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Research Protocol
ALTERNATIVE PROVISION OF MEDICATION ABORTION
VIA PHARMACY DISPENSING

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LIST OF ABBREVIATIONS

ACOG	The American Congress of Obstetricians and Gynecologists
AE	Adverse Event
CHP	Certified Healthcare Provider
CI	Confidence Interval
CFR	Code of Federal Regulations
CTCAE	Common Terminology Criteria for Adverse Events
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hCG	Human Chorionic Gonadotropin
HIPAA	Health Insurance Portability and Accountability Act of 1996
IRB	Institutional Review Board
LLC	Limited Liability company
Mcg	Micrograms
Mg	Milligrams
OCP	Ontario College of Pharmacists
PI	Principal Investigator
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
UC	University of California
UCSD	University of California San Diego
UCSF	University of California San Francisco
US	United States

PROTOCOL SYNOPSIS

TITLE	Alternative Provision of Medication Abortion via Pharmacy Dispensing
SPONSOR/PI	Daniel Grossman, MD
FUNDING ORGANIZATION	Fidelity Charitable
NUMBER OF SITES	4
RATIONALE	<p>The proposed study aims to investigate the feasibility, acceptability, and effectiveness of pharmacy dispensing of Mifeprex®; safety data will also be collected. The results of this study eventually could lead to changes in the Mifeprex® REMS that would improve access to legal, safe abortion services in the US.</p> <p>Trained pharmacists already successfully deliver care related for stigmatized health conditions, including sexually transmitted infections, family planning, and emergency contraception. In addition, pharmacy dispensing of mifepristone is already a reality in other countries, such as Australia, where it has improved access to medication abortion, particularly in rural areas (Grossman, 2015); pharmacy dispensing is also being implemented in Canada (OCP, 2017).</p> <p>Pharmacy dispensing of Mifeprex® by trained pharmacists could improve access to medication abortion for women. Pharmacy dispensing could allow women to bypass geographical, financial, or insurance obstacles to clinic-based care and receive abortion care earlier in pregnancy (Drey et al., 2006; D. A. Grossman, Grindlay, Buchacker, Potter, & Schmertmann, 2013; Jerman, Frohwirth, Kavanaugh, & Blades, 2017) and help to facilitate provision of medication abortion through telemedicine, reducing the disparity in access between rural and urban settings (D. Grossman, Grindlay, Buchacker, Lane, & Blanchard, 2011; D. A. Grossman et al., 2013). In light of a declining number of abortion providers in the US (Jones & Kooistra, 2011, Jones & Jerman, 2014), pharmacy dispensing could also help increase the number of clinicians willing and able to provide medication abortion by enabling them to avoid the associated costs and logistical challenges of stocking and dispensing the medication at their facilities.</p> <p>Pharmacy dispensing of mifepristone would not affect the standard of care or recommended clinical protocol for medication. Mifeprex® would still be prescribed to patients by clinicians who are certified prescribers of Mifeprex® following the current standard assessment of eligibility for medication abortion. The only difference in this study is that the patient would obtain the mifepristone directly from the pharmacist, rather than in a clinic facility. In most settings women go to a pharmacy for pain medications and anti-emetics, and sometimes for misoprostol.</p> <p>Home administration of Mifeprex® is now allowed under the updated Mifeprex® labeling (FDA, 2016a). Study participants will be told by the prescribing clinician when they should take the Mifeprex®, and participants will be contacted the following day to determine if they took the medication as prescribed.</p>

STUDY DESIGN	This is a phase 4 prospective cohort study.
PRIMARY OBJECTIVE	Our primary objective is to assess the feasibility of pharmacist dispensing of Mifeprex® by measuring pharmacist satisfaction and the proportion of pharmacists who refuse to dispense the medication to patients.
SECONDARY OBJECTIVES	Secondary objectives include assessing patient satisfaction with the pharmacy-dispensing model; describing clinical outcomes, including effectiveness and adverse events, with pharmacist-dispensed Mifeprex®; and comparing pharmacist knowledge about medication abortion before and after the intervention.
NUMBER OF SUBJECTS	250 patients and 50 pharmacists
SUBJECT SELECTION CRITERIA	<p><u>Inclusion Criteria:</u></p> <p>All pharmacists providing services at one of the study pharmacies during the study; and</p> <p>English- or Spanish-speaking women age 15 or older seeking medication abortion through 70 days' gestation and eligible for Mifeprex® at a study clinical site. Participants must be willing and able to participate in the study, including being willing to go to the study pharmacy to obtain mifepristone.</p> <p><u>Exclusion Criteria:</u></p> <p>We will exclude women who are not pregnant or not seeking medication abortion, under the age of 15, or who have contraindications for medication abortion.</p>
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Oral Mifeprex® 200 mg followed by misoprostol 800 mcg administered buccally (at 24-48 hours following mifepristone) or vaginally (as soon as immediately after Mifeprex®)
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	<p>The duration of the study will be 24 months. Most patient subjects' participation will end after completing the Day 14 Survey approximately 2 weeks after taking Mifeprex®. Adverse events (AEs) will be captured up to 6 weeks after Mifeprex®, and any ongoing will be followed until resolution.</p> <p>Pharmacists' participation in the study will continue throughout the study, although data will be collected from them only at specific time points before launching the study and at the end of the study.</p>
CONCOMITANT MEDICATIONS	<p>Allowed: Any</p> <p>Prohibited: None</p>
EFFICACY EVALUATIONS	The UCSF study team will train sites on standardized recruitment and consent procedures and have regular communication with study clinics and

	pharmacies to provide technical assistance and check on progress of study. Data collection tools and procedures will be pilot tested before implementation. Data will also be monitored periodically to ensure that data collection, coding, and management procedures are being conducted according to protocol and ethical guidelines.
PRIMARY ENDPOINT	The primary outcome will be <u>feasibility</u> of dispensing of Mifeprex® by pharmacists, measured by pharmacist satisfaction and the proportion of pharmacists refusing to dispense.
SECONDARY ENDPOINTS	Secondary outcomes will include <u>patient satisfaction</u> and <u>clinical outcomes</u> of patients who receive Mifeprex® dispensed in the pharmacy.
OTHER EVALUATIONS	N/A
SAFETY EVALUATIONS	Data abstraction of electronic health records will provide clinical data for analysis. We will conduct quantitative analyses of clinical data and the PI will track all reports of adverse events and serious adverse events to monitor safety.
PLANNED INTERIM ANALYSES	No formal interim analysis is planned. Serious and unexpected adverse events will be monitored on an ongoing basis throughout the study.
STATISTICS Primary Analysis Plan	We will use descriptive analyses using chi-square and <i>t</i> tests where appropriate to assess pharmacist satisfaction and patient satisfaction with the model and clinical outcomes of patient participants.
Rationale for Number of Subjects	<p>We aim to recruit up to 250 patients for this pilot study, which is a feasible sample at the study sites. With a sample size of 250, if the proportion of patients with a complete abortion is 95%, the 95% confidence interval of that proportion will be +2.7%. Abortion completion is an important clinical outcome.</p> <p>We aim to survey all the pharmacists at the study sites, up to 50. This sample size will be determined by the number of pharmacists at the study sites.</p>

1 BACKGROUND

Medical termination of intrauterine pregnancy, also known as medication abortion, is a safe and effective alternative to surgical abortion (vacuum aspiration). Mifeprex® (generic: mifepristone), which is a progestin antagonist that competitively interacts with progesterone at progesterone-receptor sites, used together with misoprostol is the gold standard regimen for medication abortion. In studies performed in the United States up to 70 days gestation using this dosing regimen, 97.4% of patients reportedly had a complete abortion (FDA, 2016a). Another 2.6% received surgical intervention, or vacuum aspiration, for reasons such as ongoing pregnancy, patient request, bleeding, medical necessity and incomplete expulsion.

