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Research Protocol
ALTERNATIVE PROVISION OF MEDICATION ABORTION VIA MAIL-ORDER PHARMACY DISPENSING

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Approval:

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LIST OF ABBREVIATIONS

ACOG	The American College 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 Mail-Order Pharmacy Dispensing
SPONSOR/PI	Daniel Grossman, MD
FUNDING ORGANIZATION	Society of Family Planning
NUMBER OF SITES	15-20
RATIONALE	The proposed study aims to investigate the acceptability, feasibility, and effectiveness of mail-order 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. Trained pharmacists already successfully deliver care 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 and Goldstone 2015); pharmacy dispensing is also being implemented in Canada (OCP 2017). Pharmacy dispensing of Mifeprex® by trained pharmacists could improve access to medication abortion for women. Mail-order dispensing in particular could allow women to bypass geographical, financial, or insurance obstacles to clinic- based care and receive abortion care earlier in pregnancy (Drey, Foster et al. 2006, Grossman, Grindlay et al. 2013, Jerman, Frohwirth et al. 2017) and help to facilitate provision of medication abortion through telemedicine, reducing the disparity in access between rural and urban settings (Grossman, Grindlay et al. 2011, Grossman, Grindlay et al. 2013). In light of a declining number of abortion providers in the US (Jones and Kooistra 2011, Jones and Jerman 2014), mail-order 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. Mail-order dispensing of mifepristone would not affect the standard of care or recommended clinical protocol for medication administration. 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 by mail directly from a mail-order pharmacy, rather than in a clinic facility. Home administration of Mifeprex® is now allowed under the updated Mifeprex® labeling (FDA 2016). Study participants will be told by the prescribing clinician when they should take the Mifeprex®, and participants will be contacted within three days of when the prescription is sent to determine if they received the Mifeprex® and if they took the medication as prescribed.
STUDY DESIGN	This is a phase 4 prospective cohort study.
PRIMARY OBJECTIVE	Our **primary objective** is to assess the acceptability for patients undergoing medication abortion with Mifeprex®

	dispensed by mail-order pharmacy.
SECONDARY OBJECTIVES	**Secondary objectives** include assessing feasibility, clinical effectiveness and safety, and provider acceptability of providing medication abortion with Mifeprex® dispensed by mail-order pharmacy.
NUMBER OF SUBJECTS	Maximum of 650 patients (and 50 provider/staff participants for end line interviews)
SUBJECT SELECTION CRITERIA	Inclusion Criteria: English- or Spanish-speaking women age 15 or older (18 or older in some states) seeking medication abortion through 63 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 receive abortion medications at a mailing address, willing to take misoprostol dosage via the buccal route of administration and willing to be contacted by email, telephone or text. All providers providing services at one of the study clinics will be invited to be trained in prescribing medication abortion pills to study participants. All providers and staff involved in the study at each study clinic (up to 50 total) will be invited to participate in qualitative in-depth interviews at the end of the study. Exclusion Criteria: We will exclude women who are not pregnant or not seeking medication abortion, under the age of 15, (or under the age of 16 or 18 in some states) who have contraindications for medication abortion, or who choose to administer misoprostol vaginally instead of buccally.
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Oral Mifeprex® 200 mg followed by misoprostol 800 mcg administered buccally (at 24-48 hours following mifepristone).
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	The duration of the study will be 48 months. Most 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 AEs will be followed until resolution or stabilization. Provider/staff interviews will be conducted only at the end of the study.

CONCOMMITANT MEDICATIONS	Allowed: Any Prohibited: None
EFFICACY EVALUATIONS	The UCSF study team will train sites on standardized recruitment and consent procedures and have regular communication with study clinics 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 acceptability of undergoing medication abortion with drugs dispensed by mail-order pharmacy, measured by the proportion of patients reporting they would use the mail-order service again if they needed another abortion, as well as the proportion who report they were "satisfied or very satisfied" with the medication abortion. We will also capture patient perspectives on receiving the medications by mail through open-ended responses. In addition, we will ask patients who decline to enroll in the study their reasons, including the reasons why they are not interested in receiving the medications by mail.
SECONDARY ENDPOINTS	**Secondary outcomes** will include feasibility of providing medication abortion with drugs dispensed by mail-order pharmacy, clinical effectiveness and safety of medication abortion with drugs dispensed by mail-order pharmacy, and provider acceptability of the mail-order pharmacy model for dispensing medication abortion drugs. Feasibility will be assessed by measuring the proportion of patients who receive the medications by Day 2 and by Day 3 and whether patients' confidentiality is maintained when they receive the medications by mail. We will also ask patients whether the medications were lost, stolen or damaged, resulting in the patients needing to return to clinic, or go elsewhere. We will also assess feasibility through open-ended interviews with providers of MA at the end of the study. Clinical effectiveness and safety will be assessed through analysis of electronic health record data, including the proportion of patients who experience a complete abortion and experience complications, including adverse events, related to the abortion. Provider acceptability will be assessed qualitatively through open-ended interviews with providers and staff involved in the study. We will identify advantages and disadvantages of mailing the medications from the perspective of providers and staff.
OTHER EVALUATIONS	N/A
SAFETY EVALUATIONS	Data abstraction of medical records will provide clinical data for analysis, including the proportion of patients who

	experience a complete abortion. 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 *t* tests where appropriate to assess patient satisfaction with the model and clinical outcomes of patient participants.
Rationale for Number of Subjects	We aim to recruit up to 25 patients for the pilot study at Montefiore Medical Center, and an additional 440 (at minimum) to 625 (maximum) patients at 15-20 sites across the country. The sample size calculation for this study is based on a measure of acceptability: the proportion of patients who report they would use medication abortion again if they needed another abortion (89.7%). We would like to determine if acceptability of medication abortion when receiving the medications by mail is no more than 5 percentage points lower than 89.7%. With a 2-sided alpha of 0.05, 10% adjustment for clustering, and 10% loss to follow-up, a final analytic sample size of approximately 400 gives us 79% power, and an analytic sample of 560 gives us 92% power to assess acceptability. We plan to recruit a minimum sample of 440 patients (main study). We aim to interview up to 50 providers/staff. This sample size will be determined by the number of providers/staff involved in the study at sites.

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), 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 2016). 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 2016).

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 2016). 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 et al. 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, Frye 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.

