

COMPARATIVE EFFECTIVENESS OF PREGNANCY FAILURE MANAGEMENT REGIMENS (PREFAIR)

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Protocol Signature Page

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Date

I, the undersigned, will conduct the clinical study as described and will adhere to the *Code of Federal Regulations*, Title 21 and Title 25, Part 46, Good Clinical Practices (GCP), International Conference on Harmonisation (ICH), and the Declaration of Helsinki. I have read and understood the contents of the Protocol.

The signature of the investigator below indicates acceptance of the protocol and a complete understanding of the investigator commitments as outlined in Form FDA 1572, Statement of Investigator.

Principal Investigator's Signature

Printed Name

Date

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Study Summary

Title	Comparative Effectiveness of Pregnancy Failure Management Regimens
Short Title	PreFaiR
Phase	Phase 3
Methodology	Pragmatic Comparative Effectiveness Trial
Study Duration	5 years
Objectives	To compare the effectiveness of combination treatment (mifepristone premedication and single-dose misoprostol) to single-dose misoprostol (standard of care) for the management of early pregnancy failure. To test the ability of trophoblastic and endometrial biomarkers in the serum of this patient population to predict successful medical management of EPF
Number of Subjects	300
Diagnosis and Main Inclusion Criteria	<ul style="list-style-type: none"> • 18 years or older • hemodynamically stable • confirmed diagnosis of intrauterine embryonic/fetal demise or anembryonic gestation
Study Product, Dose, Route, Regimen	800 µg (vaginal) misoprostol alone versus 800 µg (vaginal) misoprostol preceded by 200 mg (oral) mifepristone 24 hours prior.
Duration of administration	24 hours
Statistical Methodology	<p>The study population will be summarized overall, and by treatment group, using standard descriptive statistics. Both intent to treat and compliant populations will be analyzed. For categorical data, chi-square test will be used. For continuous variables, t-test will be used if the distribution is normal; otherwise rank-sum test or log transformation will be used. The following outcomes will be evaluated:</p> <ul style="list-style-type: none"> • Success rates between study arms for early pregnancy failure; • Side effect frequency, participant satisfaction, and acceptability of the treatment regimens; • Cost analysis to compare these two treatments. <p>Logistic regression and classification and regression trees (CART) will be used to develop a predictive model for successful management of EPF that includes the biomarker analyses to be performed, which will serve as the basis for a clinical predictive index.</p>

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1. Background

Early pregnancy failure (EPF) is the most common complication in pregnancy. An estimated 15% - 25% of clinically recognized pregnancies end in miscarriage [1-4], and approximately 1 out of 4 of women will experience a pregnancy loss over the course of her life [1]. About one million women will experience a pregnancy loss each year in the United States. Pregnancy failures most commonly occur in the early first trimester and these losses are sub typed as intrauterine embryonic demise/intrauterine fetal demise (IUED/IUFD), anembryonic gestation [5], inevitable abortion, and incomplete abortion [6]. For patients with EPF, traditional treatment has been surgical uterine evacuation with sharp uterine curettage and/or suction. This practice dates to the early 20th century when prompt treatment was required to prevent hemorrhage and infection when women presented acutely [7]. With the widespread use of transvaginal ultrasound in early pregnancy, women diagnosed with EPF no longer universally present with bleeding at the time of pregnancy expulsion (incomplete/inevitable abortion). Instead, most women learn of their pregnancy's demise during routine care prior to the onset of symptoms (missed abortion or IUED/IUFD/anembryonic gestation). This shift away from urgent/emergent care has led to an interest in pursuing nonsurgical treatment options for EPF that avoid the morbidity, time, expense and complications associated with surgery [3,4,8]. While some women pursue expectant management, the unpredictability of the bleeding and cramping, and the prolonged time-to-resolution, make this alternative less acceptable than active management to most patients [9,10]. Women generally prefer active management [3,9-12]; in fact, the ability to have control over the management of the miscarriage can relieve some of the emotional burden that accompanies first trimester pregnancy loss [13-17].

Medical management of EPF with prostaglandin analogues, at least theoretically, allows for planned, expedited expulsion of the nonviable pregnancy tissue without the morbidity and expense of surgery. Prostaglandins (PG) induce uterine contractions and, when compared with oral administration, vaginal administration has a longer-lasting effect on the myometrium [18]. Medical management of EPF is highly desired by many patients. Treatment can be self-administered and expulsion can be accomplished in the privacy of a woman's home.

The most studied and commonly used method of medical management is misoprostol. It is FDA approved and marketed for gastric ulcer disease treatment, but widely used in obstetrics and gynecology to ripen the cervix and induce uterine contractility. Misoprostol is a PGE₁ analog that is marketed in 200 µg tablets. It is inexpensive and stable at room temperature. In women with incomplete abortion, this option is almost as effective as uterine aspiration for uterine emptying. However, in women who present without active bleeding, i.e. women with missed abortion or IUED/IUFD/anembryonic gestation, misoprostol alone provides suboptimal results.

Notably, a different regimen is used for uterine evacuation of *viable* pregnancies with much better results than those reported with misoprostol alone for missed abortion. Misoprostol is combined with mifepristone for women who do not want to continue their pregnancy. Mifepristone is a 19-nor steroid with a bulky side chain responsible for inducing and stabilizing an inactive receptor conformation. In the presence of progesterone (P₄), mifepristone acts as a competitive P₄ receptor antagonist [19]. During pregnancy, uterine contractility is suppressed by progesterone. As a P₄ receptor antagonist, mifepristone primes the myometrium and cervix for prostaglandin activity and increases uterine contractility [18,19-22]. By blocking P₄, mifepristone limits the invasion of trophoblastic tissue at the level of the endometrium [23], and interrupts P₄-mediated trophoblast-decidua interactions [20,21,24].

This protocol is designed to test the efficacy of the combined regimen, mifepristone + misoprostol, among women with stable missed abortion.

1.2. Clinical Data to Date

Misoprostol has been used by millions of men and women worldwide since its approval in 1988 for prevention of gastric ulcers associated with chronic NSAID use. Notably, misoprostol has been used safely for incomplete abortion around the world. Misoprostol has not been associated with long-term effects on women's health, and prolonged or serious side effects are virtually nonexistent. Misoprostol is the most commonly used prostaglandin to effect uterine evacuation in the setting of early pregnancy failure. Its safety and effectiveness, specifically when given vaginally, have been established by multiple randomized and controlled trials, as demonstrated by two Cochrane Reviews [5, 6]. The advantages of misoprostol over other drugs (including prostaglandin E₂) are its low cost, low incidence of side effects when given intravaginally, stability at room temperature, and ready availability. The risk of a major complication is rare.