Medication abortion up to 70 days gestation with mifepristone 200 mg orally followed by misoprostol 800 mcg administered via the buccal or vaginal route has a favorable safety profile. Although serious and sometimes fatal infections have been reported with this treatment, this

complication is very rare; only 8 deaths related to sepsis have been reported among almost 3 million uses of the medication (FDA, 2011). Uterine bleeding requiring medical or surgical intervention is also a known complication of the treatment. Heavy bleeding requiring surgical treatment occurs in approximately 1% of patients, and blood transfusion is required in <0.1%. Adverse events that are more common include nausea, vomiting, weakness, fever/chills, headache, diarrhea and dizziness (FDA, 2016a).

In March 2016, the Food and Drug Administration (FDA) approved an updated label for Mifeprex® to reflect recent research published since the drug's original approval in 2000 (FDA, 2016a). The approved dosing regimen includes oral mifepristone (200 mg) followed by a dose of misoprostol (800 mcg) administered buccally 24-48 hours later. The changes made to the label included a more effective dosing regimen containing less mifepristone (200 mg instead of 600 mg) and more misoprostol (800 mcg instead of 400 mcg) via the buccal route, extension of the gestational age limit for treatment from 49 to 70 days, removal of the recommendation for in-person follow-up, removal of language indicating that the prescriber must be a physician, and elimination of the requirement to report nonfatal adverse events to Danco Laboratories, LLC, the drug's US distributor, and the FDA.

In addition, the updated label no longer requires that Mifeprex® or misoprostol be taken in the facility where they are dispensed. A systematic review of nine studies with over 4,500 participants compared outcomes of those who took misoprostol at home to those who took it in a clinical setting (Ngo, Park, Shakur, & Free, 2011). Complete abortion and complication rates were not different between the groups, but women who used misoprostol at home were more likely to be satisfied and recommend the method to a friend. In one US study of 400 women at six sites, 32% chose to take mifepristone at home, and complete abortion rates were similar between those who took the drug in the clinic and at home (96%-97%) (Chong et al., 2015). Among those who took mifepristone at home, 82% reported taking the medication at the time they planned with their provider, and no participant took it after 63 days gestation which was the gestational age limit at the time of the study.

In addition to buccal administration, misoprostol 800 mcg is commonly administered vaginally in an off-label regimen for medication abortion, which is also recommended by the American College of Obstetricians and Gynecologists (ACOG, 2014). This regimen allows for a shorter interval between the two medications, which some patients prefer. Up to 63 days gestation, vaginal misoprostol given at the same time as mifepristone results in complete abortion in approximately 95% of cases (Creinin et al., 2007). Another common regimen involves administering misoprostol 800 mcg vaginally 6-8 hours after mifepristone, which has a complete abortion rate of 95.8% up to 63 days gestation and fewer side effects compared to a 24-hour dosing interval (Creinin et al., 2004).

Numerous studies performed in the US and other countries have demonstrated that medication abortion has a high level of acceptability for a majority of women seeking pregnancy termination (Beckman & Harvey, 1997; Christin-Maitre, Bouchard, & Spitz, 2000). In a meta-analysis of approximately 4,500 patients who underwent pregnancy termination with mifepristone and misoprostol, over 85% of women were satisfied with the experience (Ngo et al., 2011). Medication abortion accounts for a growing share of US abortions, from 17% of non-hospital procedures in 2008 to 31% in 2014 (Jones, 2017). Medication abortions accounted for 45% of all abortions up to nine weeks gestation in 2014, up from 26% in 2008 (Jones, 2017).

Some evidence suggests that improved access to mifepristone is associated with a reduction in the proportion of abortions performed in the second trimester, which is important from a public health perspective because later abortion is associated with a significantly increased risk of complications and death compared to early abortion (Zane et al., 2015). In one study in Iowa, development of a program providing medication abortion using telemedicine was associated with a significant increase in the proportions of abortion that were performed with medication. After controlling for other factors, women seeking abortion in the two years after telemedicine was introduced had a significantly higher odds of obtaining a first-trimester abortion compared to the two years prior (D. A. Grossman et al., 2013). Conversely, in Texas, second-trimester abortion increased by 27% in the year after restrictions on access to abortion were imposed, including limitations on the use of medication abortion that led to a 70% decline in use of this method (D. Grossman, 2017).

Despite the increasing use of medication abortion, there is evidence that some women face barriers accessing this method, and this can be particularly distressing when they have a strong preference for the method (Baum, White, Hopkins, Potter, & Grossman, 2016). In particular, the closure of abortion facilities across the country (Deprez, 2016), which has increased the distance women must travel to access abortion care, may make it harder to access medication abortion. The longer travel distances, which increase the cost and logistical difficulty of getting to a clinic, may create delays that push women past the gestational age limit for medication abortion (Baum et al., 2016; Fuentes et al., 2016).

Medication abortion in the US is primarily offered by existing abortion providers. Uptake of medication abortion provision among private physicians has been less than expected—especially in areas not served by providers of surgical abortion. In 2005, there were only four providers of Mifeprex® medication abortion that were located more than 50 miles from any surgical abortion provider (Finer & Wei, 2009). One reason for the lack of uptake among private physicians may relate to the Mifeprex® Risk Evaluation and Mitigation Strategy (REMS) program.

The Mifeprex® REMS program has three components (FDA, 2016b):

1. Prescribers must be certified with the program by completing the Prescriber Agreement Form
2. Patients must sign a Patient Agreement Form.
3. Mifeprex® must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices and hospitals, by or under the supervision of a certified prescriber.

This third component requires that prescribers stock the medication in their facilities in order to dispense it on site. A qualified clinician who has not completed the certification process and arranged to stock the drug in his or her office cannot provide timely medication abortion care to a woman who presents unexpectedly. Consequently, treatment of such a patient would be delayed, which might increase her medical risks (Bartlett et al., 2004; Mifeprex REMS Study Group, 2017).

We recently explored this issue in a survey of practicing obstetricians-gynecologists (Grossman et al., 2017). In 2016-2017, we performed a survey with a representative sample of Fellows of the American College of Obstetricians and Gynecologists. The survey was sent by email with an online link, and non-responders were mailed paper surveys. 1,284 currently practicing Fellows responded to the survey (response rate 54%). 99% reported seeing patients of reproductive age; among these, 1,155 were included in this analysis. 75% reported having a patient in the prior year who needed or wanted an abortion. Only 23% (95% CI 21%-25%) reported performing an abortion in the prior year; 10% provided surgical and medication abortion, 9% surgical only, and 4% medication only.

Among those not providing medication abortion, 19% said they would provide the method if they could write a prescription for mifepristone and their patients could obtain the medication at a pharmacy. An additional 18% said they were unsure if they would provide medication abortion in this scenario. Our findings suggest that the proportion of obstetrician-gynecologists providing medication would at least double (from 14% to 29%) if the dispensing restriction in the REMS were removed and physicians could write a prescription for Mifeprex® that could be dispensed at a pharmacy.