Numerous studies performed in the US and other countries have demonstrated that MA has a high level of acceptability for a majority of women seeking pregnancy termination (Beckman and Harvey 1997, Christin-Maitre, Bouchard et al. 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, Park 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 and Jerman 2017). Medication abortions accounted for 45% of all abortions up to nine weeks gestation in 2014, up from 26% in 2008 (Jones and Jerman 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, Creanga 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 (Grossman, Grindlay 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 (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, which has increased the distance women must travel to access abortion care, may make it harder to access medication abortion (Cartwright, Karunaratne et al. 2018). 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, White et al. 2016, Fuentes, Lebenkoff 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 and 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 2016):

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 of complications from more advanced pregnancy and a later abortion (Bartlett, Berg et al. 2004, Mifeprex REMS Study Group 2017).

We recently explored this issue in a survey of practicing obstetricians-gynecologists (Grossman, Grindlay et al. 2017, Grossman 2019). In 2016-2017, we performed a survey with a representative sample of Fellows and Junior Fellows of the American College of Obstetricians and Gynecologists (ACOG). The survey was sent by email with an online link, and non-responders were mailed paper surveys. 655 currently practicing Fellows responded to the survey (response rate 67%). 99% reported seeing patients of reproductive age. 72% reported having a patient in the prior year who needed or wanted an abortion. Only 23.8% (95% CI 20.5%-27.4%) reported performing an abortion in the prior year; 10.4% provided surgical and medication abortion, 9.4% surgical only, and 4.0% medication only.

Among those not providing medication abortion, 28% 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 22% said they were unsure if they would provide medication abortion in this scenario. Our findings suggest that the proportion of obstetrician-gynecologists providing medication abortion would at least double (from 14% to 31%) 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 acceptability and feasibility of mail-order 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, which will be transmitted to the mail-order pharmacy. The patient will then receive the medications in the mail at the address provided. The patient will take the Mifeprex® at the time indicated by the prescribing clinician. Patients will be contacted on Day 3 and Day 14 to complete surveys about their experience, and they will undergo standard clinical follow-up. In addition, we will perform interviews with providers/staff at the end of the study to assess their experience providing medication abortion.

This study is related to another being conducting under this IND (137073), which is exploring the acceptability, feasibility, safety, and effectiveness of dispensing Mifeprex® at brick-and-mortar

pharmacies after the patient goes through an in-person clinical assessment. One finding relevant to the study proposed here is that all participants in the ongoing study have reported correctly taking the mifepristone as directed at home after obtaining the medication at the pharmacy.

2 STUDY RATIONALE

The proposed study aims to investigate the acceptability, feasibility and effectiveness of mail-order 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 MA, 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 (Grossman and Goldstone 2015, Hyland, Raymond et al. 2018); pharmacy dispensing of mifepristone is also being implemented in Canada (OCP, 2017).

Mail-order pharmacy dispensing of Mifeprex® could improve access to medication abortion for women in a number of important ways. Mail-order 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, Foster et al. 2006, Grossman, Grindlay et al. 2013, Jerman, Frohwirth et al. 2017) and help to facilitate provision of medication abortion through telemedicine, reducing the disparity in access between rural and urban settings (Grossman, Grindlay et al. 2011, Grossman, Grindlay et al. 2013). In light of a declining number of abortion providers in the US (Jones and Kooistra 2011, Jones and Jerman 2014), mail-order 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. Because some pharmacies may refuse to carry Mifeprex® efven if they were allowed to, mail-order pharmacies could improve access to the drug in the future.

Mail-order pharmacy dispensing of Mifeprex® would not affect the standard of care or recommended clinical protocol for MA 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 a mail-order pharmacy, rather than in a clinic facility.

As noted above, home administration of Mifeprex® is now allowed under the updated Mifeprex® labeling (FDA 2016). Study participants will be told by the prescribing clinician when they should take the Mifeprex®, and participants will be contacted three days later to determine if they received the medications in the mail and 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 MA, 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 (the current FDA gestational age limit). 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 3 to be certain they received and took the Mifeprex® as instructed. The eligibility criteria for this study will limit gestational age of participants to 63 days at the time of prescribing, so as to minimize the risk of patients taking the medications after 70 days due to delays in receiving the drugs. 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 providers for participating in the study. The participating clinics will not be identified in any publications. There is a potential risk that participating clinics will experience anti-abortion picketers if participation in the study becomes known, and this has been discussed with the management of each clinic.

These data will be used to assess whether it is feasible for ob/gyn and primary care clinics to provide medication abortion and for patients to receive the medications by mail, 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 acceptability of mail-order pharmacy dispensing of Mifeprex®. Our primary outcome will be acceptability measured by patient satisfaction with medication abortion (including whether they would use this mail-order MA service again if they needed another abortion, satisfaction with the medication abortion experience overall, and whether they would recommend the service to a friend), satisfaction with receiving the medications by mail, reasons for dissatisfaction (open ended questions), and perceptions about the wait time to receive the medications. We will also analyze the reasons why patients who decline participation in the study report not being interested in receiving the medications by mail, as indicated in close-ended and open-ended responses.

3.2 Secondary Objectives

The secondary objectives include to assess feasibility of the mail-order dispensing model (including the determination of the proportion of patients who receive the medications by Day 2 and by Day 3 after the prescription is sent, the quality of the packaging, whether patient confidentiality was compromised due to receiving the medications by mail, and the proportion of patients who had to go to a clinic to obtain the medications); clinical effectiveness and safety, including adverse events, with mail-order dispensing of mifepristone; and provider acceptability of the mail-order model method through qualitative analysis of in-depth open-ended interviews.

3.3 Study Overview

We will conduct a prospective cohort study of patients receiving Mifeprex® and misoprostol via mail-

order pharmacy after undergoing standard clinical evaluation. Women participating in this study will obtain Mifeprex® and misoprostol from the mail-order pharmacy instead of in the clinic. All clinical care will continue to be performed according to the FDA protocol and ACOG guidance. The only difference is that the Mifeprex® will be dispensed by a mail-order pharmacy rather than by the clinician in the clinic.

4 CRITERIA FOR EVALUATION

4.1 Primary Endpoint

Acceptability of the mail-order model will be assessed by patient satisfaction with MA (including whether they would use this mail-order medication abortion service again if they needed another abortion, satisfaction with the medication abortion experience overall, and whether they would recommend the service to a friend), satisfaction with receiving the medications by mail, reasons for dissatisfaction (open ended questions), and perceptions about the wait time to receive the medications. We will also analyze the reasons why patients who decline participation in the study report not being interested in receiving the medications by mail, as indicated in close-ended and open-ended responses.