Complete expulsion rates for women using misoprostol for miscarriage completion vary significantly in the published literature, from 25-86% [5,6,8,25-30]. This variability is due, in part, to the fact that studies have used differing definitions of pregnancy failure; as well as varying drug doses, delivery modes, criteria for success, and outcome measures [5,6,8,26,31-40]. The earlier studies helped to reveal the relative merits of different drugs, doses and routes. The data support that misoprostol 800 µg vaginally provides the best toxicity/efficacy profile [6,8]. The definitive, multi-center, randomized trial comparing surgical management to medical management with vaginal misoprostol (the 2005 MEPF trial [9]) in women through approximately 12 weeks gestation (in which our team at both centers collaborated), reported successful uterine evacuation in 71% of participants with one dose of misoprostol (800 µg vaginally). These complete abortion rates contrast dramatically with the published 98% success rate for uterine curettage [9]. While the MEPF trial found misoprostol to be "non-inferior" to surgery due to trial design, few could argue that 60-71% success compares fairly with the 98% that surgery boasts. Nevertheless, misoprostol is now widely used in the U.S. and across the globe for management of EPF; the regimen tested by Zhang et al. [9] has become the evidence-based standard of care. The efficacy of misoprostol for medical management of pregnancy failure in the first trimester was illustrated in a large, well-designed trial in which 652 women with missed, incomplete, or inevitable abortion were randomly assigned 3:1 to receive 800 µg misoprostol intravaginally or undergo vacuum aspiration as cited above [9]. The rates of complications such as fever, infection, and excessive bleeding, and emergency room visits, were very low and similar to those from uterine aspiration.

Published clinical predictors of treatment success with misoprostol for EPF include lower abdominal pain, vaginal bleeding within 24 hours of presentation, and nulliparity [25]. Misoprostol alone is highly

effective for women who present with incomplete/inevitable abortion (active bleeding and cramping, usually with an open cervical os) [6,9,28,41-43]. We propose a novel investigation of maternal serum biomarkers of implantation, endometrial maturation, and pregnancy maintenance as prognosticators of medical treatment success for EPF. Investigation of the role that Activins (intra and extra-villus cytotrophoblast) Inhibins (corpus luteum, cytotrophoblast), Glycodelin (endometrial decidua), and others (see *choice of markers* section below) play in abetting or impeding tissue expulsion with medical management are likely to further our understanding about a woman's likelihood of successful medical treatment for miscarriage. Our preliminary data show that statistically significantly depressed levels of β -human Chorionic Gonadotropin (β hCG) and elevated Activin levels are present in women who failed misoprostol treatment in the NICHD-sponsored MEPF trial. **Our goal is to improve the success of non-surgical management of EPF.**

1.3. Dose Rationale and Risk/Benefits

Studies of medical termination of *viable* pregnancies using a combination of 200 mg mifepristone with misoprostol 800 μ g demonstrate higher success rates than the use of misoprostol alone for the same indication, exceeding 95% in women up to 9 weeks gestation [22,44-46]. This is different from the FDA approved regimen of 200 mg mifepristone plus 400 μ g oral misoprostol, but it has been shown to be the most effective regimen and is the standard of care, used by over 2 million U.S. women to date. In contrast, success rates with a single dose of misoprostol alone for termination of viable pregnancy are 60-70% [47-49]), a rate similar to that found in the MEPF study for misoprostol alone for EPF [9]. While not commonly used in the U.S., multiple studies verify the efficacy of the combined use of mifepristone and misoprostol to induce viable pregnancy termination beyond 9 weeks as well [50-54].

Mifepristone, dosed as 200 mg, in combination with misoprostol, has been used by millions of women globally to induce abortion (National Abortion Federation statistics, 2010). The 200 mg dose is equally as effective and less expensive than the 600mg option [55,56]. The combination of mifepristone and misoprostol has also been used to treat women with EPF [36]. In fact, even though its efficacy has yet to be proven due to problems with trial designs, it was used in a study (the *MIST* trial) that was designed to evaluate infection risk for women undergoing miscarriage management with aspiration, medication, or expectantly [57]. The *MIST* trial confirmed low infection rates, and low complication rates overall, but the authors did not compute efficacy. In this protocol, we aim to bridge the final gap and to definitively test the *efficacy* of mifepristone combined with misoprostol for the management of missed abortion. The safety of the dosage, delivery route, and combination is well tested in pregnant women generally (see Appendix 1).

The highly effective, safe combination regimen described above may also effectively treat women with EPF [11,12,39,58]. Our preliminary observations [11] strongly support this. However, this regimen needs to be rigorously tested in a sufficiently powered clinical trial [5]. The biologic basis for why a combination regimen should be more effective and safe than misoprostol alone, even in the cases of a failed pregnancy, has been preliminarily described. We and others have hypothesized that those failed pregnancies that do not respond to uterine evacuation with misoprostol alone appear to represent a subset of EPF in which the invasion of the extravillous trophoblast into the decidualized endometrium is altered [24,59]. This enhanced "attachment" of the pregnancy may be due to a direct trophoblastic effect, and/or may be due to characteristics of the decidualized endometrium. There is evidence for a direct supportive effect of P_4 on human trophoblast function [60], and therefore, this effect could be inhibited by the use of mifepristone. In addition, mifepristone also has anti-glucocorticoid activity, with relatively high binding affinity for the glucocorticoid receptor [20,21]. Since glucocorticoids are critical to

the function of human trophoblast cells [61], the presence of mifepristone could lead to decreased proliferation, differentiation, and/or invasive properties of the trophoblast – even in a failed pregnancy [62].

2 Study Objectives

Primary Objective

To compare the effectiveness of combination treatment (mifepristone premedication plus single-dose misoprostol) to single-dose misoprostol (standard of care) for the management of early pregnancy failure.

Our hypothesis states that the combination of mifepristone and single-dose misoprostol will be more effective than single-dose misoprostol alone, and will reduce the proportion of failed medical treatments (those who require repeat dosing or surgery) by at least 20% in 300 women seeking treatment for first trimester embryonic/fetal demise and anembryonic gestation.