Given this evidence that the dispensing requirement represents a barrier to access, we propose to perform a study of the feasibility of pharmacy dispensing of Mifeprex®. For this study, all clinical activities will remain consistent with the current standard of care and Mifeprex® REMS program except for the dispensing of Mifeprex®. In particular, patients will be evaluated for all contraindications to the method according to the label, and they will sign the Patient Agreement Form. A clinician who has completed the Prescriber Agreement Form will write a prescription for Mifeprex® 200 mg for the eligible patient. The patient will then go to a designated pharmacy to fill the prescription, where it will be dispensed by a trained pharmacist. The patient will then take the Mifeprex® at the time indicated by the prescribing clinician. Patients will be contacted on Day 2 and Day 14 to complete surveys about their experience, and they will undergo standard clinical follow-up. In addition, we will perform surveys and interviews with pharmacists before and after initiating the study, as well as monitor the number of pharmacists who refuse to dispense Mifeprex® at the study pharmacies.

2 STUDY RATIONALE

The proposed study aims to investigate the feasibility, acceptability, and effectiveness of pharmacy dispensing of Mifeprex®; safety data will also be collected. Because of the data reviewed above that indicate that the dispensing restrictions on Mifeprex® limit the number of providers of medication abortion, the results of this study eventually could lead to changes in the Mifeprex® REMS that would improve access to legal, safe abortion services in the US.

Trained pharmacists already successfully deliver care related to stigmatized health conditions, including sexually transmitted infections, family planning, and emergency contraception. In addition, pharmacy dispensing of mifepristone is already a reality in other countries, such as Australia, where it has improved access to medication abortion, particularly in rural areas (D. Grossman & Goldstone, 2015); pharmacy dispensing of mifepristone is also being implemented in Canada (OCP, 2017).

Pharmacy dispensing of Mifeprex® by trained pharmacists could improve access to medication abortion for women in a number of important ways. Pharmacy dispensing in the US could allow women to bypass geographical, financial, or insurance obstacles to clinic-based care and receive abortion care earlier in pregnancy (Drey et al., 2006; D. A. Grossman et al., 2013; Jerman et al., 2017) and help to facilitate provision of medication abortion through telemedicine, reducing the disparity in access between rural and urban settings (D. Grossman et al., 2011; D. A. Grossman et al., 2013). In light of a declining number of abortion providers in the US (Jones & Kooistra, 2011, Jones & Jerman, 2014), pharmacy dispensing could also help increase the number of clinicians willing and able to provide medication abortion by enabling them to avoid the associated costs and logistical challenges of stocking and dispensing the medication at their facilities.

Pharmacy dispensing of mifepristone would not affect the standard of care or recommended clinical protocol for medication abortion in terms of the medication, dosage, timing, and follow-up care. Mifeprex® would also still be prescribed to patients by clinicians who are certified prescribers of Mifeprex® following the current standard assessment of eligibility for medication abortion. The only difference in the provision model to be evaluated in this study is that the patient would obtain the mifepristone directly from the pharmacist, rather than in a clinic facility. This model would likely not add an additional step for most women, since in most settings they go to a pharmacy for pain medications and anti-emetics, and sometimes for the misoprostol.

As noted above, home administration of Mifeprex® is now allowed under the updated Mifeprex® labeling (FDA, 2016a). Study participants will be told by the prescribing clinician when they should take the Mifeprex®, and participants will be contacted the following day to determine if they took the medication as prescribed.

2.1 Risk / Benefit Assessment

Potential medical risks to medication abortion patients participating in the study are the same as those they would incur by undergoing a medication abortion outside of the study. Because they are undergoing the same clinical assessment prior to obtaining medication abortion, there is no reason to believe that dispensing of Mifeprex® by pharmacists will increase the risks of the procedure. In addition, patients will be given detailed information about warning signs, such as heavy bleeding that should prompt them to seek care.

The main risk related to the study is that the patient may not take Mifeprex® at the time they are told to—and potentially that they may take it later than 70 days gestation. There is also a risk that they may give the medication to someone else. It should be noted that these risks exist currently since the Mifeprex® label allows them to take the medication at home, and there is no reason to believe that the risks will increase due to the study. Patients will also be surveyed on Day 2 to be certain they took the Mifeprex® as instructed. Women who do not return for follow-up at the clinic will be contacted by phone or email to obtain information about abortion completion and adverse events. Other potential risks include any social risks involved if information they reveal about their seeking an abortion or other sensitive issues were to be disclosed outside of the research.

There are minimal risks to pharmacists for participating in the study. Pharmacists who refuse to dispense Mifeprex® will not have any consequences to their employment. The participating pharmacies will not be identified in any publications. There is a potential risk that participating pharmacies will experience anti-abortion picketers if participation in the study becomes known, and this has been discussed with the management of each pharmacy.

These data will be used to assess whether it is feasible for pharmacists to dispense Mifeprex®, which could help to improve access to early abortion.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the study is to assess the feasibility of pharmacist dispensing of Mifeprex®. Our primary outcome will be feasibility measured by pharmacist satisfaction with dispensing Mifeprex® and the proportion of pharmacists who refuse to dispense the medication to patients.

3.2 Secondary Objectives

The secondary objectives include to assess patient satisfaction with the pharmacy-dispensing model, to describe clinical outcomes, and to compare pharmacist knowledge about medication abortion before and after the intervention. Secondary outcomes include patient satisfaction with the pharmacy-dispensing model; clinical outcomes, including effectiveness and adverse events, with pharmacist-dispensed mifepristone; and pharmacist knowledge about medication abortion before and after the intervention.

3.3 Study Overview

We will conduct a prospective cohort study of patients receiving Mifeprex® dispensed by pharmacists after undergoing standard clinical evaluation. Women participating in this study will obtain Mifeprex® and misoprostol from the pharmacy instead of in the clinic. All clinical procedures will continue to be performed as they currently are. The only difference is that the Mifeprex® will be dispensed by a pharmacist in the study pharmacy rather than by the clinician in the clinic.

4 CRITERIA FOR EVALUATION

4.1 Primary Endpoint

Feasibility of the pharmacy dispensing model will be assessed in quantitative analyses of the pharmacist survey responses and their willingness to dispense. In addition, feasibility will be assessed in qualitative analyses of open-ended interviews with pharmacists about dispensing Mifeprex® in pharmacies.

4.2 Secondary Endpoints

Acceptability and satisfaction with the pharmacy dispensing model among patients will be assessed primarily through surveys with patient participants using quantitative and qualitative analyses. Clinical outcomes, including effectiveness and adverse events, with pharmacist-dispensed Mifeprex® will be assessed using quantitative data abstracted from patient medical records. Pharmacist knowledge about medication abortion before and after the intervention will be assessed through quantitative analyses of surveys completed by the pharmacists.

4.3 Safety Evaluations

Data abstraction of electronic health records will provide clinical data for analysis. We will conduct quantitative analyses of clinical data, and the PI will track all reports of serious and unexpected adverse events to monitor safety.

5 STUDY SITES

The study will be performed at three sites in California and one site in Washington State. Recruiting will take place at the study clinic site, and Mifeprex® dispensing will take place at an associated study pharmacy site. Each site and site principal investigator (PI) are listed below:

5.1 Mt. Zion Women's Options Clinic, University of California San Francisco (UCSF)

Dr. Karen Meckstroth will serve as the site PI and will oversee all study activities at this site. The study pharmacy site is a community pharmacy which is not affiliated with UCSF.

5.2 Women's Health Services at University of California San Diego (UCSD)

Dr. Sarah Averbach will serve as the site PI and will oversee all study activities at this site. The study pharmacy site is a UCSD outpatient pharmacy located in the same building as the study clinic site.

