate improved because of the change in route of administration or the administration of prophylactic antibiotics, or due to some other factor such as a change in the bacteria present in the environment.

MEDICATION ABORTION PROCESS: STATE OF THE EVIDENCE

“It is highly unusual for the FDA to include such a restrictive regimen on a drug label. No other drug with a comparable safety profile carries a remotely similar label. Numerous drugs sold over the counter in the United States—such as acetaminophen, anti-histamines, and nonsteroidal anti-inflammatories—result in considerably more adverse events, including death, than mifepristone.” (Coeytaux, Hessini, & Allina, 2015)

FDA-APPROVED LABEL

The FDA-approved Mifeprex label specifies that patients must have intrauterine pregnancies of up to 49 days gestation, and that providers may determine pregnancy duration from menstrual history and clinical exam, with an ultrasonographic scan used if gestational duration is uncertain or ectopic pregnancy suspected (FDA, 2005). Mifeprex is supplied only to licensed physicians who sign and return a Prescriber’s Agreement, and patients must sign a Patient Agreement (see Appendices A and B).

The label specifies that treatment requires three office visits and that “Mifeprex may be administered only in a clinic, medical office, or hospital, by or under the supervision of a physician.” On the first visit, the patient signs the patient agreement and receives a 600 mg oral dose of Mifeprex. On the second visit two days later, she takes 400 µg of misoprostol orally. On the third visit approximately 14 days after the first one, she returns for a follow-up visit at which complete termination of the pregnancy is confirmed by clinical examination or ultrasonographic scan (FDA, 2005). In states that require a waiting period between a first visit and the initiation of medication abortion, following the FDA label’s protocol requires four visits.

Table 2: FDA Label Specifications and Off-Label Variations

	On-Label Regimen	Evidence-Based Variations
Provider	Physicians and providers under physician supervision	Physicians and mid-level providers* with or without supervision**; physicians via telemedicine
Timing	Up to 49 days from LMP (last menstrual period)	Up to 63 days from LMP in wide use; evidence supports up to 70 days
Use of Mifepristone	Day 1: 600 mg orally at clinical site	200 mg orally, may be taken at home
Use of Misoprostol	Day 3: 400 µg orally at clinical site	Typically taken at home; interval between mifepristone and misoprostol varies; 800 µg dose is common, and is generally administered buccally, sublingually, or vaginally
Follow-Up	Day 14: Confirm complete abortion	Follow up after 7-14 days; some providers offer lab follow-up or remote follow-up alternatives; self-assessment offered in some countries

* Mid-level providers include nurse practitioners (NPs), certified nurse-midwives (CNMs), and physician assistants (PAs); new WHO recommendations include nurses as well.

** As permitted by state laws, and under the Provider Agreement

EVIDENCE-BASED PROTOCOLS FOR MEDICATION ABORTION

US providers began adopting evidence-based regimens that varied from the FDA label soon after the agency approved Mifeprex. These variations – technically considered “off-label” – do not adhere to all the specifications of the FDA label but are supported by substantial evidence. (Describing these variations as “evidence-based” is not meant to suggest that the FDA label is not based on evidence; rather, it serves to distinguish between the FDA-approved regimen and the off-label regimens, which do not currently have FDA approval but do have a substantial evidence base from trials conducted after Mifeprex’s approval.)

DOSAGE

The use of 200 mg of mifepristone, rather than the 600 mg specified in the FDA label, is recommended by the World Health Organization, the American College of Obstetricians and Gynecologists (ACOG), the Society of Family Planning, and the Planned Parenthood Federation of America (Cleland & Smith, 2015). A 2014 ACOG practice bulletin notes that regimens using 200 mg of mifepristone “have similar efficacy and lower costs” than those involving 600 mg. It

also states, “Based on efficacy and the adverse effect profile, evidence-based protocols for medical abortion are superior to the FDA-approved regimen” (Committee on Practice Bulletins—Gynecology and the Society of Family Planning, 2014). The use of 800 µg of misoprostol, rather than the 400 µg in the FDA label, is also common (Committee on Practice Bulletins—Gynecology and the Society of Family Planning, 2014).

TIME INTERVALS BETWEEN MEDICATIONS

Shortening the interval between administration of mifepristone and misoprostol improves flexibility for patients and clinicians and reduces the duration of medication abortions, and many studies have demonstrated the safety and efficacy of intervals shorter than the 48 hours specified on the FDA label (Shaw et al., 2013; Wedisinghe & Elsandabesee, 2010). In 2006, a systematic review of the literature concluded that the interval could be reduced from 48 hours to 24 hours without a loss of efficacy (Schaff, 2006). A 2010 systematic review and meta-analysis of studies with intervals from 0 – 72 hours concluded that differences in overall efficacy were not statistically significant between longer and shorter intervals, but that there was a trend toward a lower success rate when dosing intervals were less than 8 hours (Wedisinghe & Elsandabesee, 2010).

Box 3. Routes of Drug Administration in Medication Abortion

Buccal: held between the gum and cheek to dissolve; remainder swallowed after 30 minutes

Oral: swallowed; common with many pills

Sublingual: held under the tongue to dissolve; remainder swallowed after 30 minutes

Vaginal: inserted into the vagina

ROUTE OF ADMINISTRATION OF MISOPROSTOL

Misoprostol can be taken orally (swallowed), buccally (held in the cheek to dissolve), sublingually (held under the tongue to dissolve), or vaginally (manually inserted into the vagina). The route of administration influences how the drug is metabolized and the peak concentration it can reach in the bloodstream. When compared to oral and vaginal administration, sublingual misoprostol reaches the highest peak concentration and has the greatest bioavailability (Tang & Ho, 2008). The FDA-approved label specifies oral administration. Vaginal administration was common in the years immediately following Mifeprex’s approval (Winikoff et al., 2008). Clinical trials found that oral and buccal administration are similarly effective for pregnancies of up to 49 days (Winikoff et al., 2008), and buccal and sublingual routes are equally effective in women with pregnancies of up to 63 days (Chai, Wong, & Ho, 2013).

GESTATIONAL LIMITS

While the FDA label specifies that medication abortions may be performed for pregnancies of up to 49 days since the last menstrual period, several large studies demonstrate the safety and efficacy of the evidence-based protocol for gestations of up to 70 days (Abbas, Chong, & Raymond, 2015; Bracken, Dabash, et al., 2014; Sanhueza Smith et al., 2015; Winikoff et al., 2012). The National Abortion Federation’s Clinical Policy Guidelines give 70 days as the limit for medication abortions using mifepristone and vaginal, buccal, or sublingual misoprostol (while the oral route of misoprostol can be used up to 63 days) (National Abortion Federation, 2015). Planned Parenthood Federation of America (PPFA) sets the gestational limit for medication abortion at 63 days, except in states that require providers to adhere to the FDA label, in which case the limit is 49 days. However, affiliates may request a waiver from PPFA to extend the limit to 70 days gestation; many affiliates have taken advantage of this option (Planned Parenthood officials, personal communication, 2015).

Outside the US, World Health Organization (WHO) recommendations frequently guide clinical practice. WHO recommendations on medication abortion regarding gestational misoprostol dose, subsequent doses should be 400 µg and repeated every three hours up to four additional doses (WHO, 2012). The UK’s Royal College of Obstetricians & Gynaecologists recommends protocols involving repeated misoprostol dosing for pregnancies of 9-13 weeks (63 – 91 days) (Royal College of Obstetricians & Gynaecologists, 2011).

HOME USE OF MISOPROSTOL

The FDA label specifies that women should return to their providers 48 hours after mifepristone administration to receive misoprostol in person, but as early as 2001, 83% of surveyed National Abortion Federation (NAF) members reported they were giving women misoprostol to take at home (Wiegerinck et al., 2008). A 2007 review found ample evidence that home use of misoprostol is safe and effective, and reported that the second visit for misoprostol administration had been replaced by home use in the US and UK (Clark, Gold, et al., 2007). Recent large studies have investigated evidence-based protocols that include home use of misoprostol and confirmed high rates of safety and efficacy (Cleland et al., 2013; Gatter, Cleland, & Nucatola, 2015).