Secondary Objective

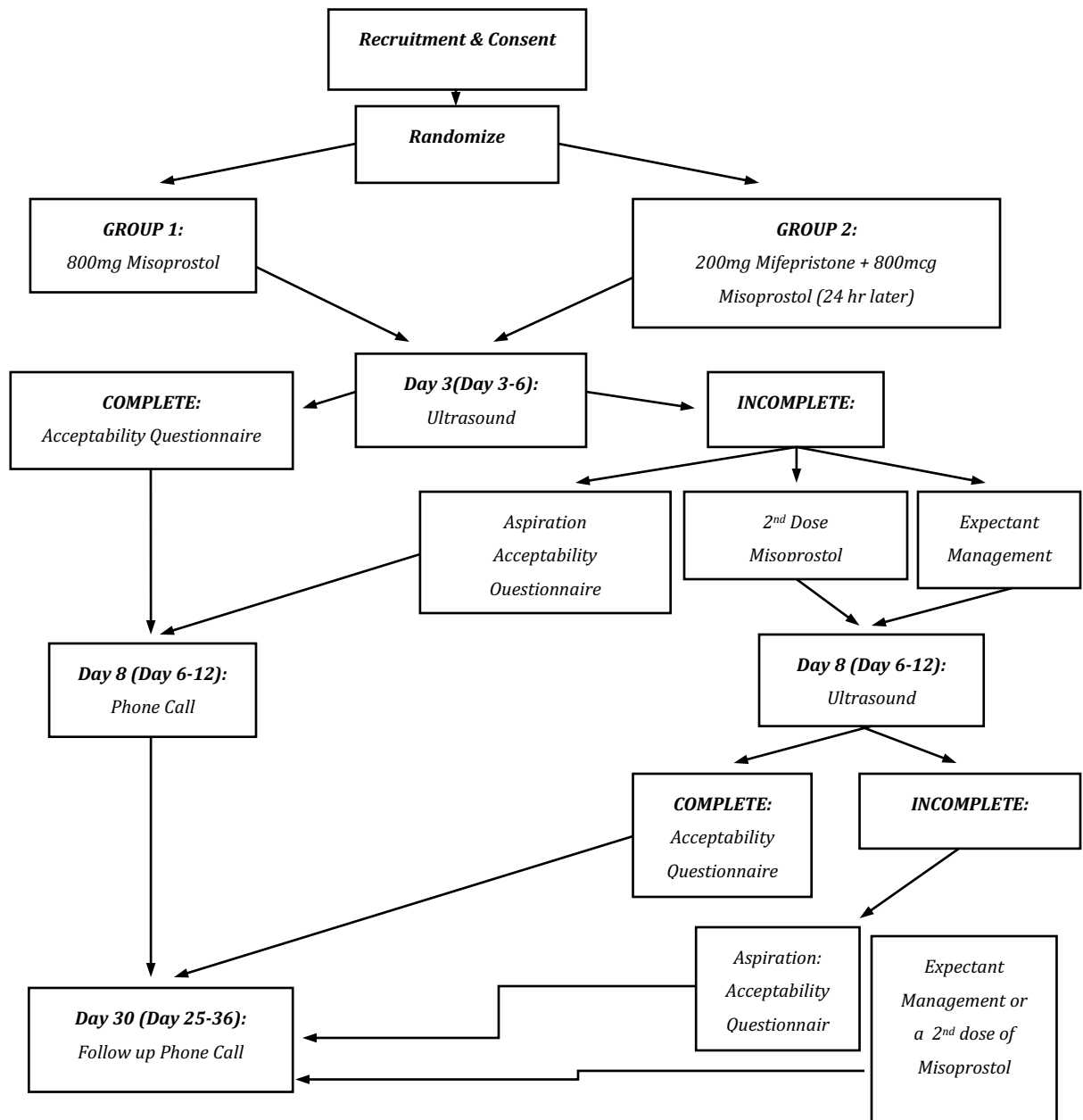
To test the ability of trophoblastic and endometrial biomarkers to predict which women are most likely to succeed with medical management of early pregnancy failure and to derive and internally validate a prediction model designed to guide individualized counseling and treatment for early pregnancy failure.

Our hypotheses state that (1) biomarkers of endometrial decidualization and trophoblast function in the maternal circulation prior to treatment will predict the success of medical management and that (2) quantitative evaluation of a single biomarker or combination of biomarkers, combined with clinical characteristics, will accurately predict the women who will benefit from medical management overall and will identify those women who may especially benefit from combination treatment.

3 Study Design

3.1. General Design

This is a pragmatic randomized, controlled trial comparing mifepristone (200mg) administered orally for premedication in office followed by vaginal misoprostol (800 µg) self-administered at home approximately 24 hours later. Misoprostol is the standard of care for medical management of EPF, and widely used across the globe for treatment of early pregnancy failure as well as for other obstetrics indications. Participants will be randomized to each group in a 1:1 ratio and treatment success will be defined as complete expulsion of the gestation by day 3 without any further intervention. Treatment success, additional interventions, adverse events, acceptability, and quality of life will be assessed at day 3, day 8, and at 30 days post treatment. The general schema is as follows:



3.2. Primary Study Endpoints

Gestational sac expulsion with one treatment dose and no need for additional medical or surgical intervention.

3.3. Secondary Study Endpoints

Regimen acceptability, side effects, participant quality of life, cost using each regimen. Biomarkers and clinical characteristics associated with complete gestational sac expulsion.

4 Subject Selection and Withdrawal

4.1. Inclusion Criteria

- between 5 and 12 completed weeks gestation
- 18 years or older
- hemodynamically stable
- confirmed diagnosis of intrauterine embryonic/fetal demise or anembryonic gestation (ultrasound examination demonstrates a fetal pole without cardiac activity measuring between 5.3 and 40 mm or an abnormal growth pattern diagnostic of early pregnancy failure)
- willing and able to give informed consent

4.2. Exclusion Criteria

- diagnosis of incomplete or inevitable abortion (absent gestational sac and/or open cervical os)
- contraindication to mifepristone (chronic corticosteroid administration, adrenal disease)
- contraindication to misoprostol (glaucoma, mitral stenosis, sickle cell anemia, or known allergy to prostaglandin)
- cardiovascular disease (angina, valvular disease, arrhythmia, or cardiac failure)
- most recent hemoglobin <9.5 g/dL
- diagnosis of porphyria
- known clotting defect or receiving anticoagulants
- pregnancy with an IUD in place
- breastfeeding during the first 7 days of study participation
- unwilling to comply with the study protocol and visit schedule
- any evidence of viable pregnancy
- possibility of ectopic pregnancy
- known or suspected pelvic infection
- concurrent participation in any other interventional trial

4.3. Subject Recruitment and Screening

This is a multi-site trial. Participants will be recruited by referral from the clinical practices and Emergency Departments within the respective health systems, as well as referring practices.

Women who meet the entry criteria will be advised of the study and, if interested, referred to the research office. All subjects will sign the informed consent form before any study procedures are performed.