5.3 Obstetrics and Gynecology Family Planning Clinic at University of California Davis (UC Davis)

Dr. Mitchell Creinin will serve as the site PI and will oversee all study activities at this site. The study pharmacy site is a UC Davis outpatient pharmacy.

5.4 University of Washington, Seattle

Dr. Sarah Prager will serve as the site PI and will oversee all study activities at this site. The study pharmacy site is a University of Washington-affiliated pharmacy located in the same building as the study clinic site.

6 SUBJECT SELECTION

6.1 Study Population

Patient participants will include women age 15 or older seeking medication abortion through 70 days (10 weeks) gestation and eligible for Mifeprex® at a study clinical site. The study will include women who are eligible for medication abortion and are willing and able to consent to participation, including being willing to go to the study pharmacy to obtain Mifeprex®. We will include minors age 15-17 because their perspectives on this service are important; in addition the study intervention is very simple and not burdensome. In both California (Cal Family Code 6920-6929) and Washington State (RCW 9.02.100 (2)), adolescent minors are able to give consent to an abortion without parental consent. UCSF's and University of Washington's Institutional Review Boards (IRBs) consider legal ability to consent for care as the standard for ability to consent to participate in research. We include only women who communicate in English or Spanish to ensure that our study team can communicate clearly with participants and they can understand and consent to study activities. Participants must also be willing and able to be contacted by email, telephone, or text message as those are our planned strategies for data collection.

Pharmacist participants will include any pharmacist working at one of the study pharmacy sites during the study who is willing to participate in the study.

6.2 Inclusion Criteria

1. Women seeking and eligible for medication abortion with Mifeprex® and misoprostol up to 70 days' gestation as determined by the site
2. Women age 15 or older
3. English or Spanish speaking
4. Written informed consent obtained from subject
5. Ability for subject to comply with the requirements of the study, including being willing to go to the study pharmacy to obtain Mifeprex® within 48 hours and before passing the 70-day gestational age limit
6. Willing and able to be contacted by email or telephone/text message

6.3 Exclusion Criteria

1. Not pregnant
2. Not interested in medication abortion
3. Under age 15
4. Contraindications to medication abortion as determined by the site
5. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible.

7.1 Allowed Medications and Treatments

All concurrent medications will be allowed. All patient participants will take misoprostol as part of the medication abortion regimen, and most will take ibuprofen and/or an oral narcotic for analgesia. Some patients may be prescribed prophylactic antibiotics such as doxycycline or azithromycin. All medications deemed necessary by the treating clinician will be allowed.

7.2 Prohibited Medications

As noted in the Mifeprex® label, although specific drug or food interactions with Mifeprex® have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum concentrations of Mifeprex®). Mifeprex® should be used with caution in patients currently or recently treated with CYP 3A4 inhibitors; however, these medications will not be prohibited.

CYP 3A4 inducers such as rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (such as phenytoin, phenobarbital, carbamazepine) may induce Mifeprex® metabolism (lowering serum concentrations of mifepristone). Whether this action has an impact on the efficacy of the regimen is unknown. As with all patients, it is important to verify that treatment was successful. Again, CYP 3A4 inducers will not be prohibited.

Based on in vitro inhibition information, coadministration of Mifeprex® may lead to an increase in serum concentrations of drugs that are CYP 3A4 substrates. Due to the slow elimination of Mifeprex® from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when Mifeprex® is administered with drugs that are CYP 3A4 substrates and have a narrow therapeutic range; however, drugs that are CYP 3A4 substrates will not be prohibited.

8 STUDY INTERVENTION

8.1 Method of Recruitment for Patients

When a patient presents at the clinical site requesting abortion, she will be evaluated in the standard manner at that site to determine if she is eligible for medication abortion. All standard procedures for medication abortion at the site will be performed by the site clinician, including completing the abortion consent and Danco Patient Agreement.

If she is eligible for medication abortion, after all procedures other than dispensing medications, she will be given a brief description of the study by the clinician and asked if she is interested in participating. A flyer will be posted in the clinic waiting room and/or examination room to inform patients about the study (see Appendix A). She will be told that the study will involve obtaining all medications at the pharmacy, rather than obtaining some medications at the clinic and some at the pharmacy. She will be told that only a limited number of pharmacies are able to dispense Mifeprex®. She will be told that there will be no additional cost to her for participating in the study; if for some reason the participant's insurance will not cover the cost of Mifeprex® because it is dispensed in the pharmacy, the study will cover that cost. She will be told that participation also involves completing an online survey the following day and another survey approximately 2 weeks later (both of which may also be performed over the phone if she prefers). If the patient is interested and eligible to participate in the study, she will undergo signed informed consent (Appendix B), HIPAA Authorization (Appendix O), and contact information and preferences will be obtained (on either a paper form or on an iPad; Appendix C). Women who do not return for follow-up at the clinic will be contacted by phone or email to obtain information about abortion completion and adverse events.

Participation in the study ends 6 weeks after the initial visit unless there is an ongoing unexpected adverse event or serious adverse event requiring follow-up. Patients will be considered lost to follow-up if they have not been contacted to complete the follow-up survey AND they did not return to the clinic site by 6 weeks after the medication abortion visit.

8.2 Method of Recruitment for Pharmacists

All pharmacists at the study pharmacies will be eligible. Pharmacists will be invited to participate in the survey/interview prior to initiating the study and at the end of the study by email/flyer and through face-to-face visits by study staff (see draft email/flyer in Appendix D). Informed consent will be obtained from pharmacists before completing the survey and interview (Appendix E and F). Interviews will be scheduled at a convenient time when they do not interfere with the pharmacists' work.

8.3 Formulation of Test and Control Products

8.3.1 Formulation of Test Product

Mifeprex®, oral: 200 mg followed by misoprostol 800 mcg administered either buccally (at 24-48 hours following Mifeprex®) or vaginally (as soon as immediately after Mifeprex®)

8.3.2 Packaging and Labeling

The pharmacy site will provide Mifeprex® in its standard packaging (blister pack of one 200 mg tablet). The medication will be labeled with the patient's information according to standard procedures prior to dispensing to the patient.

8.4 Supply of Study Drug at the Site

Mifeprex® will be procured from Danco Laboratories, LLC, by a licensed physician who has signed the Danco Prescriber's Agreement enabling provision of the drug under the current FDA guidelines and who is already ordering Mifeprex® for distribution at the clinic. This physician is also referred to as a Certified Healthcare Provider (CHP) in the Mifeprex® REMS. If the CHP and the pharmacy site are not in the same health care system, these parties will develop a legally compliant method for transferring a limited supply of Mifeprex® that is purchased by the CHP or

the CHP's employer-clinic, which will be used by the pharmacy site when dispensing Mifeprex® to patients of the CHP who are participating in this study. The pharmacy site will ensure that the transferred Mifeprex® stock is kept separate from all other drug inventories maintained by the pharmacy, and will utilize a distribution system that is secure, confidential, and controlled with regard to storage, handling, shipping, and return. Each site PI will initially transfer 5 units of the medication (Mifeprex® 200 mg) to the pharmacy and monitor use each week to replenish this stock.

In settings where the pharmacy is part of the same health care system (such as a university-based system), the medication is already ordered by the pharmacy and will simply be retained in the pharmacy rather than being transferred to the CHP. All study Mifeprex® transferred to or retained at the pharmacy site will be recorded on the Investigational Drug Accountability Log.