NON-PHYSICIAN PROVIDERS

The FDA label requires that mifepristone be administered “by or under the supervision of a physician” (FDA, 2005). Attorneys general or health departments in some states have interpreted this clause as allowing mid-level providers (MLPs) such as nurse practitioners (NPs), certified nurse-midwives (CNMs), and physician assistants (PAs) to provide medication abortion; one state, California, has passed a law authorizing MLPs to provide medication abortions (Samora & Leslie, 2007; Weitz et al., 2013). MLPs, also referred to as advanced-practice clinicians, are increasingly involved in medication abortions in Denmark, France, Great Britain, and Sweden; in the US at some clinics, MLPs handle the entire medication abortion process (Yarnall, Swica, & Winikoff, 2009). New guidelines from the World Health Organization recommend that nurses and midwives (as well as advanced associate clinicians and physicians)

provide medication abortions (WHO, 2015). The National Abortion Federation’s Clinical Policy Guidelines state, “Abortion will be provided by licensed practitioners. This category is intended to include physicians from various specialties as well as nurse midwives, nurse practitioners, physician assistants, registered nurses, and other health professionals” (NAF, 2015).

Medication abortions result in similar safety and efficacy profiles for both MLPs and physicians (Barnard et al., 2015). The primary difference between medication abortions provided by MLPs and those provided by physicians is that MLPs are more likely to seek second opinions on their ultrasound assessments during pregnancy evaluation than their physician counterparts; however, the frequency of these consultations has been shown to decrease over time, as MLPs gain experience with ultrasound dating (Kopp Kallner et al., 2015; Warriner et al., 2011). Studies in Mexico, Nepal, India, and Sweden show no difference in rates of incomplete abortion or abortion failure between MLPs and physicians (Barnard et al., 2015; Ngo, Park, & Free, 2013; Olavarrieta et al., 2015; Renner, Brahmī, & Kapp, 2013). It is important to note that most available data on this topic comes from settings outside of the US. Areas in the US where abortion providers are scarce may mirror the settings studied in Mexico, Nepal, and India, and high-resource settings in the US may be similar to those studied in Sweden, but further research in US settings could provide more direct comparisons.

Ensuring that MLPs have the legal authority and training to provide medication abortions can increase access to safe abortion services in areas with few physicians, such as rural areas where advanced practice clinicians but not obstetricians or gynecologists (OB/GYNs) are located (Foster et al., 2015; Taylor, Safriet, & Weitz, 2009). It can also enhance the cost-effectiveness of abortion care and allow providers to offer services to more women (Yarnall, Swica, & Winikoff, 2009).

EVOLVING EVIDENCE FOR ADDITIONAL VARIATIONS

Several other variations, some of which are already used widely in other countries or by some US providers, have the potential to reduce barriers to medication abortion for US women. One especially noteworthy recommendation comes from the World Health Organization, whose new guidelines recommend that women with pregnancies of up to 63 days be allowed to manage mifepristone and misoprostol medication without direct provider supervision and to self-assess abortion completion, though only “in circumstances where women have a source of accurate information and access to a health-care provider should they need or want it at any stage of the process” (WHO, 2015).

HOME USE OF MIFEPRISTONE

The FDA-approved label specifies that women take mifepristone in a clinic, medical office, or hospital. Allowing women to instead take mifepristone (in addition to misoprostol) at the time and place of their choosing can increase autonomy and privacy (Chong et al., 2015) and reduce logistical barriers. Women likely prefer to schedule medication abortions so they can experience the bleeding and cramping while they are not at work or school; however, these days may not align with the days when providers have appointments available. Timing can be especially

problematic for women without access to paid sick days, a group disproportionately composed of low-income workers (Bureau of Labor Statistics, 2015).

Raymond and colleagues note that requiring mifepristone to be administered only in a clinical setting is without medical justification; because the drug's pharmacologic action occurs several hours after ingestion, they point out that patients are nearly always elsewhere by the time any effects might occur (Raymond, Grossman, et al., 2015).

Several studies have tested protocols that allow women to leave their first appointments with mifepristone and instructions for taking it at a later time, and have reported no differences in efficacy or complications. A 2011 review considered randomized trials and prospective cohort studies from several different countries, comparing home use of mifepristone to clinic-based protocols, and found no evidence of difference in effectiveness (Ngo et al., 2011). More recent studies include one involving 400 women who received care at six US Planned Parenthood centers and were given the choice of taking mifepristone at the clinic or at home (within one week of their visit, and within the 63-day gestation window). Rates of success did not differ between the home and clinic groups; none of the home users reported taking mifepristone after the 63-day window; and home users reported missing less work and school (Chong et al., 2015).

REDUCING BARRIERS POSED BY FIRST AND FOLLOW-UP VISITS

While the second visit specified under the FDA label is easily eliminated by giving women misoprostol to take at home, eliminating or simplifying the protocol's first and follow-up visits requires more consideration. Further simplifications can improve access for women in areas without abortion providers as well as those who live near abortion providers and find multiple office visits logistically or financially challenging.

FIRST VISIT

The FDA-approved label specifies that mifepristone must be administered “by or under the supervision of a physician, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies,” but it does not specify how providers should make these determinations (FDA, 2005). Many providers use ultrasonography to confirm intrauterine pregnancy and ascertain gestational duration, but routine use of pre- and post-abortion sonograms can raise costs and limit access (Clark, Panton, et al., 2007). Practitioners without ultrasound equipment on site may be more likely to offer medication abortions if they feel they can do so without reliance on routine ultrasonography (Fielding, Schaff, & Nam, 2002). Guidelines from the American College of Obstetricians and Gynecologists, the National Abortion Federation, and the Royal College of Obstetricians and Gynecologists note that ultrasound is not required for first-trimester medication abortions (NAF 2015; Raymond, Grossman, et al., 2015). Ultrasound confirmation of gestational age is currently required for Planned Parenthood affiliates (Planned Parenthood officials, personal communication, 2015).

DETERMINING GESTATIONAL DURATION

Clark, Panton, and colleagues (2007) recommend that a woman's report of her last menstrual period (LMP) combined with a bimanual pelvic examination can be used in most cases to date the gestation. Following a chart review of medication abortion patients, they concluded that it may be safe and efficient to reserve sonography for cases in which: LMP dating may be inaccurate; an examination suggests a gestation beyond the medication abortion cutoff date; or an exam or recent medical history suggests an elevated risk of ectopic pregnancy (Clark, Panton, et al., 2007). A 2007 review found, "Women's report of their LMP, in combination with bimanual examination, can safely be substituted for routine sonography in the absence of significant discrepancies or inconsistencies for gestational dating before most cases of medical abortion" (Clark, Gold, et al., 2007). A 2011 review concluded that clinicians can reasonably estimate gestational duration from reported LMP and a physical examination (Kaneshiro et al., 2011). More recently, a 2014 review compared LMP to ultrasound for determining gestational duration, and concluded that women's report of LMP can be used to determine gestation for up to 63 days, although the authors recommend further study comparing reported LMP only to a physical exam plus LMP (Schonberg et al., 2014). Such future research could determine whether using LMP alone for gestational dating is as accurate as the combination of LMP and a physical exam.

For determining gestational duration, a 10-site US study involving women specifically seeking medication abortions found pregnancy dating based on women's LMP reports to be nearly as accurate as dating based on ultrasonography. The study authors recorded women's reported LMP and then compared those dates to ultrasound findings in order to determine whether LMP dating and ultrasound would concur in identifying women whose pregnancies were of up to 63 days. Of the more than 3,000 women certain of their LMP dates, only 2.4% would have been offered medication abortions when the determination was based on LMP alone but not when it was based on ultrasound. When reported LMP was combined with physician examination, only 1.6% of participants would have been offered a medication abortion that they would not have been eligible for based on ultrasound findings. Given that the mifepristone-misoprostol combination remains highly effective for several weeks after the 63-day cutoff, the authors note, there is a high likelihood that the treatment would still work in any women who received it based on LMP-only dating that may have underestimated gestational duration (Bracken et al., 2011). However, Raymond and Bracken (2015) caution that providing medication abortion to women beyond the gestational limit could result in complications or the need for a later, higher-risk procedure, and that expelling a fetus that is more developed than expected could be emotionally or physically traumatic.