4.4. Early Withdrawal of Subjects

4.4.1. When and How to Withdraw Subjects

A subject can be discontinued from the study at her request, or for any significant adverse experience that, in the opinion of the investigator(s), precludes further participation.

4.4.2. Data Collection and Follow-up for Withdrawn Subjects

All reasonable efforts will be made to ensure that enrolled subjects return to the sites for all study visits. Any subject who misses a scheduled visit or telephone follow-up call will receive further contact attempts by the study staff as follows:

- At least three documented attempts to contact the subject by phone, e-mail or similar mode of communication.
- If the subject cannot be contacted, or is contacted and still fails to come in for a scheduled visit, a certified letter must be sent to the subject indicating the importance of follow-up and instructing her to contact the site immediately.

A subject should be considered lost to follow-up when:

- There have been three documented attempts to contact the subject by phone, e-mail, or similar mode of communication, and a certified letter, that has not yielded a response, has been sent

Subjects who received treatment and discontinued from the study for any reason will be contacted at study day 30 for safety outcomes.

We have inflated our sample size estimate by 5% for loss to conservatively account for follow-up that may occur despite these efforts. The Zhang study [9], in which our sites participated, had a less than 1% lost to follow-up in the medical management arm. Our 5% is, therefore, a generous allotment for lost to follow-up.

5 Study Drug

5.1. Description

The mifepristone will be provided to subjects as one (1) 200 mg oral tablet. The misoprostol will be provided to subjects as four (4) 200 µg vaginal tablets.

5.2. Treatment Regimen

The subject will be randomized to receive 800 µg (vaginally) misoprostol alone or 800 µg of misoprostol (vaginally) preceded by 200 mg of mifepristone (orally) 24 hours prior.

5.3. Method for Assigning Subjects to Treatment Groups

The subject will be randomly assigned to one of two study groups: 800 µg vaginal misoprostol (group 1) or 800 µg vaginal misoprostol preceded by 200 mg mifepristone orally (group 2). Randomization will be performed through a central randomization process using REDCAP. Participants will be randomized in a 1:1 ratio of treatment groups. Randomization will be stratified by research center.

5.4. Preparation and Administration of Study Drug

Both mifepristone and misoprostol will be acquired, repackaged, and labeled for investigational use by the University of Pennsylvania Investigational Drug Service (IDS). Penn IDS will supply the investigational drugs to all study sites. Investigational drugs are procured, stored, inventoried, and dispensed in compliance with all applicable regulations and policies. Since the standard is for the drugs to be dispensed from the doctor's office, the investigational drug will be stored in a locked cabinet in the research office.

5.5. Subject Compliance Monitoring

To assess and track subject compliance with the misoprostol administration, participants' diaries will be reviewed. Subjects will also be asked to return the medication packaging at their next scheduled visit.

5.6. Packaging

The University of Pennsylvania Investigational Drug Service (IDS) will acquire both study drugs and repackage them for investigational use. Mifepristone will be packaged in blister packs of three (3) 200 mg oral tablets, with one tablet per subject being dispensed for administration in the office. Misoprostol will be packaged in quantities of four (4) 200 µg vaginal tablets.

5.7. Receiving, Storage, Dispensing and Return

5.7.1. Receipt of Drug Supplies

Upon receipt of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

5.7.2. Storage

The investigational drug is to be stored at room temperature (15-25° C). Excursions up to 30° are allowed. No special handling is required during storage.

5.7.3. Dispensing of Study Drug

The drug will be assigned to each subject per the randomization scheme. Regular drug reconciliation checks will occur by the study team. Regular study drug reconciliation will be performed to document drug assigned; drug consumed; and drug remaining. This reconciliation will be recorded, and signed and dated by the study team.

5.7.4. Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be recorded, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drugs destroyed on site will be documented in the study files.

6 Study Procedures

6.1 Screening Visit

- Informed consent will be obtained.
- Information about telephone contact will be obtained. A pelvic examination will be performed to determine that the cervical os is closed. Gonorrhea and Chlamydia testing may be performed at this time if it has not been done in this pregnancy and is indicated.
- A transvaginal ultrasound examination will be performed unless a complete report is available from an adequately detailed examination within 24 hours prior to enrollment.
- Approximately 1 tablespoon of blood will be drawn for a hemoglobin and blood type if record of these values is not available (hemoglobin must have been obtained within the past 6 months). A rapid hemoglobin (via the HemoCue) may also be utilized.

If it is determined that the subject is eligible for the study, she may proceed to study enrollment.

6.2. Study Day 1 Visit

This visit may or may not occur on the same day as the screening visit.

Pre-Treatment

- If Study Day 1 does not occur on the same day as screening and there has been active vaginal bleeding since screening, the transvaginal ultrasound must be repeated.
- The subject will be questioned to obtain baseline information about her demographic characteristics and her medical, coital, menstrual, pregnancy, and contraceptive history. She will be given the following questionnaires to complete at home prior to inserting misoprostol and return at her next visit: CES-D and the Perceived Stress Scale.
- Rh-immune globulin 50 µg (“MICRhoGAM”) will be administered within 72 hours of this visit if the subject is Rh-negative and has not recently received Rh-immune globulin.
- Additional blood will be drawn (20 cc) and it will be stored for analysis of proteins and hormones.
- Vital signs, weight, and height (to calculate BMI) will be measured.
- A pelvic examination and/or Gonorrhea and Chlamydia testing may be performed if indicated
- The subject will be randomly assigned to one of the two study groups: 800µg (vaginally) misoprostol (group 1) or misoprostol 800 µg (vaginally) preceded by 200 mg mifepristone po (group 2). See Method for Assigning Subjects to Treatment Groups Section 3.1

Treatment

- If the participant is randomized to group 2, she will be given 200mg of mifepristone. She will swallow the tablet prior to being discharged from the study visit.

- All subjects will be given four 200 µg misoprostol tablets to place vaginally approximately 24 hours later at home.
- The subject will be offered prescriptions for pain relievers per local standards at each site.
- The participant will be instructed to abstain from sexual intercourse until the passage of the pregnancy has been confirmed.
- The subject will receive instructions about what to expect after misoprostol administration as per standard of care.
- A diary will be distributed to collect information about bleeding, pain medication use, and symptoms. The subject will be instructed on how to properly complete the diary. The subject should bring this diary to each visit.
- A follow-up appointment will be made for Day 3.

Treatment may be delayed per subject preference. If treatment is delayed, and there has been active vaginal bleeding since the last transvaginal ultrasound, the ultrasound must be repeated prior to dispensing drug.

6.3 Study Day 3 Visit

This visit will occur between treatment day 3-6, ideally at least 24 hours after administration of misoprostol.