4.2 Secondary Endpoints

Feasibility will be assessed by measuring the proportion of patients who receive the medications by Day 2 and Day 3 (two and three days after enrollment (Beckman and Harvey), respectively), and whether patients' confidentiality is maintained when they receive the medications by mail. We will also ask participants whether the medications were lost, stolen or damaged, resulting in the patients needing to return to clinic, or go elsewhere. Clinical effectiveness and safety will also be assessed using data collected from medical records of participants, including pregnancy outcomes, complications and adverse events. The study team will maintain contact with participants who indicate that they plan to continue the pregnancy: every three months following Day 14 survey completion and until the end of the pregnancy, the study team will contact the participant and document whether or not there has been a change in her pregnancy status. The study team will document the expected delivery date, each attempt to contact the patient, and details on the pregnancy outcome, delivery, and assessment of the newborn on a Continuing Pregnancy Outcome form. Provider acceptability of the mail-order pharmacy model will be assessed through open-ended interviews with providers/staff of medication abortion at the end of the study.

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. Clinically significant adverse events are defined as death, blood transfusion, hospitalization, surgery (not including uterine vacuum aspiration), and emergency department visits requiring treatment for an abortion-related condition. We will also collect and report information on abortion-related emergency department visits not requiring treatment and uterine vacuum aspirations needed for incomplete abortions, bleeding, and other abortion-related conditions. The prevalence of serious adverse events (or major complications) in the study will be compared to published estimates of less than 0.5%.

5 STUDY SITES

The study will be performed at 15-20 sites around the country. These will include ob/gyn, family medicine and internal medicine clinic sites in the United States that do not currently stock mifepristone and where clinicians have been newly trained to provide MA. Sites may also include current abortion

providers. We have begun to do outreach to identify sites. Attorneys performed a legal analysis of California, New York, Rhode Island, Delaware, Colorado, and Pennsylvania and determined there are no barriers to dispensing mifepristone via mail-order pharmacy beyond the Mifeprex® REMS. Before launching the study in a new state, attorneys will perform analyses of state law and regulations to ensure that there are no barriers to dispensing mifepristone via mail-order pharmacy beyond the REMS. When identifying sites, the research team will verify that study sites will have referral systems in place to connect patients with back-up specialty care as needed and will document clear referral pathways for non-emergency aspiration and for urgent/emergent situations, where blood transfusion and resuscitation may be performed.

At each site, we will identify a site investigator who is a physician and who will oversee all clinical activities at the site. Each of the site investigators will complete a Form 1572 (Statement of Investigator), which will be submitted to the FDA to document their participation in the IND study. The site investigator will also sign the Danco Prescriber Agreement Form. The site investigator will also oversee the extraction of clinical data from the medical records of study participants. Some sites may have more than one site investigator; in this case, only one co-investigator needs to be a physician. Recruiting will take place by staff at the study clinic site, and Mifeprex® will be mailed from the pharmacy to the participant's home or other preferred address. The current sites and site principal investigators (PIs) are listed below. This protocol will be updated as additional sites are identified.

5.1 Family Health Center at Montefiore Medical Center

Dr. Marji Gold will serve as the site PI and will oversee all study activities at this site. This site is a full spectrum family medicine clinic at Montefiore Medical Center in New York, where medication abortion and first-trimester abortion procedures are already provided. The study will be piloted (n=25) at this site before recruitment begins for the main study at other clinic sites. Dr. Gold performs non-emergent uterine aspirations at the study sites. Back-up emergency care is available through the Department of Obstetrics and Gynecology at Montefiore Medical Center. Montefiore will rely on its own institutional IRB.

5.2 Benioff Children's Hospital Oakland, Teen and Adolescent Medicine Department

Dr. Lela Bachrach will serve as the site PI and will oversee all study activities at this site. Dr. Bachrach is a pediatric adolescent medicine specialist in the Teen and Adolescent Medicine Department at Benioff Children's Hospital Oakland, where abortion services are not currently offered. We aim to recruit 20 patients over two years at this site. Non-emergent uterine aspirations will be performed at Highland Hospital's K6 attached clinic. Patients needing emergent specialty care will also be referred to Highland Hospital's emergency department, and the Obstetrics and Gynecology Department is aware of the study. Children's Hospital Oakland will rely on UCSF's IRB as it is part of UCSF.

5.3 Lifespan Center for Primary Care

Dr. Mindy Sobota will serve as the site PI and will oversee all study activities at this site. Dr. Sobota is an internal medicine specialist at Rhode Island Hospital's Center for Primary Care in Providence, Rhode Island, where abortion services are not currently provided. She is also Associate Professor of Medicine at Brown University. We aim to recruit at least 20 patients over two years at this site. Patients will be referred to Women and Infants Emergency Room for emergency care needs and to Lifespan Physician Group Gynecology for non-emergent care needs, including non-emergent aspiration. Lifespan will rely on its own institutional IRB.

5.4 Highland Hospital in Oakland, CA

Dr. Stephanie Ho of Alameda Health System (Highland Hospital) will serve as site PI and will oversee all

study activities at this site. Dr. Ho specializes in obstetrics and gynecology. The study will take place at one or more of the following satellite clinics in Oakland, California that are affiliated with Highland Hospital where mifepristone is not available yet available on site: Eastmont Wellness Center, Hayward Wellness Center, and Newark Wellness Center. We will also recruit at Highland Hospital's attached clinic, K6, which currently provides medication abortion services yet experiences stock-outs of mifepristone and other delays. Highland's K6 clinic also provides aspiration services. We aim to recruit at least 20 patients over two years at this site. Non-emergent uterine aspirations will be performed at Highland Hospital's K6 attached clinic. Patients needing emergent specialty care will also be referred to Highland Hospital's emergency department. Highland will rely on its own institutional IRB.

5.5 Kent Hospital – Family Care Center

Dr. Andrea Arena of the Family Care Center at Kent Hospital (a member of Care New England) in Pawtucket, Rhode Island, will serve as the site PI and will oversee all study activities at this site. Dr. Arena is a family medicine practitioner with extensive experience in reproductive health service provision. She is also an Assistant Professor of Family Medicine and Associate Director of Medical Student Education at the Alpert Medical School of Brown University. The study will take place at the Family Care Center, where abortion services are not currently provided. We aim to recruit at least 20 patients over two years at this site. Patients will be referred to Woman and Infant Triage at Care New England Hospital for non-emergent uterine aspirations and emergent specialty care. Kent Hospital will rely on its own institutional IRB.