Raymond and colleagues suggest that testing women's blood for levels of human chorionic gonadotropin (hCG) – a hormone women's bodies produce during pregnancy – could also provide assurance of appropriate gestational duration. Because hCG production rises during the first trimester before falling and plateauing, the authors comment, "It seems possible that a concentration cutoff could be identified that in combination with menstrual history could identify a pregnancy of less than 70 days" (Raymond, Grossman, et al., 2015).

IDENTIFYING ECTOPIC PREGNANCIES

The mifepristone-misoprostol combination is not effective for terminating ectopic pregnancies, and many providers may use ultrasound routinely before medication abortions to ensure that pregnancies are located inside the uterus. However, when used for this kind of routine screening, ultrasonography may miss up to 30% of ectopic pregnancies (Clark, Gold, et al., 2007). Bracken and colleagues instead recommend, “Screening for ectopic pregnancies on the basis of risk factors, symptoms and bimanual examinations may be more effective” (Bracken et al., 2011). Women are at greater risk of ectopic pregnancy if they have previously had an ectopic pregnancy, pelvic inflammatory disease, sexually transmitted disease, tubal surgery, pelvic or abdominal surgery, infertility, or endometriosis (ACOG, 2011). In the US population as a whole, approximately 2% of pregnancies are ectopic; among patients seeking abortion, it has been found to be as low as 0.2% (Raymond, Grossman, et al., 2015).

ASCERTAINING RH STATUS

The first visit also typically involves testing for Rh factor, a protein that can be present on red blood cells. Women who are Rh-negative but carrying Rh-positive fetuses can become Rh-sensitized, which can lead to complications for their future children, specifically: severe anemia in utero. To prevent this, Rh-negative pregnant women receive Rh immunoglobulin (ACOG, 2013), though an evidence base is lacking for Rh immunoglobulin treatment in women receiving first-trimester abortions (Raymond, Grossman, et al., 2015). Raymond, Grossman, and colleagues (2015) note that 85% of US women are Rh-positive, and many women receiving abortions either know their Rh type or could get tested at a commercial laboratory.

FOLLOW-UP VISIT

Per the FDA-approved label, a third visit 14 days after mifepristone administration allows the provider to confirm that the pregnancy was completely terminated. (Women are instructed to seek medical attention before their follow-up visits if they experience any problem, such as severe bleeding.) Several of the studies on medication abortion variations involved some flexibility in the timing of follow-up, with visits scheduled for between one and two weeks after mifepristone administration (e.g., Chong et al., 2015; Gatter, Cleland, & Nucatola, 2015; Winikoff et al., 2008). National Abortion Federation guidelines state, “Follow-up evaluation should be scheduled for 7-14 days after starting medical abortion” (NAF, 2015).

The mifepristone-misoprostol combination is highly effective, but the small percentage of continuing pregnancies must be detected quickly so that women can receive additional treatment without delay – because in some cases, continuing pregnancies can be advanced enough to require higher-risk treatments or to extend past a state’s gestational limit for abortion or past the limits to which local providers adhere. Additional treatment can take the form of aspiration, surgical completion, or additional misoprostol (Committee on Practice Bulletins—Gynecology and the Society of Family Planning, 2014; Li et al., 2008; Reeves, Kudva, & Creinin, 2008; WHO 2012). Any ectopic pregnancies not detected before the medication abortion will require prompt medical attention.

Studies have found that large percentages of women do not complete their follow-up visits after medication abortion. Loss to follow-up rates vary, ranging from 16-45% (Gatter, Cleland, & Nucatola, 2015), and providers’ office staffs devote considerable time to attempting to reach women who do not keep their follow-up appointments (Pocius et al., 2015). High rates of loss to follow-up also make research challenging, because researchers are unlikely to know outcomes for patients who do not attend follow-up visits or complete other scheduled follow-up communications.

Researchers are exploring and comparing different methods for confirming the completion of medication abortions. These methods include those that can be used at follow-up visits as well as alternatives that do not require women to make additional clinic visits. The availability of such alternatives has the potential to increase abortion access by making medication abortion available in additional locations and to reduce the barriers that patients currently face.

The WHO guidelines advise, “There is no medical need for a routine follow-up visit following uncomplicated surgical abortion or medical abortion using mifepristone followed by misoprostol. However, women should be advised that additional services are available to them if needed or desired” (WHO, 2012). Currently, the follow-up visit is optional at UK provider Marie Stopes International, and approximately half of patients go for these visits (Clark, Gold, et al., 2007).

Table 3: Methods for Confirming Complete Medication Abortion

Method	Description	Considerations
Ultrasound	Transvaginal ultrasound typically used	Equipment is expensive, and not all providers have it on-site
Physical exam	May include bimanual and/or speculum examination	Requires follow-up visit
Measurement of hCG	Human chorionic gonadotropin (hCG) is a hormone produced during pregnancy	
<i>Serum hCG</i>	Blood is drawn and analyzed before and after mifepristone administration	Can be done at local commercial labs or clinicians’ offices
<i>Urine hCG</i>	High-sensitivity, low-sensitivity, or semi-quantitative tests	Women can perform the tests at home or in clinicians’ offices
Discussion with clinician	Medical history, questions about still feeling pregnant/having passed the pregnancy, etc.	Can be done in person or by phone
Questionnaire	Questions about symptoms experienced, still feeling pregnant, etc.	Can be administered by non-clinicians, e.g., call center staff

METHODS FOR CONFIRMING COMPLETE MEDICATION ABORTION

In the US, confirmation of complete medication abortion typically involves either an ultrasound or blood tests comparing a new serum hCG measurement with one that was taken on the first visit (Pocius et al., 2015). Other methods – including urine hCG measurement, physical examination, and a discussion of symptoms – can be used in addition to or instead of the ultrasound or serum hCG measurement. Research into alternatives is ongoing, and some providers have updated their protocols as new studies have been published. This section briefly describes the different methods for determining abortion completion, and the following sections summarize some of the key studies incorporating these methods into alternative follow-up regimens.

Ultrasound: Transvaginal ultrasounds are commonly performed one week after treatment (Horning et al., 2012).

Physical exam: Physician assessment can include bimanual or speculum exams or both (Clark et al., 2010). Providers typically also ask women about bleeding and other symptoms they have experienced.

Blood tests: Studies have demonstrated that comparing baseline and post-abortion levels of serum hCG can reliably indicate successful medication abortions (Dunn et al., 2015). According to ACOG, a serum hCG level decrease of at least 80% six or seven days after mifepristone administration indicates a successful abortion (Committee on Practice Bulletins—Gynecology and the Society of Family Planning, 2014).

Home urine tests: HCG is also present in pregnant women’s urine, and women can use inexpensive urine tests at home to measure hCG. However, although hCG levels drop after termination of pregnancy, low levels of hCG can persist for a month or longer (Godfrey et al., 2007). Some of the studies involving urine pregnancy tests have used high-sensitivity tests, which can detect hCG at low concentrations (25–50 mIU/mL), while others have used low-sensitivity tests (1000 mIU/mL). Low-sensitivity tests can be used sooner after a medication abortion (Godfrey et al., 2007), because they will not detect the low levels of hCG that may still be present even though the woman is no longer pregnant.

Another option for urine tests is the semi-quantitative urine test, which provides an indication of the level of hCG in women’s urine by including multiple sensitivity levels on the same test. The tests require interpretation (e.g., to read the current level of hCG and compare it to a pre-abortion level), so clear instructions are important if women will be using the tests on their own (Blum, Shochet, et al., 2012; Lynd et al., 2013).

Discussion with clinician: Several studies assess the effectiveness of a symptom questionnaire or checklist, which is often delivered by clinic staff during a follow-up phone call. Asking women about symptoms, including duration of heavy bleeding and ongoing symptoms of pregnancy, following medication administration is one way to identify possible incomplete abortions.

Questionnaire: Like discussions with clinicians, questionnaires typically include standardized questions about bleeding following medication administration and whether women think they

are still pregnant. However, questionnaires can be delivered by non-clinical staff, or women can complete them on their own.