- Vital signs will be measured.
- A transvaginal ultrasound examination will be performed by a masked ultrasonographer. A pelvic exam will be performed if indicated.
- If the gestational sac is absent, the subject will need no further scheduled visits. She will receive a contraceptive prescription or device, if desired. She will receive a phone call on study day 8 to assess well-being.
- If the gestational sac is still present, the participant may opt for an aspiration procedure, a second dose of misoprostol or expectant management.
- If she opts for a second dose of misoprostol or expectant management she will be scheduled for an office visit on study day 8.
- If she has an aspiration procedure, no further visits are required and her study day 8 visit will instead be a phone call. She will receive a contraceptive prescription or device, if desired. If she chooses an aspiration procedure, but does not have the procedure prior to the day 8 time point, she will come to the office for the study day 8 visit for assessment.
- Approximately 20 cc of blood will be drawn and stored for analysis of possible biomarkers.
- Completed diary will be reviewed with subject. Adverse events will be reviewed and recorded.
- If subject requires a visit on study day 8, a new diary will be distributed.

6.4 Study Day 8 Visit (or Phone Call)

This visit will occur between study day 6-12. For those who were confirmed to have passed the pregnancy or had an aspiration procedure on Study Day 3, this visit will instead be a phone call to evaluate for bleeding or possible need for further evaluation.

- If this visit occurs in person, vital signs will be measured.

- Subjects who are scheduled to return for a visit on study day 8 will have a transvaginal ultrasound examination performed by a masked ultrasonographer. A pelvic exam will be performed if indicated.
- If no gestational sac is seen, the subject will receive contraception counseling and plan for a follow-up phone call on study day 30.
- If the examination demonstrates a persistent gestational sac, the options will be given for an aspiration procedure, a second dose of misoprostol or expectant management. The expectant management plan will include weekly visits for evaluation until the miscarriage is complete. These weekly visits will include a review of symptoms and adverse events, and an exam or ultrasound as indicated. They will also be offered active management if appropriate.
- Completed diary will be reviewed with subject. Adverse events will be reviewed and recorded.
- If subject requires additional visits, a new diary will be distributed.

6.5 30 Day Phone Call

All subjects will be contacted by telephone 30 days (range 25-36) after study day 1. Information on additional symptoms and treatment during the extended period will be recorded. Subjects will be asked to report any additional adverse events. The Post-Study Acceptability Questionnaire will be completed at this time, which will include the following scales: CES-D, Perceived Stress Scale, Adverse Child Experiences Questionnaire (ACE), and the Social Support Interview. The primary outcome of success (tissue expulsion after 1 dose of misoprostol with no additional need for medical/surgical intervention) or failure is ultimately confirmed at this 30-day point.

6.6 Additional Visits

- If an extrauterine pregnancy is diagnosed at any point during the study, appropriate management (medical or surgical) will be instituted within the standard of care and after a full discussion of appropriate options with the subject.
- Contraceptive counseling will be initiated at the study day 1 visit and performed throughout the study. If the participant desires a method of contraception, she will be instructed to begin its use after the study is completed.
- If the subject does not return for any visit, she will be telephoned to reschedule the visit. All efforts will be made to maintain confidentiality if telephone calls are necessary. If the subject is unable to be reached by phone within one week of her scheduled visit, a certified letter must be sent indicating her need to return.

7 Statistical Plan

7.1. Sample Size Determination

Sample size calculations are based on detecting differences in the success rates between the misoprostol only and combined groups. Based upon prior research, we would expect a 60-71% single-dose success rate in the misoprostol only group [25]. Our preliminary data showed a 90% single-dose

success rate in the combined group using the proposed study regimen [11]. If we assume a conservative 85% success rate estimate for combined (C) and 70% success in the misoprostol only (M), we require 134 participants/group to show a difference if one is there (Table 2). To arrive at the total number of women needed to enroll, we inflate this estimate by 10% for loss to follow-up (5%) and interim analysis (5%). We will have adequate power to show a difference in success rates for all proportions above 10%. Thus, our proposed recruitment goal of 300 women (150/group) will enable us to find a clinically meaningful difference of 15% and confidently find the expected difference (20%) between groups.

Combination success rate	Misoprostol only success rate				
	50%	60%	65%	70%	75%
80%	n = 45 C: ±11.7% M: ±14.6%	n = 91 C: ±8.2% M: ±10.1%	n=151 C: ±6.4% M: ±7.6%	n = 313 C: ±4.4% M: ±5.1%	n = 1134 C: ±2.2% M: ±1.7%
85%	n = 33 C: ±12.2% M: ±17.1%	n = 57 C: ±9.3% M: ±12.7%	n=83 C: ±7.7% M: ±10.3%	n = 134 C: ±6.8% M: ±7.8%	n = 270 C: ±4.2% M: ±5.1%
90%	n = 25 C: ±11.8% M: ±19.6%	n = 38 C: ±9.5% M: ±15.6%	n=51 C: ±8.2% M: 13.1%	n = 72 C: ±6.9% M: ±10.6%	n = 113 C: ±5.5% M: ±8.0%
95%	n = 18 C: ±10.3% M: ±23.8%	n = 26 C: ±8.4% M: ±19.2%	n = 31 C: ±7.7% M: ±17.0%	n = 42 C: ±6.5% M: ±14.0%	n = 55 C: ±5.8% M: ±11.5%

7.2. Statistical Methods

Primary Analysis: Baseline demographic characteristics of the subjects in the two groups will be examined. If the randomization is executed correctly, we expect no significant difference between the two groups on these variables. If there is an imbalance on certain variables (mostly likely by chance) and these variables also affect the outcomes variables, we will control for these variables using indirect standardization, Mantel-Haenzel stratified analysis or multivariable logistic (for categorical outcome) or linear regression (for continuous outcome). If there is a gross imbalance between the two groups, we will conduct in-depth evaluation to identify factors that may adversely affect randomization. Multivariable logistic and linear regressions will be used to adjust for the imbalance.

We will explore outcomes by clinical site; if there is no significant overall difference among the sites (homogeneous), we will pool sites together. However, if there is significant overall difference, we will identify which site(s) differ from others. Pairwise comparison will be conducted with Scheffe adjustment of significance level. In all following analyses, site will then be an independent variable for adjustment.

Both intent to treat and compliant populations will be analyzed. For categorical data, chi-square test will be used. For continuous variables, t-test will be used if the distribution is normal; otherwise rank-sum test or log transformation will be used. The following outcomes will be evaluated:

- Success rates between study arms for early pregnancy failure;
- Frequency of side effects and serious adverse events between study arms;
- Patient's satisfaction, anxiety, and acceptability of the treatment regimens;
- Cost analysis to compare these two treatments.