5.6 Allegheny Reproductive Health Center

Dr. Grace Ferguson of the Allegheny Reproductive Health Center clinic in Pittsburgh, Pennsylvania, will serve as the site PI and will oversee all study activities at this site. Dr. Ferguson is a practicing obstetrician and gynecologist with extensive experience in reproductive health service provision. She is a Faculty Physician with Allegheny Health Network, Division of Family Planning and a Visiting Instructor at University of Pittsburgh School of Medicine. We aim to recruit at least 20 patients over one year at this site. This site currently provides abortion care. Non-emergent uterine aspirations will be performed at the Allegheny Reproductive Health Center, as needed. Patients needing emergent specialty care will be referred to the Emergency room at West Penn Hospital. Allegheny Reproductive Health Center will rely on UCSF's IRB.

5.7 Delaware County Women's Center

Dr. Bryanne Robson, MD and Curtiss Hannum, MSN, APN will serve as the site PIs. Dr. Robson will oversee the prescribing of mifepristone and clinical activities. Ms. Hannum will oversee all other study activities at the Delaware County Women's Center in Chester, Pennsylvania. Ms. Hannum is a practicing women's health Nurse Practitioner and Senior Vice President at The Women's Centers and Dr. Bryanne Robson is a family medicine physician employed by The Women's Centers, which include Atlanta Women's Center, Cherry Hill Women's Center, Delaware County Women's Center, Hartford GYN Center, and Philadelphia Women's Center. We aim to recruit at least 20 patients over two years at the Delaware County site. This site currently provides medication abortion services. Non-emergent follow-up aspirations will be performed for study participants as needed at the Delaware County Women's Center. Patients will be referred to Philadelphia Women's Centers for emergent specialty care needs. Delaware County Women's Center will rely on UCSF's IRB.

5.8 Christiana Care Health System

Dr. Diana Wohler, MD will serve as the site PI. Dr. Wohler will oversee the prescribing of mifepristone and clinical activities. Dr. Wohler is a family medicine physician employed by Christiana Care Health System in Wilmington, Delaware. She is a faculty member at Christiana Care's family medicine

residency program, where she practices outpatient primary care including prenatal and inpatient obstetrics. We aim to recruit at least 20 patients over two years at the Delaware site. This site does not currently offer medication abortion services. Non-emergent follow-up aspirations will be performed for study participants as needed at the Christiana Care Center for Reproductive Health. Patients will be referred to Christiana Hospital OB Triage for emergent specialty care needs. Christiana Care Health System will rely on its own institutional IRB.

5.9 Planned Parenthood Rocky Mountains (PPRM)

Dr. Kristina Tocce, MD will serve as the site PI. Dr. Tocce will oversee the prescribing of mifepristone and clinical activities. Dr. Tocce is an obstetrician-gynecologist physician and medical director at Planned Parenthood Rocky Mountains (PPRM), where she currently provides abortion care. We aim to recruit at least 20 patients over two years at PPRM's Colorado sites: Denver Park Hill and Colorado Springs. These sites currently offer medication abortion services. Non-emergent follow-up aspirations will be performed for study participants as needed at PPRM health centers. If patients need emergent care, they will be referred to the emergency department closest to them PPRM will rely on UCSF's institutional IRB.

5.10 Southern Tier Women's Services

Dr. Susan Seibold-Simpson, PhD and Dr. Amy Cousins, MD will serve as the site co-PIs. Dr. Cousins will oversee the prescribing of mifepristone and clinical activities. Dr. Cousins is an obstetrician-gynecologist physician and provider at Southern Tier Women's Services in Vestal, New York, where she currently provides abortion care. Dr. Seibold-Simpson will oversee the identification, recruitment and enrollment of eligible patients and the data collection and follow up. We aim to recruit at least 20 patients over one year at this site. This site currently offers medication abortion services. Non-emergent follow-up aspirations will be performed for study participants as needed at the recruitment site. If patients need emergent care, they will be referred to the emergency department closest to them. Southern Tier Women's Services will rely on UCSF's institutional IRB.

5.11 Atlanta Comprehensive Wellness Center

Dr. Tamer Middleton, MD will serve as the site PI. She will oversee the prescribing of mifepristone and clinical activities. Dr. Middleton is a family medicine doctor in Atlanta and currently provides abortion care at Atlanta Comprehensive Wellness Center. She will oversee the identification, recruitment, and enrollment of eligible patients and the data collection and follow up at her clinic. We aim to recruit at least 20 patients and up to 50 patients at this site in total. The clinic currently provides medication abortion services. Non-emergency follow-up aspirations will be performed for the study participants as needed at the recruitment site. If patients need emergent care, they will be referred to Emory Hospital Obstetrics and Gynecology or the emergency department closest to them. Atlanta Comprehensive Wellness Center will rely on UCSF's institutional IRB.

6 SUBJECT SELECTION

6.1 Study Population

Patient participants will include women age 15 or older seeking medication abortion through 63 days (9 weeks) gestation and eligible for Mifeprex® at a study clinical site. The gestational age eligibility will be limited to 63 days (instead of 70 days) to ensure that women remain eligible for the desired medication abortion even if there are unexpected delays in receiving pills by mail. The study will include women who are eligible for MA and are willing and able to consent to participation, including being willing to receive Mifeprex® from a mail-order pharmacy. We will include minors age 15-17 (in states where

participation in abortion research is allowed without parental consent, and after obtaining parental consent in states where it is required), because their perspectives on this service are important. In California (Cal Family Code 6920-6929) and New York, adolescent minors are able to give consent to an abortion without parental consent. In Delaware, minors are considered those under age 16 (Del. Code Ann. tit. 24 §§ 1782(6)); those age 16 and over may give consent to an abortion without parental consent. 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.

All clinicians employed at the clinic sites will have a choice about participating in the research in terms of prescribing medication abortion and receiving the training, and in terms of completing the interviews at the end of the study. Providers who are interested in doing an interview at the end of the study will be consented prior to the interview.

A participant who does not receive the medications within 3 days will be referred to another facility that offers abortion services, as needed. (Patients recruited at sites where abortion is currently provided and who do not receive the medications within 3 days, may return to the study site to receive abortion medications). The number of patients who are referred elsewhere or who return to the study clinic for MA care will be documented.