Combinations of methods: In a large, multi-site retrospective study, Clark and colleagues (2010) arranged for women to receive blinded clinical assessments before undergoing ultrasonography to confirm complete medication abortions. They constructed five algorithms that included different combinations of the following seven indicators: (1) positive results on a low-sensitivity urine pregnancy test, (2) not experiencing at least one day of heavy bleeding, (3) experiencing less than two days of heavy bleeding, (4) still feeling pregnant, (5) uncertainty about still feeling pregnant, (6) exhibiting any pregnancy symptom, and (7) a clinician determining before sonography that further evaluation was desirable. The authors concluded that screening algorithms that included patients’ observations, a low-sensitivity pregnancy test, and non-sonography clinical evaluation were as effective as sonography in identifying women who received additional medical intervention (Clark et al., 2010).

Table 4: Alternatives to Returning to Provider’s Office for Follow-Up

Method	Description	Considerations
Laboratory visit	Women have blood drawn at a local lab for serum hCG measurement.	Results go to the provider, who must then communicate with the patient.
Follow-up by phone or text	Clinicians or operators contact women to screen for possible continuing pregnancies.	Calls can include the ability to schedule follow-up appointments for those with possible continuing pregnancies or other complications.
Self-assessment	Women complete a questionnaire and a urine test, and contact the provider only if results indicate a possible continuing pregnancy or if they have concerns.	Providers are only assured that the self-assessment was completed when women contact them about possible ongoing pregnancies or other concerns.

CLINICAL VISITS WITHOUT ULTRASONOGRAPHY

As noted previously, routine use of pre- and post-abortion ultrasonography can raise costs and limit access (Clark, Panton, et al., 2007). A 2011 review concluded that confirmation of pregnancy expulsion can come primarily through patient history (e.g., description of bleeding since medication administration) and physical examination, and that urine tests could also play

a role (Kaneshiro et al., 2011). Substituting the history and physical exam for typical follow-up methods can allow providers without ultrasonography equipment to offer medication abortions, which is especially important in low-resource settings.

LABORATORY FOLLOW-UP

Using pre- and post-abortion serum hCG measures to confirm abortion completion requires two in-person visits to a facility for the baseline and post-procedure measurements, but that facility could be a community laboratory rather than the office of an abortion provider. As Dunn and colleagues note, “multiple clinic visits may jeopardize privacy and be inconvenient and costly for women who must travel, miss work or make child-care arrangements” (Dunn et al., 2015). Laboratories may be more conveniently located for many women, and may have extended hours or allow drop-ins. However, costs may still be high (Grossman & Grindlay, 2011). This method still requires providers who receive the lab results to contact patients to discuss them (Committee on Practice Bulletins—Gynecology and the Society of Family Planning, 2014).

In 2008, Planned Parenthood Federation of America adopted a protocol change that allows its clinics to offer women the option of having a serum hCG level drawn at the time of mifepristone administration and obtaining a follow-up measure at another site approximately one week later (Horning et al., 2012).

FOLLOW-UP BY CALL OR TEXT

Some of the studies that contribute to the evidence base for phone follow-up have required participants to visit the clinic for follow-up, but have recorded patients’ and/or clinicians’ assessments of abortion completion before performing ultrasonography and then comparing the assessments to the sonographic images. Studies have also compared phone follow-up to clinic follow-up to test the feasibility of offering the remote follow-up alternative, and these report on the number of continuing pregnancies detected even when that was not the primary outcome being studied. After studies demonstrated that assessments based on history and symptoms could assess abortion completeness with a high degree of accuracy, some providers began offering women the option of telephone follow-up. Such remote follow-up options typically involve administration of a standardized questionnaire (either by nurses or non-clinical staff), and women whose answers indicate possible continuing pregnancies or other complications are instructed to return to the provider’s office or visit another clinical site.

One large study asked 931 women who attended a follow-up visit seven days after receiving mifepristone about their symptoms and whether they thought they had expelled their pregnancies, and the clinicians could ask additional questions before recording both their opinions and their patients’ opinions as to whether the pregnancies had been expelled. Clinicians then performed ultrasounds, and in 99% of the cases in which both the clinician and patient thought the pregnancy had been expelled, sonography confirmed that to be the case (Rossi, Creinin, & Meyn, 2004). This study, however, only included four abortion failures, which is unsurprising given the efficacy of the mifepristone-misoprostol combination. To

study a larger number of failed abortions, Jackson and colleagues (2012) conducted a case-control study involving 53 women who had a retained gestational sac or ongoing pregnancy following medication abortion, plus 53 controls whose abortions were successful. While they found that subjects with a continuing pregnancy were more likely to have reported minimal bleeding and doubt about having expelled their pregnancies, creating a system to identify these women solely by these symptoms found only 68% of them. The authors concluded, “An objective measure of complete abortion, such as a pregnancy test, is still required” (Jackson et al., 2012).

For the studies described in this section, it is important to note that studies involving medication abortion rarely (if ever) achieve 100% follow-up with patients, and it is possible that study participants lost to follow-up or not communicating with investigators after a protocol's completion had ongoing pregnancies or other outcomes that are not reflected in results.

In Pittsburgh, Perriera and colleagues (2010) evaluated the use of phone follow-up, in which clinicians called women one week after mifepristone administration and asked a standardized set of questions, including whether the women thought they had passed their pregnancies. If either the patient or clinician did not think the pregnancy had passed, the woman was asked to return to the clinic within seven days for an ultrasound. Patients were also instructed to perform a high-sensitivity urine pregnancy test 30 days after taking mifepristone, and received a second follow-up call about those results. Out of 139 study participants, four were found to have continuing pregnancies. One visited the clinic before the first follow-up phone call, two were instructed to come to the clinic and received surgical intervention, and one was not instructed to return for a visit after the first call but presented for an interim visit at which the continuing pregnancy was discovered and treated (Perriera et al., 2010).

Several studies in the United Kingdom involved the use of low-sensitivity urine pregnancy tests. At British Pregnancy Advisory Service clinics, Bracken and colleagues (Bracken, Lohr, et al., 2014) instructed half of study participants to take a low-sensitivity urine test two weeks after mifepristone administration, and non-clinician phone operators followed up with them by phone, text, or online communication. The operators asked about symptoms and the test results, and instructed those whose answers indicated possible ongoing pregnancy to schedule a clinic visit. The comparison group received the usual instruction to return for a follow-up visit; however, they also received high-sensitivity pregnancy tests, which they were instructed to take three weeks after mifepristone administration if they missed their follow-up appointment. The proportion of participants not completing their scheduled follow-up (either by phone/internet or at the clinic) did not differ between groups, and the study found no evidence of a difference between groups in ascertainment of ongoing pregnancy (Bracken, Lohr, et al., 2014).

In a study in Moldova and Uzbekistan, women who completed a semi-quantitative urine test and standardized checklists two weeks after mifepristone administration also received follow-up phone calls; this protocol also detected all of the ongoing pregnancies among participants who completed follow-up (99.6% of those enrolled) (Platais et al., 2015).

In 2010 the Royal Infirmary of Edinburgh (Scotland), the main provider of abortion services in its region, began offering women who received medication abortions the option of phone follow-up instead of an in-clinic follow-up visit. Women receive a low-sensitivity urine pregnancy test to take two weeks after mifepristone administration, and at that time they receive a call from a nurse who asks about the duration and nature of bleeding and whether pregnancy symptoms continued. Women with a positive test result or symptoms indicating a possible ongoing pregnancy are instructed to come in for ultrasonography. An evaluation of the service, involving the records of 476 women who chose phone follow-up, found that the urine test with phone screening failed to identify one of four ongoing pregnancies that the investigators found (Cameron et al., 2012). A larger, more recent database review at the same site (involving 943 women’s records) found no false negatives – that is, no woman was discovered to have an ongoing pregnancy after having been told at the phone follow-up that she did not need to return for further evaluation (Michie & Cameron, 2014).

SELF-ASSESSMENT

Researchers are also investigating the use of self-assessment protocols, in which women receive tests and information to allow them to determine whether their abortions are complete, and they need only communicate with their providers if they have symptoms of continuing pregnancy or other concerns. Studies in the US and Vietnam involved a semi-quantitative urine test on the day of mifepristone administration and another test either one week (US) or two weeks (Vietnam) later, and women were instructed on how to interpret their results. Women recorded their self-assessments and presented them at a follow-up clinic visit. In both studies, women’s interpretations of the tests identified all of the ongoing pregnancies detected – one in the US, and 11 in Vietnam (Blum, Shochet, et al., 2012; Lynd et al., 2013).