The outcome is defined as gestational sac expulsion with one treatment dose on Study Day 3 and no need for surgical intervention or medical intervention within 30 days of treatment. The overall success proportion, along with 95% confidence intervals, will be calculated for each treatment group. The

proportion of successful outcomes within the two treatment groups will initially be compared via calculation of relative risk and odds ratio. The relative strength of the difference in success between groups, as measured by the odds ratio, will be further evaluated via logistic regression. The study population will be summarized overall, and by treatment group, using standard descriptive statistics. Bivariate methods, such as chi-square or Fisher's exact tests (categorical variables) and t-tests or Mann-Whitney U tests (continuous/ordinal variables) will be used to compare the treatment groups' demographic and clinical characteristics. These same methods will be used to initially evaluate differences in the success by demographic and clinical characteristics. The bivariate analyses will be used to select variables for inclusion in subsequent multivariable regression models. We will stratify our results by presenting symptomatology (spotting/cramping etc.). Multivariable logistic regression will be used to evaluate the odds of success within each treatment arm and adjusted for demographics (including race and ethnic variation) and clinical variables that may affect the odds of success. The variables found to be related to the success rate on the bivariate level will be entered one at a time into the model, iteratively comparing the adjusted odds ratios. The final regression models will include the treatment group, study sites, characteristics associated with success rate at the $p < 0.1$ level, as well as covariates that altered the unadjusted ratios by at least 10%. Graphical techniques, such as lowess plots, will be used to assess the assumptions of the models.

The acceptability will be assessed by descriptive statistics. We will query participants using validated instruments [9,11,63] about perceived acceptability of the procedure, adverse effects, pain, bleeding, and duration of symptoms and treatment, as well as whether the procedure met the expectations for the experience, would be chosen again, and would be recommended to a friend. The mean values \pm standard deviation of the VAS measurements will be compared using the Student's t-test. As above, bivariate methods will also be used to assess any demographic or clinical characteristics that may be associated with acceptability. We will calculate treatment recovery time [63] as assessed by the extent to which participants missed school or work due to treatment recovery, required the help of others in their recovery, and the duration of physical and self-reported psychological symptoms as recorded on the daily diary maintained by participants.

In order to assess the impact of our results on health care costs, we will calculate whether there is an increased or decreased cost from adding mifepristone to the medical management regimen. Mifepristone is priced at \$90 per tablet. However, depending on how much it decreases extra medical and surgical care, this price may be more than off-set [64]. The cost for each woman will be computed including hospital resource costs (ER visits, physician time, ultrasounds, etc), cost to the woman (days off work, childcare expenses, travel expenses, etc), and lost productivity. Total costs will be compared between treatment arms using standard bivariate techniques. The nonparametric bootstrap method will be used to present cost-effectiveness acceptability curves and net benefit statistics at alternative willingness to pay thresholds held by decision makers for preventing a need for surgery [65].

Once all participant phlebotomy specimens have been obtained, we will be able to derive a predictive model for successful medical management vs. failure for all subjects. Separate predictive models will then be built for each treatment arm, and any differences found here will lay foundations for future research. Accurate assessment of gestational age (GA) can be a challenge in women who present with EPF, and GA may in fact be a confounder in the relationship between hormone levels and the nature of the demise. Depending on time of presentation relative to time of demise, biomarker levels may be more a reflection of the actual GA, or may in fact be impacted by duration of demise (i.e. β hCG, P_4 may start declining after demise occurs). We can utilize last menstrual period dating (LMP) with the caveat that LMP is not always certain. To overcome this measurement error problem, we will also analyze a

subset of women with a sure LMP and for whom ultrasound dating is consistent with LMP. If the model for this subset is consistent with the model for the full data, or GA is not found to significantly modify the relationship, only the full data model will be presented.

Biomarker levels will be summarized overall, and by treatment group, using standard descriptive statistics. We will use graphical methods, such as lowess smoothers, to determine the shape (linear or non-linear, potential cut-points for classifying levels) of the relationship between the biomarker level and probability of success, and subsequently for inclusion as predictors in a multivariable logistic model. We will analyze a subset of women with a sure LMP and for whom ultrasound dating is consistent with LMP separately for the most accurate analysis of the relationship between biomarker concentration and the characterization of an EPF that will respond well to medical management. We can compare this definitive LMP group to the group of women in whom LMP is unsure. We will calculate the sensitivity, specificity, and positive and negative predictive values for each biomarker. The predictive accuracy of different cutoffs will be evaluated using ROC curves.

Logistic regression and classification and regression trees (CART) will be used to develop a predictive model for successful management of early pregnancy failure, which will serve as the basis for a clinical predictive index [66-68]. Our group has used this methodology with success [69,70]. Initially the predictive model will only include biomarkers, and then both biomarkers and epidemiologic and clinical characteristics will be considered in the predictive model. The sensitivity of the predictive index (i.e., proportion of patients with success who are defined as “high chance of success” by the rule) will be of primary interest [71]. The negative predictive value will also be calculated using the derived sensitivity and specificity with the population prevalence of success. This value is also of clinical interest.

For model building, we will enter all biomarkers that will have shown in the bivariate analysis at least borderline associations with the endpoints of interest ($p < 0.20$), as well as interaction terms that are suggested by the results of the explanatory model. Terms will then be removed from the model using a backward elimination procedure, removing factors which cause an insignificant change in the sensitivity of the model. To test the change in sensitivity between models (with and without the variables), we will use McNemar’s test. In particular, we will be comparing the proportion of correctly classified cases of success between models. The rule would involve calculating a score for each person, based on the actual values of the regression coefficients. The goal is to utilize all variables that improve the sensitivity of the model. Unlike the explanatory model, whose goal is to determine which variables are associated with success, the predictive models will be developed in order to determine which combination of variables best predicts the outcome. Additionally, variables and interactions included in the model must be biologically plausible.

To be useful, a clinical rule must be easily applied. In order to ensure easy understanding and unhindered application, the variables and parameters comprising the predictive score will be simplified with two methods: 1) by recalculating the predictive score using values of the coefficients, rounded to the nearest integer, and 2) by calculating the score simply as the sum of the dichotomous independent variables identified by the model. (It will be necessary, for this approach to recode continuous predictors as dichotomous variables.) This will result in the most parsimonious model. The performance of the new rules will then be compared with that of more complete models using ROC curves. We plan to evaluate potential cutoffs of each marker to optimize our ability to distinguish among successes and failures.