8.4.1 Dosage/Dosage Regimen and Administration

Subjects will receive 200 mg of Mifeprex® to be taken orally at the time indicated by the patient's clinician. This will be followed by misoprostol 800 mcg administered either buccally (at 24-48 hours following mifepristone) or vaginally (as soon as immediately after Mifeprex®; beyond 56 days gestation, patients will be strongly encouraged to wait at least six hours before vaginal administration of misoprostol).

8.4.2 Storage

Per the directions on the product label, Mifeprex® will be stored at room temperature (15 to 30°C or 59 to 86°F) in the pharmacy.

8.5 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff based on the records maintained by the pharmacists at the pharmacy site. The number of study drugs transferred to the pharmacy site, dispensed and returned by the subject will be recorded on the Investigational Drug Accountability Log. The study PI will verify these documents throughout the course of the study.

8.6 Measures of Treatment Compliance

Participant patients will be contacted on Day 2 to complete the Day 2 Survey, which is detailed below in section 10.2. As part of this survey, patients will be asked if and when they took the Mifeprex®. If they have not yet taken the Mifeprex®, they will be asked when they plan to take it, and they will be contacted after that date to complete the Day 2 Survey. If they obtained the Mifeprex® in the study pharmacy but decided not to take it, they will be asked whether they returned it to the study clinic or pharmacy as instructed.

9 STUDY PROCEDURES AND GUIDELINES

The UCSF study team will train sites on standardized recruitment and consent procedures and have regular communication with study clinics and pharmacies to provide technical assistance and check on progress of the study. Data collection tools and procedures will be pilot tested before implementation. Data will also be monitored periodically to ensure that data collection, coding, and management procedures are being conducted according to protocol and ethical guidelines.

Prior to conducting any study-related activities, written informed consent must be signed and dated by the subject. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

All clinical assessments will be documented in the medical record, and this information will be abstracted from the medical record for analysis.

9.1.1 Concomitant Medications

Concomitant medications such as antibiotics and analgesics will be documented at each clinical visit, and this information will be abstracted from the medical record.

9.1.2 Demographics

Demographic information (age, parity, race, and ethnicity) will be recorded as part of the initial visit and will be abstracted from the medical record (see list of variables to be abstracted in Appendix G). The site PI will supervise the data abstraction and replace the name with the Study ID prior to transferring the data to the UCSF research team. Demographic information will also be collected on the Day 2 Survey (see section 10.2).

9.1.3 Medical History

At the initial visit, the following will be recorded in the medical record: date of service, gestational age by ultrasound and date of ultrasound, past medical history, current medications, blood pressure, weight, height, and medications prescribed or dispensed (Mifeprex® 200 mg, misoprostol 800 mcg, antibiotics, analgesics, other). At any follow-up visits, unusual symptoms such as heavy bleeding, pain or fever will be recorded, as well as any treatment given. Women will also be asked if they sought care elsewhere since the prior visit, and if so, what treatment, if any, they were given.

9.1.4 Physical Examination

Blood pressure, weight, height, and ultrasound data will be collected at the initial visit. A targeted physical examination will be performed at the clinic site according to their current practice.

9.1.5 Vital Signs

Vital signs will be recorded at each clinical encounter.

9.1.6 Ultrasound

Ultrasound may be performed at the initial visit to determine gestational age of the pregnancy (if it is not performed at the clinic site, the date and result of an outside ultrasound must be documented). Ultrasound may be performed at a follow-up visit to determine whether the abortion is complete or incomplete or if there is an ongoing pregnancy.

9.1.7 Other Clinical Procedures

Patients may undergo uterine aspiration in case of heavy bleeding, incomplete abortion or ongoing pregnancy. This procedure will be detailed in the medical record.

9.1.8 Adverse Events

We will track adverse events (AEs) as described in section 11.

9.2 Clinical Laboratory Measurements

9.2.1 Pregnancy Test

Women will be presenting for pregnancy termination, so pregnancy will be confirmed as part of the visit prior to recruitment, consent, and enrollment.

9.2.2 Hemoglobin

Most patients will have hemoglobin measured in the clinic, and this result with the date of the test will be abstracted from the medical record.

9.2.3 Serum human chorionic gonadotropin (hCG)

Some patients will have serum hCG measured on the day of Mifeprex® administration and again approximately 8 days later to assess for completion of the abortion. These results with the date of the tests will be abstracted from the medical record.

10 ACTIVITIES BY DAY –PATIENTS

10.1 Day 1

This is the day the patient participant is enrolled in the study. Patients choosing medication abortion will undergo standard assessment, including an ultrasound for gestational age assessment, if it has not yet been performed, and counseling. Once women have signed the Danco Patient Agreement and any other specific consent forms for the site, they will be assessed for eligibility to participate in this study and undergo the informed consent process for this study (Appendix B). Contact information and contact preferences will also be obtained (on either a paper form or on an iPad; Appendix C). Study participants will be given a prescription for Mifeprex® 200 mg, misoprostol 800 mcg, and any other necessary medications (or the prescriptions will be electronically transmitted), as well as information about when and how to take the medications. At the pharmacy, the pharmacist will review the prescription and dispense Mifeprex® 200 mg (1 tablet) and misoprostol 200 mcg (4 tablets) as ordered. The lot number of all medications will be recorded in the standard fashion, and the dispensing pharmacist will also record the dispensing of the study medication in the Investigational Drug Accountability.

10.2 Day 2 Survey

On the following day, patient participants will be sent by email or text message, depending on their preference, a link to an online survey about their experience obtaining the medications, as well as to collect sociodemographic information (see Day 2 survey, Appendix H). Participants will be asked to complete the survey after going to the pharmacy to obtain Mifeprex®. If a participant prefers, or if she does not respond to the email link, she may be contacted by telephone to complete the survey over the phone or sent reminders by text message. The survey will focus on her experience in the pharmacy, including how she was treated and the information she received, as well as her experience taking the Mifeprex®. If the participant went to a pharmacy that was not her usual pharmacy, we will ask about her perspective on having to go to a different pharmacy. We will also collect information about if and when the Mifeprex® and misoprostol and if the Mifeprex® might have been diverted to another person. If they do not respond to the survey by Day 4, participants will be contacted up to three times (each day for three subsequent days to complete the survey). If a participant has decided not to proceed with medication abortion (because she has decided to have a surgical abortion or continue the pregnancy or because she needs more time to decide), she will be encouraged to complete the Day 2 survey, where this information will be captured. If a woman

obtained the Mifeprex® and/or misoprostol and has decided not to take the medication(s), she will be asked to return them to the pharmacy or the clinic.

10.3 Clinical follow-up

Women undergoing medication abortion generally undergo clinical follow-up to ensure that the abortion is complete. This may include a follow-up visit or a phone call from clinic staff approximately 7-14 days after the initial visit. In some cases, serum hCG may be measured on the day of Mifeprex® administration and again approximately 8 days later to assess for completion of the abortion. No study-related activities will be performed as part of this clinical follow-up. Management of incomplete abortion without hemorrhage will be done according to the standard practice at the site, and may include expectant management, an additional dose of misoprostol, or vacuum aspiration. Participants with ongoing pregnancy will be managed according to the standard practice at the site, and may include an additional dose of misoprostol, repeating Mifeprex® and misoprostol or vacuum aspiration. No study activities will take place at this visit, although clinical information recorded at this visit will be later abstracted from the patient's record (see section 9.1).