6.2 Inclusion Criteria

1. Women seeking and eligible for MA with Mifeprex® and misoprostol up to 63 days' gestation as determined by the site
2. Women age 15 or older (depending on the state, may be age 16 or age 18 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 receive Mifeprex® at a mailing address and take it before the 70-day gestational age limit
6. Willing to take misoprostol dosage via the buccal route of administration
7. 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 (under age 16 or 18, depending on the state)
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.
6. Choose to administer misoprostol vaginally instead of buccally

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 or an anti-emetic such as ondansetron. 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, co-administration 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

If a patient expresses interest in medication abortion during her visit at the clinic, she will be informed about the study by her treating clinician. If interested in participating in the study, she will be evaluated for study eligibility and eligibility for medication abortion. If she is not interested in participating in the study, the patient will be provided standard care or referred elsewhere as needed. If still interested and eligible to participate, she will be provided with further information about the study and asked to sign the study consent, HIPAA forms, and Danco Patient Agreement on paper or electronically. Patients will be told that the study will involve obtaining all medications by mail, rather than obtaining medications at the clinic and/or brick-and-mortar pharmacy. Patients will be told that if they have any problems receiving the medications, including more than a 3-day wait, they should contact the clinic. Participants will be told that there will be no additional cost for participating in the study. Patients will also be informed that the study will cover the cost of their abortion medications, mifepristone and misoprostol, as well as ibuprofen (if prescribed), and that all other costs (including lab tests, ultrasound, exam visit) will be billed to insurance where possible, as they would be for standard care outside of the study. Participation in the study will not result in any increased out-of-pocket payment by patients. At some sites where billing is not possible, the study will also cover the cost of other clinical services as needed. After consenting to participation, the patients will complete a secure electronic form to submit their contact information and

contact preferences to the UCSF study team, so that UCSF can send the web-based surveys; the mailing address will also be transmitted to the pharmacy for mailing the medications.

Participants who agree to participate in the study will receive the Mifeprex Medication Guide, a copy of the Patient Agreement Form, and a study information sheet. Patients will review the Medication Guide with the provider during the initial visit and the provider and patient will write down on the information sheet (that the patient will keep) the planned dates and times when the patient will expect to receive the medications by mail, when the patient will take mifepristone and misoprostol, and when the patient will follow up with the clinic (either in person or by phone). If a follow-up laboratory test is required (such as a serum hCG measurement), this will also be noted on the information sheet. As part of routine instruction in the FDA's Mifeprex Medication Guide provided to women undergoing medication abortion, participants will be instructed to contact the study site using its 24-hour telephone line 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. The name and number of nearby emergency facilities will be provided on the information sheet that patients will take home with them and will be documented in the patient's chart.

Participants will undergo standard clinical follow-up, either in person or by telephone, after the abortion. This is in accordance with the FDA's updated label for Mifeprex, which no longer includes a requirement for in-person follow-up after medication abortion. Patients will discuss the follow-up plan with their provider at the time of initial recruitment visit, and this plan will be written down on the information sheet that patients take home with them and will be documented in the patient's chart. Participants who do not return for follow-up at the clinic after their abortion will be contacted by phone or email to obtain information about abortion completion, complications and adverse events.

Patients will be considered lost to follow-up if they have not completed the follow-up surveys AND they do not return to or contact the clinic site after the medication abortion visit.

8.2 Method of Recruitment for Providers

Providers will be invited to participate in the training on medication abortion and to prescribe medication abortion to their patients as part of the research study. UCSF will identify a primary administrative or clinician study site lead at each site; this person will serve as the main point of contact for the site to the UCSF team. This person will inform providers at the study site about the study and invite them to participate in the study training and provision of medication abortion. The training on medication abortion provision will take place at the start of the study at each respective clinic site and last for a duration of about two hours. After the training, providers will be invited to informally evaluate the training and provide suggestions for its improvement. At the training, providers will be asked to provide their contact information so that the study team can follow up with any relevant information or updates about the study. If a provider joins the clinic after the training has been completed, but is interested in participating in the provision of medication abortion, a second training will be arranged as needed. Each physician site investigator will oversee all clinical activities at their respective sites and will sign the Danco Prescriber Agreement Form.

In addition to their participation as collaborators in the research study, providers at the study site will also be invited to participate in an in-depth interview at the end of the study about their experience with the mail-order model. Providers may opt to prescribe medication abortion as part of the study but decline to do an interview, or they may decline to prescribe and opt to do the interview. Interviews at the end of the study will be conducted by telephone or in person and last about 30 minutes. Providers will be asked to provide their oral informed consent before participating in the interview.

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 buccally (at 24-48 hours following Mifeprex®).

8.3.2 Packaging and Labeling

The mail-order pharmacy 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

Mifeprex® will be procured from Danco Laboratories, LLC, by the study PI, who is a licensed physician who has signed the Danco Prescriber's Agreement. We will use the existing distribution system for Mifeprex® that Danco Laboratories has established. In the signed Prescriber Agreement for the study, the study PI will designate the mail-order pharmacy as the site to which the Mifeprex® will be shipped. This distribution system is considered to be secure, confidential and controlled. UCSF will purchase the medication and have it shipped to the mail-order pharmacy.

The mail-order pharmacy will ensure that the Mifeprex® stock is kept separate from all other drug inventories maintained by the pharmacy. All study Mifeprex® received and dispensed from the mail-order pharmacy will be recorded.

8.4.1 Dosage/Dosage Regimen and Administration

Subjects will receive 200 mg of Mifeprex® to be taken orally at the time agreed on by the patient and the clinician. This will be followed by misoprostol 800 mcg administered buccally (at 24-48 hours following mifepristone).

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) at the mail-order 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 mail-order pharmacy and the clinics. The number of study drugs transferred to the mail-order pharmacy, 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.

Participants who receive mifepristone by mail as part of the study but subsequently indicate that they do not plan to take the medications will be encouraged by the study team to return the medications to the clinic site. The clinic site will document that the medications were returned and then either safely dispose of the medications, deliver the medications to a pharmacy where safe disposal is possible, or mail the medications to the UCSF study team and the UCSF study team will take the medications to a

safe disposal site. If the participant does not want to go to the clinic site, the study team will send the participant a postage-paid mailer to ship the unused medications to the UCSF study team, who will then safely dispose of them.