We will also approach our predictive modeling using CART. Candidates that have an individual area under the curve (AUC) > 0.6 will be considered. CART is useful in identifying complex relationships between biomarkers and clinical outcomes. These analyses recursively split observations into two

groups (nodes), t_L and t_R , based on the covariate that maximizes a given split function. In the case of a continuous outcome, a commonly used split function is the reduction in sums of squares error, i.e. the amount of variability explained by the split. The best split is defined to be the one that best predicts the response where the best predictor is defined to be the one that maximizes the split function. All splits of the observations in each of the resulting nodes are then considered and the best split identified. This process is repeated recursively until a stopping rule is achieved (e.g. no further splits exist with greater than 5 observations in each of the resulting nodes). We will employ 10-fold cross-validation to assess the significance of the resulting tree as described in Breiman [72]. The sensitivity and specificity of the CART versus logistic model will be compared using ROC curves, to determine the best predictive rule for management success. CART software will be used to evaluate combinations of biomarkers creating a tree maximizing sensitivity and a tree maximizing specificity. Data will be combined into a three-tiered algorithm to maximize accuracy.

The prediction rule will be internally validated with a “bootstrap” approach [73-78]. With this approach, a large number of samples are taken from the original data (with replacement) and the predictive accuracy is tested in each of these samples. Sampling with replacement generates a population identical in composition to the observed sample. This method provides a relatively unbiased estimate of the test characteristics of the predictive rule [78].

7.3. Subject Population(s) for Analysis

All-randomized population will be subject to analysis.

7.4. Interim Analysis

Since safety and failure is a consideration in this study, we have chosen to use a group sequential design. Thus, in addition to the final analysis, we are planning on performing an interim statistical analysis during the course of the study. The purpose of the interim analyses will be to determine whether or not there is sufficient evidence of an increased failure rate in the combined arm compared to the control such that the trial should be discontinued prior to reaching the target accrual goal. The interim analysis will be performed after approximately 1/2 (150 subjects) of the total required patients have completed their primary outcome. This interim analysis will also examine whether or not there is sufficient evidence of an increased infection rate in the combined arm.

The primary outcome for the interim analyses will be the comparison of success/failure rates between the treatment arms. This comparison will be accomplished by means of a simple logistic regression model for the outcomes versus treatment. An approximate O’Brien-Fleming boundary will be used at the interim look to calculate the nominal significance level to which interim p-values are compared (O’Brien PC 1979). Using the O’Brien Fleming spending function, the two analyses (interim + final) should use the following incremental α values (0.003, 0.047) in order to achieve an overall $\alpha=0.05$.

Stopping criteria are for:

(1) **Clear superiority** -- whether the misoprostol alone is clearly inferior to combined treatment. For these calculations, we trade off the power to detect a difference and the size of that difference. Assuming $\alpha=0.003$ for boundaries for the interim analysis when 150 women have been followed to completion power is limited except to detect large reductions in failure rates. For example, power is approximately 0.80 to detect a reduction from 30% in the misoprostol alone arm to 6.7% in the

combination arm. Thus, early or premature stopping for superiority is unlikely, without dramatic improvement from the combined treatment.

(2) **Inferiority.** Power is limited to identify inferiority of the combined treatment, with 0.8 power to demonstrate a 30%-point increase in the risk of failure from 30% in the misoprostol alone arm to 60.7% in the combined treatment arm. Instead, we will base inferiority on the safety concern (see (4)) of an increased failure rate in the combination arm.

(3) **Futility.** Early stopping based on futility of the primary outcome will not be considered independently of the secondary clinical and safety outcomes. In the event that the intervention arm has equivalent BPD/death rates to the standard care arm, it would still be clinically useful to know if the intervention improves any of the secondary outcomes (that are closer to the time of the intervention) or decreases the serious adverse event rate.

(4) Safety.

(a) *Failure:* Failure rates may be different via weeks of gestation at the time of treatment. Based on prior studies, we would expect the proportion of women recruited by gestational strata to be 50% at 5-7 weeks, 40% at 8-9 weeks and 10% at 10-12 weeks. Since this would mean only 7-8 women would be enrolled at the interim analysis time point in the 10-12 weeks strata, formal statistical tests will not power to detect anything but an extreme difference. Instead, in these gestational strata, stoppage will be based on seeing a failure rate greater than the 95% confidence interval expected in the misoprostol alone group. Thus, recruitment will be stopped at the interim analysis in any gestational age group for which the combined arm has a 40% or higher failure rate.

(b) An important safety outcome is the rate of infection, (and/or other serious adverse events that have been adjudicated as potentially relating to the intervention). In order to minimize the risk, this safety outcome will be compared between treatment arms at the planned interim analysis for the primary outcome. Based on prior studies, we would expect a conservative 2% infection rate in the combined arm. We have 80% power to detect a clinically important increase at study end to a 6% infection rate in the combined arm (double that expected in surgical management). Using the O'Brien-Fleming alpha of 0.003 at the interim analysis, we would stop the study if the overall infection rate was >17% in the combined arm after half the subjects have completed the study. Since we would not expect such a high infection rate at the interim analysis; we will instead look for a clinically meaningful double the rate in the combination versus that previously found using surgical management techniques (i.e. 6%).

In summary, given the projected number of patients to be enrolled, early stopping will be unlikely unless the observed effect of combination therapy is clearly better or worse than misoprostol alone at the planned early stopping assessment time.

The results of the interim analysis will be judged by the DSMB. This committee will act completely independently of the clinical investigators, including the Principal Investigator. However, the ultimate decision to stop the study will rest with the Principal Investigator.

8 Safety and Adverse Events

8.1. Definitions

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Not all events that would traditionally be defined as AEs will be collected by the sponsor for this trial.

There are a number of expected side effects related to the medical management of miscarriage with misoprostol including abdominal cramping, vaginal bleeding, fevers, chills, nausea, vomiting, diarrhea, dizziness, and endometritis. Sepsis (infection of the bloodstream): sepsis is a known risk related to any type of spontaneous or induced abortion. There have been reports of deaths due to sepsis in women who have had induced abortion with mifepristone and misoprostol. Most of these women were infected with the same type of bacteria, known as *Clostridium sordellii*. The symptoms in these cases of infection were not the usual symptoms of sepsis. It is not known whether using mifepristone and misoprostol caused these deaths. Reports of fatal sepsis in women undergoing medical abortion are very rare (approximately 1 in 100,000). There is also the chance that uterine aspiration will be required in the setting of failure or emergency. These symptoms will be collected from patient self-report and subject diaries, but may also be discovered in the medical record. The only non-serious events that will be specifically collected by the sponsor and classified as AEs for this study are those that are both unexpected and considered to be related to study procedures or study drug. All attempts will be made to obtain records of care obtained outside the study sites for adverse events that are possibly related to the study treatment. Subjects will be informed that these records may be needed, and will be asked to sign a release form when they enroll in the study.