10.4 Day 14 Survey

On Day 14 after the initial clinic visit, patient participants will be sent by email or text message, depending on their preference, a link to an online survey about their overall satisfaction with the medication abortion process and to obtain information about whether the abortion has been completed (see Day 14 Survey, Appendix I). If a participant prefers, or if she does not respond to the email link, she may be contacted by telephone to complete the survey over the phone or sent reminders by text message. If the participant is unsure if the abortion is complete, we will ask for permission to contact her one week later. If they do not respond to the survey, participants will be contacted up to three times (each day for three subsequent days to complete the survey).

10.5 Data Abstraction

As noted above in section 9, de-identified data about the clinical visits of participants consenting for the study will be abstracted from the electronic medical record system of the participating sites. This includes clinical information including demographics (age, parity, race, ethnicity), initial visit information (date of service, gestational age, past medical history, medications, laboratory values), and follow-up visit information (date of service, treatment given, symptoms, outcome of abortion, adverse events, and other follow-up care). The site PI will perform a chart review for each participant 6 weeks after enrollment. De-identified data will be entered into a Qualtrics or REDCap electronic form (see Appendix G for the variables that will be abstracted). As noted above, the site PI will supervise the data abstraction and replace the participant name with the Study ID prior to transferring the data to the UCSF research team.

11 EVALUATIONS – PHARMACISTS

11.1 Baseline Survey/Interview

Each of the pharmacists at the study sites will be invited to participate in a survey and interview prior to the initiation of Mifeprex® dispensing. This survey and interview will focus on baseline knowledge of medication abortion, comfort with dispensing Mifeprex®, anticipated challenges of dispensing Mifeprex®, and whether the respondent plans to refuse to participate in Mifeprex® dispensing (and why). The survey may be completed on paper or online (see Appendix J), and the pharmacists will provide verbal or click-through consent (Appendix F). The interview, which may be performed in person or over the phone and will be recorded if participants agree, will allow for collection of qualitative data about their perceptions of implementing the new service (Appendix

K). Verbal consent will be obtained prior to the interview, as well as consent to record the interview (Appendix E).

11.2 Monthly Assessments

Each month after initiating the study, research staff at UCSF will contact the supervising pharmacist at each pharmacy site to assess the number of pharmacists working at the site, whether any pharmacist has started to dispense Mifeprex®, and whether any pharmacist has stopped dispensing Mifeprex®.

11.3 End-line Survey

Each of the pharmacists at the study sites will be invited to participate in a survey and interview at the end of the study. This survey and interview will focus on knowledge of medication abortion, comfort with dispensing Mifeprex®, experienced challenges of dispensing Mifeprex®, and whether the respondent refused to participate in Mifeprex® dispensing at any point (and why). Respondents who report having refused to dispense Mifeprex® will be asked about whether patients were referred to another pharmacist who was able to dispense, and if so, how that process worked. The survey may be completed on paper or online (see Appendix L), and the pharmacists will provide verbal or click-through consent (Appendix F). The interview, which may be performed in person or over the phone and will be recorded if participants agree, will allow for collection of qualitative data about their perceptions of implementing the new service (Appendix M). Verbal consent will be obtained prior to the interview, as well as consent to record the interview (Appendix E).

12 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

12.1 Adverse Events

Adverse Events (AEs) are to be reported only for untoward medical events that occur in participants after they have enrolled in the study. Only new untoward events, or a worsening of an existing condition, are considered AEs. Conditions that were present before enrollment into the study, and that remain stable or improve during the study, are not considered AEs. Untoward events that seem clearly unrelated to the study intervention, such as bone fractures or lacerations sustained during car accidents, will also be reported as AEs or SAEs.

Information regarding AEs or SAEs may be first obtained by the clinical or study staff, as both will communicate with the participant at her visits and by phone.

Details about each AE or SAE will be recorded on an AE/SAE Form (Appendix N). This form will require the following information to be collected: diagnosis, onset date, resolution date, source of information, severity, treatment given, relationship to the study, action taken, and comments.

The PI will determine the relationship of the AE to study treatment as definitely related, probably unrelated, possibly related, or unrelated; and the severity of the AE as mild, moderate or severe. For AEs or SAEs that have not resolved at the time of learning of the event, the study team will monitor the event until the event is resolved or the study is completed.

The PI is also responsible for reporting all AEs to all relevant Institutional Review Boards (IRBs). All AEs that are related to the study and are serious or affect IRB approval will be reported by the PI to the relevant IRBs according to IRB requirements. UCSF requires that an internal (on-site) AE that the PI determines to be related to the study and serious or unexpected shall be reported within 5 working days of the UCSF PI's knowledge. External (off-site) AE's that change the study

risks/benefits or requires a UCSF IRB modification must be reported within 10 working days of the UCSF PI's knowledge.

An AE is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Mifeprex® label or of greater severity or frequency than expected based on the information in the label.

The following definitions apply to adverse events occurring in clinical studies involving drugs:

- An AE is any health-related reaction, effect, toxicity or abnormal laboratory result that a participant experiences during the course of the study, irrespective of relationship to study product use.

In this study, the following routine study measurements will not be considered AEs because they are anticipated participant outcomes:

- Abortion
- Symptoms associated with medication abortion (pain, vaginal bleeding, fever, chills, nausea, vomiting, headache, weakness, dizziness and diarrhea), unless they are so severe as to meet the criteria for a SAE (see section 12.2 below)

12.1.1 AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

12.1.2 AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

12.2 Serious Adverse Events (SAE)

A serious adverse event (SAE) is defined as any untoward medical occurrence that:

- Is life threatening or results in death.
- Requires in-patient hospitalization or prolongs existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect (in the offspring of a participant).
- Jeopardizes participant and required medical/surgical intervention to prevent serious outcome, *or*
- Any other event that the investigator considers serious.

12.2.1 Serious Adverse Event Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per [UCSF IRB Guidelines](#). The collection period for all SAEs will begin after informed consent is obtained and end six weeks after the visit where Mifeprex® is prescribed.

In accordance with the standard operating procedures and policies of the local IRB/the site PI will report SAEs to the IRB.

12.3 Medical Monitoring

Site PIs should contact the PI, Daniel Grossman, MD, directly at this number to report medical concerns or questions regarding safety:

Phone: 510-986-8941

13 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

13.1 Early Discontinuation of Study Drug

Because participants will only take a single dose of Mifeprex®, there will be no opportunity to discontinue treatment. If a patient vomits within 30 minutes after taking Mifeprex®, she will be instructed to return to the clinic site for further evaluation and management.

13.2 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the site PI, or the PI feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the site PI to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's data collection documents.

12.3 Replacement of Subjects

If any subject withdraws or does not complete the study as planned, they will be replaced with an additional participant.

14 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigator, or clinic or pharmacy staff fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Potential protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Failure to comply with Good Clinical Practice (GCP) guidelines. The PI will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the site PI and a Protocol Violation Form detailing the violation will be generated. This form will be signed by the PI and the site PI. A copy of the form will be filed in the site's regulatory binder and in the PI's files.

15 DATA SAFETY MONITORING

Safety oversight will be under the direction of the PI. Because Mifeprex® is already approved, and there is a great deal of safety data on its use for this approved indication, we think it is reasonable for safety monitoring to occur through the standard review of S/AE reports (see section 12).

As part of routine instruction in the FDA's Mifeprex® Medication Guide provided to women undergoing medication abortion, participants will be instructed to return to the study site or a nearby facility offering emergency care in the case of heavy bleeding (more than 2 full-size pads soaked per hour for 2 hours), abdominal pain or "feeling sick", fever of 100.4 degrees or higher persisting more than 4 hours or for any signs of complications.