8.6 Measures of Treatment Compliance

Participant patients will be contacted on Day 3 and Day 14 after the prescription is sent to complete online surveys, which are detailed below in section 10.2. As part of these surveys, patients will be asked if and when they took the Mifeprex® and if and when they took misoprostol. 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 3 Survey. If they received the Mifeprex® but decided not to take it, they will be asked whether they returned it to the study clinic as instructed.

The research team will review all participant survey responses upon submission to ensure treatment compliance. If a participant reports being seen somewhere else for a complication or reports any unusual symptoms in either survey, the research team will inform the site PI and encourage the patient to contact the clinic. In addition, the research team will receive automatic notifications through the online survey platform, Qualtrics, in the following cases, after which the team will contact the participant by email and/or telephone to follow up:

- If a participant reports taking the misoprostol vaginally (instead of buccally)
- If a participant reports not taking the misoprostol after taking mifepristone
- If a participant reports taking mifepristone at >70 days gestation (based on the gestational age dating at initial clinic visit)
- If a participant reports taking the misoprostol <24 hours or >48 hours after the mifepristone
- If a participant reports taking the misoprostol but not taking the mifepristone

This information will enable the research team to monitor and capture all episodes of incorrect administration of mifepristone and/or misoprostol.

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 the pharmacy 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 study patients. 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, insurance status, and ethnicity) will be recorded as part of the initial visit and will be abstracted from the medical record. 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 3 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 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, excessive 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, and height will be collected at the initial visit. A targeted physical examination will be performed at the clinic site according to their current practice. At some sites, gestational age of the pregnancy may be determined by patient history and physical examination.

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 will 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 viable 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 12.

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

If hemoglobin is measured, 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® prescription and again approximately 8 days after taking Mifeprex® to assess for completion of the abortion. These results with the date of the tests will be abstracted from the medical record.

9.2.4 Rhesus (Rh) factor

Rh factor status will be determined for all patients. If the patient has a documented laboratory result of her Rh status, this will be added to her clinical record. If the patient does not have a documented laboratory result, a blood draw will be performed to assess Rh status. Patients who are found to be Rh-negative will be contacted to receive immunoglobulin (Rhlg) within 72 hours of taking mifepristone, either at the clinic site, or arrangements will be made to administer it at a nearby clinic or hospital.

10 PATIENT ACTIVITIES BY DAY

10.1 Day 0

This is the day the patient participant is enrolled in the study. Patients who indicate they are interested in medication abortion will be informed about the study by their treating clinician. If they are interested in participating in the study, they will undergo standard assessment, including an assessment for gestational age, which will include either an ultrasound or physical examination, and counseling for medication abortion. They will also be informed about the study activities and asked to consent for participation. Once eligible participants have signed the Danco Patient Agreement and any other specific consent forms for the site, they will be asked to complete a contact information sheet, which includes their contact information and preferences. Patients may be enrolled during the initial visit if they are eligible based on the information available at the time. It is possible that at this point ultrasound results may still be pending (for example if the patient needed to be referred elsewhere for an ultrasound); if this is the case, patients will be tentatively enrolled in the study (asked to complete the informed consent process and the contact form) and informed that their participation is contingent on confirmation of their gestational age. Once the ultrasound results are known, the provider will update the eligibility form. After determining that a patient is eligible for the study, a clinician at the site will then transmit a prescription for Mifeprex® 200 mg, misoprostol 800 mcg, and any other necessary medications (such as 800 mg ibuprofen) to the mail-order pharmacy, and the patient will be given information about when and how to take the medications. The patient will be informed that the pharmacy will contact them by phone to confirm their mailing address, drug allergies, and whether they have additional questions (note: the patient may also call the pharmacy directly). The patient will be informed to expect the delivery of medications as soon as the following business day and no later than 3 business days later.

10.2 Day 3 Survey

On Day 3 (after the prescription is sent), patient participants will be sent by email or text message, depending on their preference, a link to an online survey about their experience receiving the medications, as well as to collect sociodemographic information (see Day 3 survey). 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 receiving the medications by mail, including whether and when she received the medications and the quality of the packaging, as well as her experience taking the Mifeprex®. We will also collect

information about if and when the Mifeprex® and misoprostol might have been diverted to another person. If they do not respond to the survey within two days, participants will be contacted by telephone or text message up to three times. If a participant has decided not to proceed with medication abortion (for any reason), she will be encouraged to complete the Day 3 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 clinic.

10.3 Clinical follow-up

Women undergoing medication abortion generally undergo clinical follow-up to ensure that the abortion is complete. Follow up to ensure no ongoing pregnancy at approximately 7-14 days after the initial visit may be completed in one of three ways: 1) an in-person clinic visit with ultrasound, 2) an in-person clinic visit with serum hCG (in the case that serum hCG was measured on the day the Mifeprex® was prescribed; the follow-up laboratory test may be performed at an off-site laboratory), or 3) a telephone follow-up with the clinic at approximately 1 week after Mifeprex® was taken, followed by a urine pregnancy test at 3-4 weeks (at home) post medication abortion. Results from these measures will be documented in the clinical record and later abstracted for data collection. No study-related activities will be performed as part of this clinical follow-up. 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. Those who need additional medications will receive either a prescription or referral to another facility. If the participant is referred to another facility for a vacuum aspiration or other treatment related to the medication abortion or if the participant spontaneously goes to another facility, the site PI or delegate will contact the referral site to document the treatment given, abortion outcome (if relevant), and any AEs or SAEs. No study activities will take place at follow-up clinical visits, although clinical information recorded at these visits will be later abstracted from the patient's record (see section 9.1).

10.4 Day 14 Survey

On Day 14 after the prescription is sent, 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), and whether she has sought care at another facility. If she did obtain care at another facility, we will ask for details of the care given to determine if an AE or SAE has occurred, and we will follow up with the participant by telephone to obtain additional details as needed. If the participant reports being seen at another facility, we will alert the site PI. 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 follow-up for the abortion is not yet complete at the Day 14 survey, we will instruct the patient to contact the clinic and ask for permission to contact them again later. If they do not respond to the Day 14 survey, participants will be contacted up to three times.

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(s) 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 REDCap electronic form. 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.

The study team will request consent from participants to obtain access to medical record data related to the abortion, pregnancy, and subsequent birth (if relevant) including through records' release from other facilities. This will enable the study team to collect data on visits to other medical facilities and on pregnancy outcomes for participants.