A large study in four European countries (with a total of 924 participants) instructed women in the self-assessment group to take a semi-quantitative urine test between one and three weeks after mifepristone administration, and they received a follow-up call at one month. The self-assessments with the urine tests failed to detect three of 27 continuing pregnancies found in the self-assessment group; these were then discovered in the second trimester. The group receiving in-clinic follow-up had no undetected pregnancies (Oppegaard et al., 2015). While the authors reported that statistically the remote follow-up method was non-inferior (Oppegaard et al., 2015), an editorial accompanying the published study highlights the three undetected continuing pregnancies and notes that failing to detect ongoing pregnancies within two weeks can be problematic because “second-trimester abortion confers greater risk of complications, is less widely available, and in some countries is illegal” (Hickey & Moore, 2015).

After receiving requests from patients to not receive follow-up calls, the Royal Infirmary of Edinburgh (whose remote follow-up option is described above) introduced a “self-assessment” option in 2012, allowing women to opt out of receiving the call if they understood and felt confident carrying out instructions on how to interpret their low-sensitivity urine tests and the kinds of symptoms indicating they should call the provider. A database review of women choosing self-assessment found eight ongoing pregnancies, and

four of those were not detected until the women had missed one or more menstrual periods. All four of these women received follow-up termination procedures at between 12 and 22 weeks of pregnancy. The authors note that providers may be particularly concerned about not detecting continuing pregnancies promptly in countries where second-trimester abortions are illegal or unavailable (Cameron et al., 2015).

The World Health Organization recommends that self-assessment be an option for women using mifepristone and misoprostol for pregnancies of up to 63 days and in circumstances “where women have a source of accurate information and access to a healthcare provider should they need or want it at any stage of the process” (WHO, 2015). The guidelines note, “There is evidence that the option is safe and effective including in low-literacy, low-resource settings” (WHO, 2015).

FOLLOW-UP CONSIDERATIONS

It is important to stress that the elimination of routine visits does not mean that women should not have access to follow-up medical care if they are experiencing severe pain or bleeding or another adverse event. (All the above studies instructed women to access care as soon as they experienced problems, rather than waiting for a scheduled follow-up.) When alternative follow-up methods are used, women whose results indicate possible incomplete abortions will still need to access additional care.

In all of these studies involving remote follow-up, many more women were flagged for needing follow-up than actually needed additional medical intervention for either incomplete abortions or for adverse outcomes such as continued heavy bleeding. The number who returned to the clinics or other sites for care was still far lower than the total number receiving medication abortions, translating to a reduced burden for women as a whole and for providers. Women gave remote follow-up methods high marks for acceptability (Bracken, Lohr et al., 2014; Cameron et al., 2012; Michie & Cameron, 2014; Platais et al., 2015).

Given that many women who are instructed to return to providers’ offices for follow-up (as the FDA label specifies) do not do so, more convenient follow-up methods may be attractive as a way to reduce loss to follow up. In addition, many providers use follow-up visits to counsel women about contraception and start them on their chosen method, so those who make the follow-up visit optional may need to address contraception at a different point in the process.

TELEMEDICINE

The Institute of Medicine has defined telemedicine as “the use of electronic information and communications technologies to provide and support health care when distance separates participants;” today, “telemedicine” and “telehealth” are often used interchangeably. Telemedicine can provide access to care for residents of rural areas and patients living in medically underserved areas. Approximately 10 million patients receive telemedicine services in the US each year, although licensure regulations can pose a barrier to the provision of services across state lines (National Research Council, 2012).

In the US, little published research on use of telemedicine for medication abortion exists; the exception is a set of studies on telemedicine abortion in Iowa (Grindlay, Lane, & Grossman, 2013; Grossman et al., 2013; Grossman, Grindlay, Buchacker, et al., 2011). In 2008, the Iowa clinic network Planned Parenthood of the Heartland, which provided 74% of abortions in the state that year, began offering medication abortion by telemedicine at clinic sites not staffed by physicians (Iowa is one of the states where only physicians may provide medication abortions; see “State Level Medication Abortion Policies” on page 28). Clinic staff members take each patient’s history, perform an ultrasound, provide information about medication abortion, and receive the patient’s informed consent; they then upload the medical history and ultrasonographic image to a secure server so the physician can view them. The physician then uses video teleconference equipment to have a discussion with the patient. If the patient is eligible for a medication abortion, the physician enters a password that remotely unlocks a drawer that contains the mifepristone and misoprostol, watches the patient take the mifepristone, and provides the remaining instructions (Grossman, Grindlay, Buchacker, et al., 2011).

A study using follow-up data from 223 telemedicine patients and 226 face-to-face patients in Iowa found that the two methods had equivalent success rates and few adverse events (Grossman, Grindlay, Buchacker, et al., 2011). A study of data on all abortions in the two years before and two years after the telemedicine option was introduced found that the proportion of abortions in the clinics that were medical (as compared with surgical) increased, and clinic patients had an increased odds of obtaining either form of abortion before 13 weeks’ gestation (Grossman et al., 2013). A study that involved interviews with abortion patients and clinic staff found that many who chose telemedicine abortions did so because they could visit a closer facility and initiate an abortion more quickly. Several cited concerns about taking time off work or school, spending money on travel, and explaining their out-of-town trip to others if they were to travel long distances to facilities where they could see the physician in person. Clinic staff reported increased efficiencies and fewer cancellations and delays related to travel in severe weather (Grindlay, Lane, & Grossman, 2013).

In the 18 states that specifically require physicians who prescribe mifepristone to do so in person (Guttmacher Institute, 2015b), telemedicine cannot be used to provide medication abortion.

Women in many countries where abortion is restricted and medication can be imported may receive medication abortion via telemedicine from the organization Women on Web. This nonprofit, established in 2006 with the aim of increasing access to safe termination of pregnancy and improving maternal health, refers website visitors seeking abortions to a physician for an interactive online consultation. Women who indicate that they have pregnancies of 63 days or fewer (based on their last menstrual period), do not have contraindications, and reside in eligible countries can then receive mifepristone and misoprostol by mail or courier, as well as information from the organization about medication use and possible side effects and complications. Women are advised to have an ultrasound before taking the medications to determine gestational duration, and to complete a pregnancy test and ultrasound three weeks later. A helpdesk is available seven days a week to provide

support throughout the process. A 2011 study of 2,585 women from 88 countries who received medication from Women on Web and provided follow-up information found a continuing pregnancy rate of 0.9% (Gomperts et al., 2012).

MISOPROSTOL-ONLY ABORTIONS

The mifepristone-misoprostol combination is currently the gold standard for medication abortion because it is more effective and has fewer side effects than the alternatives, but misoprostol alone is commonly used in settings where mifepristone is unavailable (due to either abortion restrictions or mifepristone not being licensed in all countries). Misoprostol is licensed as a drug for gastrointestinal conditions in approximately 90 countries, and its low price and stability at room temperature make it well-suited for abortions in low-resource settings (Winikoff & Sheldon, 2012). Where mifepristone is not available, the World Health Organization recommends repeated doses of misoprostol (800 µg administered vaginally or sublingually and repeated at intervals of 3-12 hours for up to three doses) (WHO, 2012).

A 2011 review concluded that misoprostol alone is less effective than the combined regimen (Kulier et al., 2011). Since then, randomized controlled trials comparing the mifepristone-misoprostol combination to misoprostol alone (using the buccal route of administration) have provided additional data. In a trial involving 441 women with pregnancies of up to 63 days' gestation in Tunisia and Vietnam, Blum and colleagues found complete abortion without surgical evacuation occurred in 78% of the misoprostol-only group and 93% of the mifepristone-misoprostol group (Blum, Raghavan, et al., 2012). In a study involving 100 women with pregnancies of up to 56 days in India, 74% of misoprostol-only patients and 92% of mifepristone-misoprostol patients had complete abortions (Dahiya et al., 2012). A trial in Vietnam involving 400 women with pregnancies of up to 63 days found complete abortions in 76% of the misoprostol-only group and 97% of the mifepristone-misoprostol group (Ngoc et al., 2011).