16 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

16.1 Data Sets Analyzed

All eligible patients who receive the dose of the study drug will be included in the analysis. All eligible pharmacists who complete at least one survey or interview will be included in the pharmacist analysis.

16.2 Demographic and Baseline Characteristics

The demographic information that will be collected: Age, parity, race/ethnicity. At the initial visit, we will also collect: date of service, gestational age by ultrasound and date of ultrasound, past medical history, current medications, blood pressure, weight, height, and medications prescribed or dispensed. All participants will receive the same dose of Mifeprex®.

16.3 Analysis of Primary Endpoint

Feasibility of the pharmacy dispensing model will be assessed in quantitative descriptive analyses of satisfaction variables from the pharmacists' end line survey (overall satisfaction, perceived benefits/challenges, and ease of implementation of pharmacy dispensing) using chi-square and *t* tests where appropriate. We will also calculate the proportion of pharmacists who refused to dispense Mifeprex® during the study. In addition, feasibility will be assessed in qualitative analyses of open ended interviews with pharmacists about dispensing Mifeprex® in pharmacies.

16.4 Analysis of Secondary Endpoints

Acceptability and satisfaction with the pharmacy dispensing model among patients will be assessed primarily through surveys with patient participants using quantitative and qualitative analyses. The particular Day 2 survey variables we will analyze include those on overall satisfaction with the pharmacy, reasons for dissatisfaction, and perceptions about the wait time, the way the patient was treated and the information she received. Clinical outcomes, including effectiveness and adverse events, with pharmacist-dispensed mifepristone will be assessed using quantitative data abstracted from patient medical records, as well as information on clinical outcomes captured in the Day 14 patient survey. Pharmacist knowledge about medication abortion before and after the intervention will be assessed through quantitative analyses of surveys completed by the pharmacists.

Adverse event rates will be coded by body system and MedDra classification term. Adverse events will be tabulated and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study drug.

16.5 Interim Analysis

No interim analysis is planned. Unexpected and serious adverse events will be monitored as noted above (see section 12).

16.6 Sample Size

We aim to recruit up to 250 patients for this pilot study, which is a feasible sample at the study sites. With a sample size of 250, if the proportion of patients with a complete abortion is 95%, the

95% confidence interval of that proportion will be +2.7%. Abortion completion is an important clinical outcome.

We aim to survey all the pharmacists at the study sites, up to 50. This sample size will be determined by the number of pharmacists at the study sites.

17 DATA COLLECTION, RETENTION AND MONITORING

17.1 Data Collection Instruments

Survey data will be collected directly from medication abortion patients using an online survey at Day 2 and Day 14 following the medication abortion. Clinical data will also be abstracted from the electronic medical record system at each study site. Pharmacists will be invited to complete a survey and interview prior to the initiation of mifepristone dispensing, as well as at the end of the study. All study instruments will be submitted for review prior to initiating data collection.

Study Population	Study instruments	Consent forms
Medication abortion patients	Day 2 survey Day 14 survey Clinical data abstraction form	Patient informed consent (written) HIPAA Authorization Form
Pharmacists	Baseline survey Baseline interview guide End-line survey End-line interview guide	Pharmacist informed consent for survey (click through) Pharmacist informed consent for interviews (verbal)

17.2 Data Management Procedures

Survey data will be collected in Qualtrics, an online survey software. The UCSF research team will access it securely through a protected account. Participants' personal identifiers (including first name and last initial, phone number and email address) will be collected and stored separately from clinical, survey, and interview data.

Clinical information (including date of clinic visit/s, success of the abortion, and adverse events) will be extracted from the electronic health record. These data will be de-identified, linked with a unique study ID, and entered into a Qualtrics or REDCap electronic form by the study site.

Interview data will be audio-recorded, transcribed and imported into the analysis software. Identifiers will be stored separately.

17.3 Data Quality Control and Reporting

The UCSF study team will train sites on standardized recruitment and consent procedures and have regular communication with study clinics and pharmacies to provide technical assistance and check on the progress of the study. Data collection tools and procedures will be pilot tested before implementation. Data will also be monitoring periodically to ensure that data collection, coding, and management procedures are being conducted according to protocol and ethical guidelines.

Survey data gathered through Qualtrics, an online survey software, will be secure and HIPAA compliant. Because of its high level of data security, it is the recommended survey software for UCSF research. Data are collected and stored on a secure server and scanned regularly to ensure vulnerabilities are quickly found and patched. UCSF will also take special precautions to collect and store personal identifiers separately from research data on participants on password protected secure accounts, using encrypted, physically secure computers and devices. Results will be presented in aggregate and will not share identifying information about participants.

17.4 Archiving of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

Surveys, interview recordings, transcripts, and forms will be stored in a locked cabinet at the study site and on computers only accessible by core members of the research team. When these procedures are followed, it is highly unlikely that any of the information revealed by participants during the course of the interviews will be disclosed to anyone outside the research team.

17.5 Availability and Retention of Investigational Records

The site PI must make study data accessible to authorized representatives of the PI (or designee), IRB, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent and copies of all source documentation related to that subject. The site PI must ensure the reliability and availability of source documents.

All study documents (patient files, signed informed consent forms, etc.) will be kept secured for a period of two years following the completion of the study.

17.6 Monitoring

Site-specific periodic monitoring visits at the sites will be undertaken for study audits as part of our plan to assure quality. The monitor, consisting of the PI and/or his designee from the UCSF research team, will also provide monitoring reports promptly following each visit and present this information to the site PI.

17.7 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on documentation.

Potential participants will have the option of not participating in any part of the study, including any part of the interview (pharmacists), and they may refuse to be audio-recorded during the interview, without any adverse consequences for their medical treatment (patients) or employment (pharmacists). Attempts to contact participants will be limited and should a message be left for the woman on her voicemail, no information related to the details of her study participation or nature of her care will be recorded. If at the time the woman is reached, she wishes to reschedule contact at a more appropriate or convenient time, staff will be flexible and accommodating, particularly to safeguard confidentiality.

All interviews with pharmacists will be conducted in a private area or private room designated for this purpose at the study sites or at another mutually agreed upon location. No identifying information will be included on the audio recording of the interview.

18 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all data collection forms will be identified by a coded number and initials only. All study records will be kept in secured files only accessible to the UCSF or site-specific research team. Data with patient identifiers used for contact purposes will be stored separately from survey/interview responses. Any paper forms will be stored in a locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The PI and site PIs must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

18.1 Protocol Amendments

Any amendment to the protocol will be written by the PI. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

18.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the UCSF IRB, as well as the University of Washington IRB, prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB written unconditional approval of the study protocol and the informed consent form will be in the possession of the PI and site PI before the study is initiated. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

18.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The consent form must be approved by the IRB. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations.

Participants will be given information about the study and their rights as part of the informed consent process. On agreeing to participate, they will be asked to sign an informed consent form. For patients, the form will seek consent both for obtaining clinical data from medical records, as well as for participation in the online or telephone surveys. Medical record data will only be abstracted from patients who also provide consent using the HIPAA Authorization form. Pharmacists will be consented for their participation in the survey and interview separately; for the survey, the consent will be a click-through consent on the online platform and for the interview the consent will be verbal. As part of this informed consent process, potential participants will be informed of: (1) the purpose and methods of the study, (2) alternatives to participation in the study, (3) procedures to protect confidentiality, (4) the right to withdraw from the study at any time, (5) the fact that participation or non-participation will not affect the medical care that they receive, and (5) persons to contact for any questions about the study. The participants will also be given names and phone numbers of persons to contact with any questions regarding the study.