11 PROVIDER ACTIVITIES

11.1 Needs assessment, training, and post-training evaluation

At baseline, we will conduct a needs assessment focused on provider knowledge of medication abortion, comfort with dispensing Mifeprex®, and anticipated challenges of dispensing Mifeprex®. This needs assessment will be informal, and conducted through conversations with the site investigator(s). Each of the providers interested in being involved in medication abortion provision at the study sites will be required to participate in a training. The training will focus on gaps in knowledge identified in the baseline needs assessment, including specifics about the medication abortion protocol, mifepristone and misoprostol mechanisms of action, side effects, potential complications and follow up. After the training, providers will be asked to complete a brief informal evaluation, which will serve to improve future trainings on the topic.

11.1 Provider interviews

At the end of the study period, providers will be invited to participate in a 30-minute in-depth interview by telephone or in person. The interview will explore the providers' experiences with providing medication abortion and any challenges faced. Providers who participate in prescribing medication abortion to study patients may decline to participate in the interview. Providers will be asked for oral consent to the interview and consent to record the interview will be confirmed and documented.

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. Only serious or unexpected AEs that are possibly, probably, or definitely related to the research will be submitted to the UCSF IRB. Diversion of Mifeprex® obtained in the study to someone other than the participant will also be considered an AE.

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. 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 physician site PI will have safety oversight of participants at the site, will assess AEs and SAEs, and will report them to the study PI and research team, who will then report to the UCSF IRB as

needed. The site PI, in consultation with the study PI, will determine the relationship of the AE to study treatment as definitely related, probably related, 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 and the site PI will monitor the event until the event is resolved or has stabilized.

The study 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. Diversion of Mifeprex® will be reported to the FDA within 15 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 Adverse Event 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 study PI, Daniel Grossman, MD, directly at this number to report medical concerns or questions regarding safety: 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, and reasons for any early discontinuation of participation in the study, will be specified in the subject's data collection documents.

13.3 Replacement of Subjects

If any subject withdraws prior to taking the medications, an additional subject will be recruited to maintain the initial target sample and this will be included in the final report. If a subject withdraws after taking any of the medications and does not complete follow-up, they will be reported as lost to follow-up.

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.

14.1 Study Stopping Criteria

The following criteria will be used to determine whether and when to stop the study prior to meeting recruitment targets:

- If there are 3 cases where mail-order delivery of the medication is delayed by more than 7 days, we will temporarily halt the study and assess the need to adjust the inclusion criteria to less than 57 days' gestation (instead of 63 days) in order to eliminate the possibility that participants receive mifepristone past 70 days' gestation. We will also investigate all cases of medication delivery being delivered more than 4 days after the prescription was sent to understand the factors that contributed to delay and address them. In addition, we will contact all participants on Day 3 after the prescription was sent, and if they have not received the medications, we will encourage them to contact the study site to make other arrangements to obtain the mifepristone and misoprostol.
- If there are 12 cases (3% of total sample) where the participant takes mifepristone after 70 days' gestation, we will assess the need to stop the study. All cases of use past 70 days will be investigated to understand why they occurred and efforts will be made to ensure such errors do not occur in the future. There is evidence that the medication abortion regimen works through 11 weeks of gestation (Kapp, Eckersberger et al. 2019); with regard to clinical safety, this is why the research team feels comfortable with 12 potential cases beyond 70 days gestation. Finally, if 1% of participants (4 cases) take the mifepristone after 84 days (12 weeks), we will stop the study.
- Every AE and SAE will be reviewed by the study PI, and if there is a pattern of definitely-, probably-, or possibly-related SAE/AEs that raise concerns about the safety of the mail-order model of dispensing mifepristone, the study will be stopped. Based on evidence that 0.3% of medication abortions have serious adverse events (Upadhyay, Johns et al. 2018), we will stop the main study if the number of SAEs fall outside of a 95% confidence interval as estimated in a sample of 465 (-0.24% to 0.84%) (minimum sample of 440 plus 25 pilot study participants). Thus we will stop the study if more than 0.84% (n=4) of abortions result in an SAE that is possibly or probably related to the study intervention.

15 DATA SAFETY MONITORING

The site PI will have safety oversight of participants at the site, will assess AEs and SAEs, and will report them to the study PI and research team, who will then report them to the UCSF IRB. Data safety monitoring and review of AEs and SAEs will occur on an ongoing basis through each participant's involvement in the study (up to 6 weeks from day of enrollment). The site PI, in consultation with the study PI, will determine the relationship of the AE to study treatment as definitely related, probably related, 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 and the site PI will monitor the event until the event is resolved or the study is completed. 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 providers who complete an interview will be included in the provider 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 and method of determining gestational age, past medical and surgical history, current medications, and medications prescribed or dispensed. Blood pressure, weight, and height will be collected. All participants will receive the same dose of Mifeprex®.

16.3 Analysis of Primary Endpoint

Acceptability and satisfaction with the mail-order model among patients will be assessed through patient surveys, which will include some open-ended items. The particular variables we will analyze include those on overall satisfaction with the medication abortion service (including whether they would use this mail-order medication abortion service again if they needed another abortion, and whether they would recommend the service to a friend), satisfaction with receiving the medications by mail, reasons for dissatisfaction (open ended questions), and perceptions about the wait time to receive the medications. We will also analyze the reasons why patients who decline participation in the study report not being interested in receiving the medications by mail, as indicated in close-ended and open-ended responses.

We plan to recruit for the main study a minimum sample of 440 participants and a maximum of 625 patients. With the addition of 25 patients in the pilot study, the target minimum number of patients recruited for the study is 465 and the maximum number is 650.

The sample size calculation for this study is based on two measures of acceptability: the proportion of patients who report they would use medication abortion again if they needed another abortion and the proportion who report they were “satisfied” or “very satisfied” with the medication abortion. For both power calculations, we assume 10% loss to follow up, 10% adjustment for clustering, a 5% non-inferiority margin, and a two-sided alpha of 0.05. Research with patients obtaining clinic-based medication abortion has estimated the proportion who would use medication abortion again as 89.7% (Teal, Dempsey-Fanning et al. 2007). Based on our assumptions, with a minimum sample of 440 patients, we will have a final analytic sample of approximately 400 patients, which gives us 79% power to assess this measure of acceptability; with a maximum sample of 625 recruited patients, we will have a final analytic sample of approximately 560 patients, which gives us 92% power.