Worldwide, use of misoprostol alone for medication abortions is often off-label or clandestine (Winikoff & Sheldon, 2012), and it is difficult to study success rates or complications from clandestine home use. While misoprostol is available over-the-counter in many countries, it is only available by prescription in the US. Two relatively recent US surveys of women seeking abortions found low rates of attempting self-induced abortion: Grossman and colleagues (2010) found 4.6% of respondents reported attempting to induce abortion by any means, while Jones (2011) found that 1.2% reported using misoprostol to self-induce an abortion, and 1.4% reported using other substances.

Attempts to self-induce abortions may be more common in areas where access to abortion is limited. A survey conducted among women seeking abortions at Texas clinics in 2012, after new abortion restrictions took effect in the state, found that 7% reported having first tried taking something on their own to induce abortion – and that number rose to 12% when considering only the clinics near the Texas-Mexico border (Grossman et al., 2014). In Mexico, misoprostol is available from pharmacists without a prescription, but the drug does not come with instructions on use for abortion. Grossman and colleagues warn that “if women do not

have accurate information, they may use ineffective dosages and may not realize the abortion failed until much later in pregnancy, forcing them to seek a second-trimester abortion or continue the pregnancy and have a child they do not want or feel they cannot care for” (Grossman et al., 2014). A 2015 survey of a statewide representative sample of Texas women ages 18 – 49 found that 4.1% reported either trying to end a pregnancy on their own or having a best friend who they knew or suspected had done so. Based on the survey responses, the authors estimate that between 100,000 and 240,000 women in Texas have tried to end a pregnancy on their own without medical assistance (Grossman, White, Fuentes, et al., 2015).

Many advocates believe that all women should have access to the medication abortion method with highest efficacy and fewest side effects, mifepristone with misoprostol (Winikoff & Sheldon, 2012). However, in the face of increasing barriers that deny many women that ideal, some advocates have called for educating US women about the recommended use of misoprostol and making that drug more widely available (Coeytaux, Hessini, & Allina, 2015). Further research is needed to optimize repeat dosing and interval scheduling in misoprostol-alone abortions.

SUMMARY: COMMON PRACTICE VARIATIONS AMONG ABORTION PROVIDERS

The evidence-based protocols most common in current clinical practice involve 200 mg of Mifeprex (rather than 600 mg) (Cleland & Smith, 2015) followed by 800 micrograms of misoprostol that women take at home rather than in a provider’s office (Clark, Gold, et al., 2007; Cleland et al., 2013; Wiegerinck et al., 2008). The interval between mifepristone and misoprostol dosage and the route of administration may also vary – e.g., a woman may take misoprostol buccally and may do so one day after mifepristone rather than two.

Providers may also offer medication abortions later in pregnancies, with most providers currently using 63 days as the cutoff (Jones & Jerman, 2014). Depending on state laws, medication abortions may be performed by mid-level providers (also referred to as advanced practice clinicians) such as nurse practitioners, certified nurse-midwives, and physician assistants.

Ongoing research is exploring other variations that have the potential to improve access. Home use of misoprostol, which eliminates the second of the three visits specified in the FDA label, is already common (Clark, Gold, et al., 2007; Cleland et al., 2013; Wiegerinck et al., 2008); now, researchers are exploring ways to simplify or eliminate the initial visit and follow-up visit to further reduce barriers (Chong et al., 2015; Gold & Chong, 2015; Swica et al., 2013). Provision of medication abortions via telemedicine or by providers not currently offering the service would also improve access in areas where it is currently limited. Some advocates also suggest the safe and informed use of misoprostol alone for women who lack access to abortions with the mifepristone-misoprostol combination. While misoprostol alone is less effective than the two-drug combination, its efficacy is still high, and this regimen is used extensively in other countries where mifepristone is unavailable.

The research described in the preceding section aims to identify practices that can provide women with safe and effective abortion care while accommodating their preferences and safeguarding their privacy and dignity. Reducing barriers to medication abortion can allow more women to receive abortion services early in their pregnancies, when risks are lowest, and may also lower costs and improve efficiency. However, several current and proposed policies create barriers to the adoption of evidence-based practices.

CLAIMS ABOUT “REVERSAL”

Progesterone is a naturally occurring hormone, and synthetic versions of it are used during pregnancy for several established and tested clinical purposes. These include prevention of preterm birth and supplementing other hormones used in assisted reproductive technologies (Grossman, White, Harris, et al., 2015). Some have suggested that progesterone can reverse the abortion process after a woman has taken mifepristone by countering its effect.

However, there is virtually no credible evidence to support this claim. Researchers recently conducted a systematic literature review to identify any manuscripts that examined the question of medication abortion reversal. Only one article met the inclusion criteria, and its methods are highly flawed. This article describes a case series of seven women who received progesterone treatment after taking mifepristone at 7-11 weeks; the exact dosage of mifepristone was not noted. Patients received progesterone to “reverse” the effects of the mifepristone. At the end of the study, one patient had been lost to follow-up, four patients continued their pregnancies and delivered at term, and two patients had completed their abortions within three days of taking mifepristone. Based on the six patients with data, 67% (95% CI 30-90%) continued the pregnancy; assuming the seventh patient aborted, 57% (95% CI 25-84%) continued the pregnancy (Grossman, White, Harris, et al., 2015). This rate is within the expected rate of continuing pregnancy with mifepristone alone.

As Grossman and colleagues note, even this lone study is methodologically flawed in a number of ways and fails to meet basic human subjects research requirements. First, there is no mention of an ethics board or internal review board (IRB) giving approval for the study. Ethically sound research involving humans must meet this basic requirement. Second, the study authors did not report how many women were excluded from the study because they had already aborted after taking mifepristone alone. Failing to include these women in the final proportions of women who “reversed” their medication abortions could dramatically alter the study’s findings. Third, there were no rigorous research studies (to date) that examined the use of mifepristone alone beyond 56 days, yet the study team included women up to 11 weeks’ (77 days) gestation and did not make any comparisons between their “intervention” and the effects of taking only mifepristone. This failure to include relevant enrollment criteria for participants is not only a failure to meet basic research requirements but also can impact the outcomes of the study, as women at later gestations might be more likely to continue their pregnancies after taking only mifepristone, regardless of any intervention.

In more rigorous studies of taking mifepristone alone, the proportions of participants with continuing pregnancies ranged from 8-46% (Grossman, White, Harris, et al., 2015). This finding is

important to mention because women who had no additional intervention after taking mifepristone (e.g., no progesterone) may have been likely to *continue* their pregnancies in nearly half of all cases, which should not be confused with *reversing* the effects of mifepristone, as claimed by the original study authors.

STATE-LEVEL MEDICATION ABORTION POLICIES

The number and type of restrictive abortion policies have been increasing over the last several years. For medication abortion specifically, these policies can affect one or more aspects of the medication abortion process, including the type of provider allowed to provide medication abortion, the exact protocol that must be followed, and the specific guidance that a clinician can provide to a patient.

PROTOCOL, CLINICIAN, AND TELEMEDICINE RESTRICTIONS

Many states restrict the way in which women can access medication abortion. As of September 2015, 38 states allow only licensed physicians to provide medication abortion,² three states require medication abortion to be provided according to the FDA label, and 18 states require that the clinician be physically present for the medication abortion process (Guttmacher Institute, 2015b). The first type of restriction prohibits mid-level providers, such as physician assistants, nurse practitioners, and certified nurse midwives, from prescribing Mifeprex, despite significant evidence that these advanced practice clinicians can safely and effectively provide the same quality of care as physicians. The second type of restriction prohibits use of any evidence-based protocols, including the one most commonly used in the US: a 200-mg dose of mifepristone taken at the clinic, followed by an 800-µg dose of misoprostol at home, with a follow-up clinic visit to confirm whether the abortion is complete. This particular restriction does not allow for any deviation from the protocol currently described in the FDA label, unless FDA approves a label change that allows it – or unless a state’s law specifies that certain variations are allowed. Texas law HB 2 permits dosage variations described in a recent practice bulletin from the American College of Obstetricians and Gynecologists (Texas House Bill 2, 2013), and provisions of this bill are the subject of a pending Supreme Court case.³ Costs can be higher when clinics must use the higher doses of Mifeprex in the FDA protocol (the drug is not available in generic form) and must see women for three visits – or four, in those states that also require a waiting period between the first visit and the start of the procedure.