18.4 Reimbursement or compensation to study participants

Patients obtaining medication abortion who participate in the study will be reimbursed \$25 for completing each of the two surveys, for a maximum reimbursement of \$50. Reimbursement will be in the form of an online Amazon gift card.

Pharmacists will be reimbursed \$25 for completing the surveys, and another \$25 if the interview is completed. Both the survey and interview may be completed at baseline (before the study is initiated) and at the end of the study, for a maximum reimbursement of \$100. Reimbursement will be in the form of an online Amazon gift card.

Each pharmacy will be reimbursed \$8 for each dose of Mifeprex® that is dispensed. Since Mifeprex® is not generally a covered benefit for pharmacy dispensing, we do not anticipate that pharmacies will be able to bill insurances for their standard dispensing fee, so this will be provided as part of the study.

18.5 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study PI and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

19 REFERENCES

References

- ACOG. (2014). Practice bulletin no 143: medical management of first-trimester abortion. *Obstet Gynecol*, 123, 676.
- Bartlett, L. A., Berg, C. J., Shulman, H. B., Zane, S. B., Green, C. A., Whitehead, S., & Atrash, H. K. (2004). Risk factors for legal induced abortion-related mortality in the United States. *Obstet Gynecol*, 103(4), 729-737.
doi:10.1097/01.AOG.0000116260.81570.60
- Baum, S. E., White, K., Hopkins, K., Potter, J. E., & Grossman, D. (2016). Women's Experience Obtaining Abortion Care in Texas after Implementation of Restrictive Abortion Laws: A Qualitative Study. *PLoS ONE*, 11(10), e0165048.
doi:10.1371/journal.pone.0165048
- Beckman, L. J., & Harvey, S. M. (1997). Experience and acceptability of medical abortion with mifepristone and misoprostol among U.S. women. *Womens Health Issues*, 7(4), 253-262.
- Chong, E., Frye, L. J., Castle, J., Dean, G., Kuehl, L., & Winikoff, B. (2015). A prospective, non-randomized study of home use of mifepristone for medical abortion in the U.S. *Contraception*, 92(3), 215-219. doi:10.1016/j.contraception.2015.06.026
- Christin-Maitre, S., Bouchard, P., & Spitz, I. M. (2000). Medical termination of pregnancy. *N Engl J Med*, 342(13), 946-956. doi:10.1056/NEJM200003303421307
- Creinin, M. D., Fox, M. C., Teal, S., Chen, A., Schaff, E. A., Meyn, L. A., & Group, M. O. D. S. T. (2004). A randomized comparison of misoprostol 6 to 8 hours versus 24 hours after mifepristone for abortion. *Obstet Gynecol*, 103(5 Pt 1), 851-859.
doi:10.1097/01.AOG.0000124271.23499.84
- Creinin, M. D., Schreiber, C. A., Bednarek, P., Lintu, H., Wagner, M. S., Meyn, L. A., & Medical Abortion at the Same Time Study Trial, G. (2007). Mifepristone and misoprostol administered simultaneously versus 24 hours apart for abortion: a randomized controlled trial. *Obstet Gynecol*, 109(4), 885-894.
doi:10.1097/01.AOG.0000258298.35143.d2
- Deprez, E. (2016, February 24 2016). Abortion clinics are closing at a record pace. *Bloomberg Businessweek*. Retrieved from
<https://www.bloomberg.com/news/articles/2016-02-24/abortion-clinics-are-closing-at-a-record-pace>
- Drey, E. A., Foster, D. G., Jackson, R. A., Lee, S. J., Cardenas, L. H., & Darney, P. D. (2006). Risk factors associated with presenting for abortion in the second trimester. *Obstet Gynecol*, 107(1), 128-135. doi:10.1097/01.AOG.0000189095.32382.d0
- FDA. (2011). *Mifepristone U.S. Postmarketing Adverse Events Summary through 04/30/2011*. Retrieved from
- FDA. (2016a). *Medication Guide Highlights of Prescribing Information*. Washington DC: US Food and Drug Administration Retrieved from
https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf

- FDA. (2016b). *Mifeprex Risk Evaluation and Mitigation Strategy (REMS) program*. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2016-03-29_REMS_document.pdf
- Finer, L. B., & Wei, J. (2009). Effect of mifepristone on abortion access in the United States. *Obstet Gynecol*, 114(3), 623-630. doi:10.1097/AOG.0b013e3181b2a74d
- Fuentes, L., Lebenkoff, S., White, K., Gerdt, C., Hopkins, K., Potter, J. E., & Grossman, D. (2016). Women's experiences seeking abortion care shortly after the closure of clinics due to a restrictive law in Texas. *Contraception*, 93(4), 292-297. doi:10.1016/j.contraception.2015.12.017
- Grossman, D. (2017). The Use of Public Health Evidence in Whole Woman's Health v Hellerstedt. *JAMA Intern Med*, 177(2), 155-156. doi:10.1001/jamainternmed.2016.6839
- Grossman, D., & Goldstone, P. (2015). Mifepristone by prescription: a dream in the United States but reality in Australia. *Contraception*, 92(3), 186-189. doi:10.1016/j.contraception.2015.06.014
- Grossman, D., Grindlay, K., Buchacker, T., Lane, K., & Blanchard, K. (2011). Effectiveness and acceptability of medical abortion provided through telemedicine. *Obstet Gynecol*, 118(2 Pt 1), 296-303. doi:10.1097/AOG.0b013e318224d110
- Grossman, D., Grindlay, K., Buchacker, T., Potter, J. E., & Schmertmann, C. P. (2013). Changes in service delivery patterns after introduction of telemedicine provision of medical abortion in Iowa. *Am J Public Health*, 103(1), 73-78. doi:10.2105/AJPH.2012.301097
- Grossman D., Grindlay K., Schulkin J. (2017). Abortion provision among a national sample of obstetrician-gynecologists. *Contraception*, 96(4), 272-3. doi:10.1016/j.contraception.2017.07.044
- Jerman, J., Frohwirth, L., Kavanaugh, M. L., & Blades, N. (2017). Barriers to Abortion Care and Their Consequences For Patients Traveling for Services: Qualitative Findings from Two States. *Perspect Sex Reprod Health*, 49(2), 95-102. doi:10.1363/psrh.12024
- Mifeprex REMS Study Group. (2017). Sixteen Years of Overregulation: Time to Unburden Mifeprex. *N Engl J Med*, 376(8), 790-794. doi:10.1056/NEJMs1612526
- Ngo, T. D., Park, M. H., Shakur, H., & Free, C. (2011). Comparative effectiveness, safety and acceptability of medical abortion at home and in a clinic: a systematic review. *Bull World Health Organ*, 89(5), 360-370. doi:10.2471/BLT.10.084046
- OCP. (2017). *Dispensing MifeGyMiso: Guidance for Pharmacy Professionals Who Are Dispensing Mifegymiso*. Retrieved from Ontario: http://www.ocpinfo.com/library/practice-related/download/Dispensing_Mifegymiso.pdf
- Zane, S., Creanga, A. A., Berg, C. J., Pazol, K., Suchdev, D. B., Jamieson, D. J., & Callaghan, W. M. (2015). Abortion-Related Mortality in the United States: 1998-2010. *Obstet Gynecol*, 126(2), 258-265. doi:10.1097/AOG.0000000000000945