A meta-analysis reviewed 8 studies investigating satisfaction with medication abortion (Ngo 2011); of those who had a home-based medication abortion (n=3,138), the average proportion reporting they were “satisfied or highly satisfied” was 88.4%. Based on our assumptions, with a minimum sample of 440 patients, we will have a final analytic sample of approximately 400 patients, which gives us 77% power to assess this measure of acceptability; with a sample of 625 recruited patients, we will have a final analytic sample of approximately 560 patients, which gives us 90% power.

16.4 Analysis of Secondary Endpoints

Feasibility of the mail-order pharmacy dispensing model will be assessed through surveys with patients, and include determination of the proportion of patients who receive the medications by Day 2 and by Day 3 after the prescription is sent, the quality of the packaging, whether patient confidentiality was compromised due to receiving the medications by mail, as well as the proportion of patients who had to go to the clinic to obtain the medications.

Clinical effectiveness and safety outcomes, including adverse events, with medication abortion obtained via mail-order pharmacy 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. The analysis populations for the effectiveness and safety endpoints will include patients who enroll in the study, take either of the medications, and for whom we have follow-up data. We will not assume that patients who do not have follow-up data had a successful abortion.

Effectiveness will be defined as the successful completion of abortion (versus incomplete abortion or continuing pregnancy), without vacuum aspiration. Continuing pregnancy will be defined as a viable pregnancy following treatment and need for vacuum aspiration to terminate the pregnancy or cases where a patient elects to continue the pregnancy after failed treatment (Creinin & Chen 2016). We will document vacuum aspiration abortions, including reasons for aspiration, reported by participants and those determined as necessary by the study providers at follow-up visits. We will compare effectiveness (the proportion of our sample that experiences a complete abortion not requiring vacuum aspiration) with published estimates (97.4%) (FDA 2016), using an exact binomial test. Assuming 10% loss to follow-up and 10% adjustment for clustering, and a two-sided alpha of 0.025 (to account for type I error), we estimate that a final analytic sample ranging from approximately 400 to 560 patients gives us 98% to 100% power to determine that mail-order medication abortion is as effective as in-person dispensing, if effectiveness in the mail-order model is no lower than 92.4%. A non-inferiority limit is defined as -5% and as an acceptable difference in the proportion of complete abortions.

We are unable to similarly assess whether the prevalence of clinically significant adverse events differs between the mail-order dispensing model and historical controls given the very low frequency of this outcome (<0.5%) (Upadhyay, Desai et al. 2015). A sample size of over 10,000 is required to power such an analysis and is not feasible in the proposed study. Thus, our analysis of safety outcomes will be exploratory. Using a patient survey and medical record review, we will thoroughly document women's experiences with any adverse events. In particular we will be interested in documenting adverse events that could be related to mail-order dispensing. For example, if the delivery of the medication was delayed, which caused a patient to undergo medication abortion after 70 days gestation and she had heavy bleeding requiring an emergency department visit, we would consider this to be possibly related to the mail-order dispensing model. Additional safety outcomes include the proportion of participants who take mifepristone after 70 days gestation and the proportion that divert the medication to someone else.

Provider acceptability, including clinician and staff perspectives on the timing and logistics, quality of care, clinic flow, cost, and sustainability of the mail-order dispensing of mifepristone and misoprostol, will be explored through qualitative analysis of in-depth open-ended interviews. We will invite all clinicians and staff who were involved in identifying and recruiting patients, communicating with the mail-order pharmacy, and/or following up with patients about their clinical care in the study, to participate in an interview at the end of the study period.

16.5 Interim Analysis

An interim descriptive analysis may be conducted when approximately half of the minimum sample is recruited. Unexpected and serious adverse events will be monitored as noted above (see section 12).

16.6 Sample Size

In addition to the 25 patients in the pilot study, we aim to recruit a minimum of 440 and a maximum of 625 patients for this study, across 15-20 sites. The sample size calculation for this study is based on a measure of acceptability: the proportion of patients who report they would use medication abortion again if they needed another abortion. Research with patients obtaining clinic-based MA has estimated that proportion as 89.7% (Teal, Dempsey-Fanning et al. 2007). We would like to determine if acceptability of medication abortion when receiving the medications by mail is no more than 5% lower than 89.7%. Assuming 10% loss to follow-up, with a minimum sample of 440 patients, we will have a final analytic sample of approximately 400 patients; with a sample of 625 recruited patients, we will have a final analytic sample of approximately 560 patients. With a 2-sided alpha of 0.05 and 10% adjustment for clustering, a final analytic sample size of approximately 400 gives us 79% power, and an analytic sample of 560 gives us 92% power to assess this measure of acceptability.

We aim to interview all the providers (or staff administrators) involved in medication abortion provision at the study sites, up to 50. This sample size will be determined by the number of providers/staff 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 3 and Day 14 following the medication abortion. Clinical data will also be abstracted from the electronic medical record system at each study site. Providers and staff will be invited to complete a survey after the training and an interview 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 3 survey Day 14 survey Clinical data abstraction form Ongoing pregnancy form	Patient informed consent (written) HIPAA Authorization Form
Providers	Post-training evaluation Open-ended interview guide	Provider informed consent for interview (oral)

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 monitored 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 (providers and staff), and they may refuse to be audio-recorded during the interview, without any adverse consequences for their medical treatment (patients) or employment (providers and staff). 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 providers 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 and the Einstein IRB, and any other relevant site IRBs, 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, 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 relevant 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 surveys. Medical record data will only be abstracted from patients who also provide consent using the HIPAA Authorization form. Providers will be consented for their participation in the interview separately; the consent will be provided orally on the telephone or in person. 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 will be compensated for each phase of the study they complete. This includes being reimbursed $25 for completing each of the two surveys, in addition to $15 for the enrollment visit when they provide contact information, for a maximum reimbursement of $65. Reimbursement will be in the form of a gift card. Patients will be informed that the study will cover the cost of mifepristone, misoprostol, and ibuprofen (if prescribed), and that all other costs (including lab tests, ultrasound, office visit, etc.) will be billed to insurance where possible as they would be for standard care. At sites where this is not possible, the study will cover the cost of other clinical services, patients will be informed of this as well. At all sites, participation in the study will not result in any increased out-of-pocket payment by patients.

The mail-order pharmacy will be reimbursed for the dispensing fees associated with mifepristone and

misoprostol ($18 each at $36/participant), the cost of other medications (misoprostol, antibiotics if used, ibuprofen; up to $25/participant), and the shipping costs (approximately $15/participant for overnight delivery). UCSF will purchase the mifepristone that will be sent from the mail-order pharmacy ($54/participant).

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.

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