Another type of restriction effectively prohibits the use of telemedicine for the medication abortion process, an option that may become increasingly important if additional clinics providing abortion are required to close due to other state laws designed to reduce abortion availability.

² 38 states also allow only licensed physicians to provide surgical abortion. The states only limiting a single type of abortion are New Jersey (limits only surgical abortions) and Colorado (limits only medication abortions).

³ As of December 2015.

Telemedicine also presents a promising option for women in rural or other health professional shortage areas, where travelling to a clinic for multiple visits may require days off from work or even overnight stays hundreds of miles from home.

In the last 15 years, knowledge about safe, effective, and accessible medication abortion practices has advanced well beyond where it was when FDA considered the Mifeprex application. States that have imposed the restrictions listed above will restrict access to safe abortion care, not improve safety or efficacy as supporters of those laws commonly claim. Several lawsuits have challenged these restrictions, or are in the process of doing so. Some judges have allowed the regulations to go into effect while litigation is pending, while others have halted the laws' implementation.

REQUIRED COUNSELING ON “REVERSAL”

In addition to restricting the ways in which providers can offer medication abortion, some states have introduced or passed legislation mandating that providers tell patients it may be possible to reverse a medication abortion after they have taken the initial dose of drugs. The claim is that if a woman is treated with progesterone after taking mifepristone and before taking misoprostol, she might halt the abortion process and allow her pregnancy to continue. As previously discussed, this claim is not supported by the evidence.

In April 2015, the Governor of Arizona signed SB 1318 into law, requiring providers to use the following language with patients seeking a medication abortion: “It may be possible to reverse the effects of a medication abortion if the woman changes her mind but that time is of the essence” (Grimes, 2015). The statute also requires the state’s Department of Health Services to list “information on and assistance with reversing the effects of a medication abortion” on their website.

The Arizona law has been temporarily enjoined because of a pending lawsuit filed in the federal court (Guttmacher Institute, 2015a). However, Arkansas has also passed a law requiring that women receive information on reversing abortion (HB 1578), and legislators in Louisiana have announced their intention to introduce similar bills (Resnick, 2015; Wilson, 2015).

The authors of the recent systematic review of evidence on medication abortion reversal cited above clearly summarize the implications of the faulty research that the legislation is based on and of the laws themselves:

“The new laws in Arizona and Arkansas have now bypassed the research process, in effect making all women who undergo this treatment subjects in an uncontrolled, unmonitored experiment. Providing evidence-based care is part of how physicians meet their beneficence-based obligations to patients, and therefore, it is a moral as well as a clinical mandate to base care on accepted scientific fact. The new laws compel physicians to say things that may contradict their clinical knowledge and judgment. Some physicians will not be able to do so in good conscience.” (Grossman, White, Harris, et al., 2015)

POLICY & RESEARCH IMPLICATIONS

Looking forward, access to safe and effective medication abortion services will continue to be influenced by state and federal policy. There are clear areas of needed policy change and ongoing research to ensure that women benefit from the best available information and high-quality medical care.

POTENTIAL TO EXPAND ACCESS TO ABORTION CARE THROUGH MEDICATION ABORTION

When Mifeprex first received FDA approval, supporters of abortion care hoped that the availability of medication abortion would expand access to all abortion care by allowing clinicians who could not or did not want to perform surgical abortions to offer abortion services (Coeytaux Hessini, & Allina, 2015; Leeman et al., 2007). However, there is little evidence to show that access to abortion care has expanded substantially in underserved areas since the approval of Mifeprex in 2000.

Immediately following the approval of Mifeprex, provision of medication abortion grew rapidly at first but has leveled off in recent years (Jones & Jerman, 2014). While the overall rate of medication abortion continues to grow nationally, certain populations may still not experience expanded access. Most facilities that offer only medication abortion are located in areas where other providers offer surgical abortion, with only a small percentage serving as the sole abortion provider in their metropolitan areas (Jones & Jerman, 2014). This analysis suggests that, even as the number of abortion providers may be increasing, they are largely serving areas where women already had access to care, while women living in areas where there is a lack of providers continue to face barriers to access.

Some studies have examined the barriers to providing medication abortion in settings that previously did not perform any type of abortion. For example, at the University of New Mexico (UNM), elective abortions (either surgical or medication) were unavailable for the 10 years prior to FDA approval of Mifeprex. After adding medication abortion as an on-site service, 85% of eligible women who received pregnancy options counseling at UNM chose medication abortion, rather than surgical abortion at an external site (Leeman et al., 2007). This study suggests that patients may be receptive to obtaining medication abortion services at practices that do not offer surgical abortion. However, there may be substantial barriers for providers wishing to add these services to their practices, including clinicians' lack of abortion training or personal or religious objections to providing the service (Espey et al., 2011).

DIRECTIONS FOR FUTURE RESEARCH

Significant evidence exists on multiple ways to improve medication abortion services, from dosage and timing of each drug to new directions for follow-up care. However, some gaps in the research persist.

One area that would benefit from further research is the proportion of medication abortions that are complete after the initial dose of misoprostol, versus those that require an additional dose of misoprostol for completion. Cases in the latter category are often not included in counts of

ongoing pregnancies following medication abortion (Cleland et al., 2013), but women considering medication abortion may want to know the likelihood that they will need an additional dose of misoprostol to have a complete abortion.

While the safety and efficacy of medication abortion offered by mid-level providers is well-documented in other countries, there are few published studies examining MLPs in the US. Evidence from practice guidelines supports the ability of MLPs to provide medication abortion with equivalent clinical efficacy as their physician peers, but more research would bolster the case for allowing MLPs in all states to offer medication abortion services.

More research into remote follow-up methods and self-assessment could help identify the most effective alternatives to multiple in-person visits.

Information about methods and outcomes of attempted self-induced abortion will be especially important as more state-level abortion restrictions take effect. Research into these restrictions, some of which is ongoing, will be essential for documenting the impacts on access, costs and other hardships, and health for women who seek both medication and surgical abortions. Additionally, the existing literature about the potential to “reverse” a medication abortion does not support the claim that it can be done, but if policy-makers continue to propose and pass laws that require clinicians and/or other health entities to describe reversal, additional research with appropriate safeguards should be conducted. Furthermore, research into the impact of restricting providers’ interactions with patients by requiring them to discuss reversal merits investigation as well.

Additional research is also needed to explore the impact that medication abortion has had on access to abortion care more generally. The number of abortion providers has declined in recent years, as has the abortion rate. How has availability of medication abortion interacted with other developments, such as new legal restrictions on abortion care broadly, to affect these trends? Do extensive label requirements (provider agreement, rigid protocol, etc.) pose a challenge for uptake among providers and decisions by patients?

ADVOCACY FOR LABEL CHANGE

Informed by the robust body of evidence regarding the safety and efficacy of mifepristone, reproductive health advocates are making a case that current FDA restrictions on distribution of the drug make medication abortion far more complicated and heavily medicalized in the United States than is necessary to ensure the health and safety of women using the drug. They further argue that the drug regimen outlined on the US mifepristone label actually serves as a barrier to providing the highest standard of medication abortion care to women.

The consequences of labeling a drug with outdated information and imposing an overly restrictive regimen are far-reaching. The problem is particularly acute in states where politicians have interfered with physicians’ authority to practice evidence-based medicine by enacting laws that require rigid adherence to the FDA label when prescribing mifepristone. But the label has effects in other states as well, lending the appearance of legitimacy to otherwise medically unsupported legislative proposals such as those limiting provision of abortion services to physicians or requiring a physician’s physical presence when medication abortion services are provided (Foster

et al., 2015; Sheldon & Winikoff, 2015). Additionally, although health care providers in most states are not required to adhere strictly to the labeled use or regimen for a drug, drug companies are prohibited from distributing information that is not consistent with the drug label (Ventola, 2009), which, in the case of Mifeprex, prevents the company from promoting the best and safest way to use the drug.

PROTOCOL

In recent years, advocates have begun to call for changes in how FDA regulates the distribution and use of mifepristone. In addition to asking the agency to update the drug label to reflect the current evidence, they are urging FDA to eliminate unnecessary regulatory barriers so that medication abortion can be provided in the ways that are safest, most effective, and most responsive to women's needs. They point out that the restrictions embedded in the mifepristone label are not supported by the evidence (Cleland & Smith, 2015) and that no other drug with a comparable safety profile is burdened with the kind of restrictions that have been imposed on mifepristone (Coeytaux, Hessini, & Allina, 2015).