All adverse events will be collected, recorded, and assessed locally by the investigator or his/her designee. Events that are determined to be both unexpected and related to the study will be entered into the electronic CRF and thus reported to the sponsor.

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above.

All serious adverse events will be reported to the medical monitor, regardless of causality assessment. Serious adverse events will also be reported by the sponsor to the FDA and to Danco Laboratories, Inc.

If a subject becomes pregnant again after resolution of her EPF within the 30 day study window, this will not be considered an adverse event and will not be followed.

Adverse Event Reporting Instructions

Any serious adverse event or concomitant illness, whether or not it is considered related to the study medication, will be reported by telephone, email or fax within 24 hours of awareness to the study sponsor:

Courtney Schreiber, MD, MPH
Tel: 215-615-6531
Fax: 215-615-5319
Cell: 215-880-9234
Email: cschreiber@obgyn.upenn.edu

The investigator will complete a SAE Form, which will be sent immediately (preferably by fax) to the study sponsor. A SAE form will be completed for any SAE that is experienced after the subject has signed the Informed Consent Form.

The Principal Investigator will submit updated SAE. The Principal Investigator will evaluate women who experience a SAE as necessary until the event is resolved. Adverse events that are both serious and unexpected will be reported to the FDA per the Federal Code of Regulations 21 Part 312.32 (IND Safety Reports).

It is the responsibility of the study sponsor to notify all participating investigators, in a written IND safety report, of any adverse event associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects. Additionally, sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

The study sponsor will also report all SAEs to the FDA and to Danco Laboratories, Inc.

The principal investigator will report adverse events for review by the IRB/EC per their local reporting requirements.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

9 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the study documents.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

10 Data and Safety Monitoring Plan

Patient safety will be monitored continuously by the Sponsor-Investigator, Dr. Courtney Schreiber. Dr. Kurt Barnhart will serve as the medical monitor for the study. The Principal Investigator at each site has the primary responsibility for identifying potential adverse events experienced by study participants and reporting the experience as outlined in the protocol to the Sponsor and to the IRB as required by local standards. The Sponsor-Investigator is responsible for reviewing these reports and making the final determination of relatedness, reporting to the medical monitor, and distributing reports to the other site investigator as needed.

Data Monitoring

Monitor Selection and Training

One monitor will be assigned for this trial and will be responsible to complete the monitoring process. The monitor will be an employee of the University of Pennsylvania Women's Health Research Center

who is not involved in the local site conduct of the study. The monitor will have experience in the conduct of clinical research and will be familiar with research regulations and Good Clinical Practice. The monitor will be trained by the University of Pennsylvania Office of Clinical Research and supervised by the Sponsor-Investigator. Training will include review of 21 CFR 312, ICH GCP, safety and adverse event review and reporting, the study protocol, the study database, the informed consent forms and processes from each site, and this monitoring plan.

Study Initiation

A Study Initiation Visit will be conducted with each participating site PI and key study personnel.

The Principal Investigator at each site will ensure that he or she understands and accepts responsibility for the protocol and the requirements for an adequate and well-controlled study; the obligation to conduct the clinical investigation in accordance with the applicable federal regulations; the obligation to obtain informed consent in accordance with 21 CFR Part 50; the obligation to obtain IRB review and approval of a clinical investigation before the investigation may be initiated and to ensure continuing review of the study by the IRB in accordance with 21 CFR Part 56; and to keep the sponsor informed of such IRB approval and subsequent IRB actions concerning the study.

Monitoring Activities

Frequency

Enrollment will be complete when 300 subjects are enrolled into the trial. Approximately 6 subjects will be enrolled per month across both sites. Monitoring will be conducted periodically throughout the study as described below:

- The **first monitoring time-point** will occur after the first 5 subjects have been enrolled at the site and have reached clinical resolution, OR after 12 months have passed since study initiation, whichever occurs first.
- If no issues of concern are noted during the first monitoring time-point, subsequent monitoring will occur at least annually.
- The **final monitoring time-point** will be conducted when 100% of the subjects have been enrolled and completed the study. This visit will also serve as the close-out monitoring visit

Additional monitoring may occur on an as-needed basis as determined by the Sponsor.

Data Review

All database entries for the first 5 subjects at each site will be 100% source data verified. In addition, the database entries for one in every cohort of 10 subjects at each site will be 100% source data verified.

If a greater than 10% error rate is noted during the data review, the monitor will request additional documents to source verify 100% of the data on a larger sample.

The following variables will be 100% source data verified for *all* subjects enrolled in the study.

- Informed Consent
- Inclusion/Exclusion Criteria
- Drug Accountability
- Serious Adverse Events
- Primary Outcomes/Endpoint Data Verification

Regulatory Document Review

The Regulatory Documents will be maintained at each site in the Regulatory Binder, with all applicable documents additionally maintained by the Sponsor. The Regulatory Binder will be reviewed by the monitor in an ongoing manner.

Documentation of Monitoring Activities

Monitoring Log

The monitor is required to sign and date the monitoring log documenting the dates of the monitoring activity.

Monitoring Report

All monitoring activities will be documented on the Monitor's Report and Visit Checklist. The original report for each visit will be filed in the Sponsor section of the Regulatory Binder.

Data Management

Most of the data will be directly entered into REDCap – the source itself therefore is a secure, web-based database. Any other data will be entered directly from source documents into REDCap, a secured, web-based study database that complies with Title 21 CFR Part 11. This database will be maintained at the University of Pennsylvania. Data will be entered by site personnel delegated by the site Principal Investigator to perform this function. Double data entry will not be used. Data queries and database corrections will be performed by staff at the University of Pennsylvania responsible for maintaining the database.

Study Close Out

The monitor will conduct the study close out at the time of the final monitoring time-point and within 3 months after the last patient has completed the study.

The following activities will be completed by the monitor to close out the study:

- Ensure all data has been reviewed and collected;
- Ensure all outstanding queries are answered;
- Confirm all Serious Adverse Events, if applicable, have been reported to the IRB(s) and the FDA;
- Review the Regulatory documentation and Subject Files for completeness and compliance with GCP and all applicable federal regulations;
- Ensure all protocol violations were submitted to the IRB per local requirements;
- Ensure that all continuing review reports were submitted to the IRB;
- Perform drug accountability; and
- Review requirements for record retention with the investigator and the clinical staff.

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