Specifically, advocates support updating the mifepristone dose on the drug label to 200 mg, which has been shown to be the safest, most effective dose (Cleland & Smith, 2015). They also call for the label to state that mifepristone has been shown to be effective when used up to 70 days gestation instead of the 49 days on the label today (Abbas, Chong, & Raymond, 2015). They point out that the label specification that patients make three office visits and complete extensive follow up imposes unnecessary medical costs as well as logistical burdens on women seeking medication abortions (Cleland & Smith, 2015; Raymond, Grossman, et al., 2015). Furthermore, they argue that FDA should eliminate mifepristone's Risk Evaluation and Mitigation Strategy (REMS) and the associated Elements to Assure Safe Use (ETASU), which were established based on the regimen used in the clinical trials the agency reviewed at the time of the drug's approval.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) AND ELEMENTS TO ASSURE SAFE USE (ETASU)

FDA can require a REMS for a drug if it determines that risk management measures are necessary to ensure safe use of the drug. The most extensive REMS plans include ETASU requirements, which are actions that health care professionals must take before prescribing or dispensing the drug. Because FDA recognizes that imposing ETASU requirements has the potential to create a barrier to access, it has established provisions to ensure that the REMS is as efficient as possible, including stating that ETASU requirements must be commensurate with the specific, serious risks listed in the drug labeling and cannot be unduly burdensome on patient access to the drug (FDA, 2015).

The current ETASU requirements for mifepristone include:

- Limitation of the authority to prescribe mifepristone to providers who have signed Prescriber Agreements, even though other licensed health care professionals may be

trained to perform all the services necessary to safely provide medication abortion (Foster et al., 2015);

- A requirement that a woman using mifepristone sign an agreement stating that she will take the drug according to the label, even though the drug regimen described on the label is not the safest and most effective way to use the drug;
- A requirement that mifepristone be administered in a medical facility, despite research showing that offering women the option to self-administer the drug is safe and highly acceptable (Gold & Chong, 2015); and
- Restrictions on dispensation of the drug, requiring that it be dispensed in a medical facility – though several other countries permit pharmacy dispensation (Grossman & Goldstone, 2015) – and only by providers who have signed Prescriber Agreements.

Advocates contend there is strong evidence that these requirements are not commensurate with mifepristone's risks and that they do, in fact, create unnecessary barriers to patient access to the drug (Cleland & Smith, 2015).

Without those medically unsupported regulatory hurdles, a wider range of providers would be able to offer medication abortion, potentially increasing access for women who are currently not able to obtain abortion care.

This paper has explored some of the existing research on the medication abortion process. It is not meant to be an exhaustive literature review but rather an overview of current evidence and its impact on policy. Exchange of accurate scientific and clinical information between researchers and policy makers has the potential to help ensure that policies are grounded in science. Making the connection between policy and science is critical if we are to promote women's health through improved access to high-quality health care.

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APPENDIX A: MIFEPREX PRESCRIBER AGREEMENT

M I F E P R E X[®] (Mifepristone) Tablets, 200 mg **PRESCRIBER'S AGREEMENT**

We are pleased that you wish to become a provider of Mifeprex[®] (Mifepristone) Tablets, 200 mg, which is indicated for the medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period (see full prescribing information). Prescribing Information, Mifeprex Medication Guides and PATIENT AGREEMENT forms will be provided together with your order of Mifeprex.

Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below. If you oversee more than one office facility, you will need to list each facility on your order form prior to shipping the first order.

By signing the reverse side, you acknowledge receipt of the PRESCRIBER'S AGREEMENT and agree that you meet these qualifications and that you will follow these guidelines for use. You also understand that if you do not follow these guidelines, the distributor may discontinue distribution of the drug to you.

Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex. The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to these qualifications, you must provide Mifeprex in a manner consistent with the following guidelines.

- Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself.
- The patient's follow-up visit at approximately 14 days is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify Danco Laboratories in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an on-going pregnancy which is not terminated subsequent to the conclusion of the treatment procedure.
- While serious adverse events associated with the use of Mifeprex are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.
- Each package of Mifeprex has a serial number. As part of maintaining complete records for each patient, you must record this identification number in each patient's record.

Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

*MIFEPREX is a registered trademark of Danco Laboratories, LLC.

**MIFEPREX® (mifepristone) Tablets, 200 mg
For Oral Administration Only**

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following Mifeprex® use. No causal relationship between the use of Mifeprex and misoprostol and these events has been established. Before prescribing Mifeprex, inform the patient about the risk of these serious events and discuss the MEDICATION GUIDE and the PATIENT AGREEMENT. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if she experiences sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if she experiences abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol.

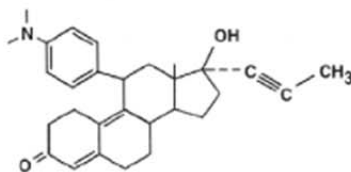
- **Atypical Presentation of Infection.** Patients with serious bacterial infections (e.g. *Clostridium sordellii*) and sepsis can present without fever, bacteremia or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis (see WARNINGS).
- **Bleeding.** Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding (see WARNINGS).

Patients should be advised to take their MEDICATION GUIDE with them if they visit an emergency room or another health care provider who did not prescribe Mifeprex, so that provider will be aware that the patient is undergoing a medical abortion.

DESCRIPTION

Mifeprex tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical and biconvex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11β-[p-(Dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is C₂₉H₃₅NO₂. Its structural formula is:



The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 192-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

PATIENT AGREEMENT
Mifeprex (mifepristone) Tablets

1. I have read the attached MEDICATION GUIDE for using Mifeprex and misoprostol to end my pregnancy.
2. I discussed the information with my health care provider (provider).
3. My provider answered all my questions and told me about the risks and benefits of using Mifeprex and misoprostol to end my pregnancy.
4. I believe I am no more than 49 days (7 weeks) pregnant.
5. I understand that I will take Mifeprex in my provider's office (Day 1).
6. I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3).
7. My provider gave me advice on what to do if I develop heavy bleeding or need emergency care due to the treatment.
8. Bleeding and cramping do not mean that my pregnancy has ended. Therefore, I must return to my provider's office in about 2 weeks (about Day 14) after I take Mifeprex to be sure that my pregnancy has ended and that I am well.
9. I know that, in some cases, the treatment will not work. This happens in about 5 to 8 women out of 100 who use this treatment.
10. I understand that if my pregnancy continues after any part of the treatment, there is a chance that there may be birth defects. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about my choices, which may include a surgical procedure to end my pregnancy.
11. I understand that if the medicines I take do not end my pregnancy and I decide to have a surgical procedure to end my pregnancy, or if I need a surgical procedure to stop bleeding, my provider will do the procedure or refer me to another provider who will. I have that provider's name, address and phone number.
12. I have my provider's name, address and phone number and know that I can call if I have any questions or concerns.
13. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.
14. I will do the following:
 - contact my provider right away if in the days after treatment I have a fever of 100.4°F or higher that lasts for more than 4 hours or severe abdominal pain.
 - contact my provider right away if I have heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours).
 - contact my provider right away if I have abdominal pain or discomfort, or I am "feeling sick", including weakness, nausea, vomiting or diarrhea, more than 24 hours after taking misoprostol.
 - take the MEDICATION GUIDE with me when I visit an emergency room or a provider who did not give me Mifeprex, so that they will understand that I am having a medical abortion with Mifeprex.
 - return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant.
 - return to my provider's office about 14 days after beginning treatment to be sure that my pregnancy has ended and that I am well.

Patient Signature: _____

Patient Name (print): _____

Date: _____

The patient signed the PATIENT AGREEMENT in my presence after I counseled her and answered all her questions. I have given her the MEDICATION GUIDE for mifepristone.

Provider's Signature: _____

Name of Provider (print): _____

Date: _____

After the patient and the provider sign this PATIENT AGREEMENT, give 1 copy to the patient before she leaves the office and put 1 copy in her medical record. Give a copy of the MEDICATION GUIDE to the patient.

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