# Ulipristal Acetate for use in early pregnancy loss: A Phase 2 pilot feasibility study

Protocol and Statistical Analysis Plan
Version 8.0 Date: 6/2/22
NCT: NCT05216952
Date of Submission: 5/5/23

# Ulipristal acetate for use in early pregnancy loss: A Phase 2 pilot feasibility study

*UPA for EPL*

**Protocol Number: 1.0**

**National Clinical Trial (NCT) Identified Number: N/A**

**Principal Investigator: Jill M. Hagey, MD MPH**

**Mentor: Amy Bryant, MD MSCR**

**Funded by: UNC Chapel Hill, Division of Family Planning**

**Version Number: 8.0**

**2 June 2022**

## Summary of Changes from Previous Version:

| Affected Section(s) | Summary of Revisions Made | Rationale |
|---|---|---|
| 1.3, 2.2, 4.1, 4.3, 5.1, 5.2, 5.4, 5.5, 9.1, 9.2, 9.4, 10.1 | See Track Changes | SRC Revision |
| 4.1 | Updated Visit Days | SRC Revision |
| 1.3, 4.1, 5.2, 7.3, 8.2, 8.3.5, 8.3.6, 10.1.2 | See Track Changes | FDA IND Revision |
| 5.2, 5.5, 7.2, 9.3, 9.4.1, 9.4.3 | See Track Changes | FDA IND Revision |
| 2.3.1, 5.2, 8.3.6, 10.1.9.1 | See Track Changes | IRB Revision |

| | | |
|---|---|---|
| 2.3.1, 4.1, 5.5, 10.1.9.1 | See Track Changes | IRB Modification |
| 3, 4.1, 5.4, 5.5, 8.1, 9.1 | Updated Outcome Measure | IRB Modification |
| 5.5 | Updated Recruitment Methods | IRB Modification |

## Table of Contents


STATEMENT OF COMPLIANCE ..... 1
1 PROTOCOL SUMMARY ..... 1
1.1 Synopsis ..... 1
1.2 Schema ..... 2
1.3 Schedule of Activities (SoA) ..... 4
2 INTRODUCTION ..... 4
2.1 Study Rationale ..... 4
2.2 Background ..... 5
2.3 Risk/Benefit Assessment ..... 6
2.3.1 Known Potential Risks ..... 6
2.3.2 Known Potential Benefits ..... 7
2.3.3 Assessment of Potential Risks and Benefits ..... 7
3 OBJECTIVES AND OUTCOMES ..... 7
4 STUDY DESIGN ..... 8
4.1 Overall Design ..... 8
4.2 Scientific Rationale for Study Design ..... 10
4.3 Justification for Dose ..... 11
4.4 End of Study Definition ..... 11
5 STUDY POPULATION ..... 11
5.1 Inclusion Criteria ..... 11
5.2 Exclusion Criteria ..... 11
5.3 Lifestyle Considerations ..... 12
5.4 Screen Failures ..... 12
5.5 Strategies for Recruitment and Retention ..... 13
6 STUDY INTERVENTION ..... 14
6.1 Study Intervention(s) Administration ..... 15
6.1.1 Study Intervention Description ..... 15
6.1.2 Dosing and Administration ..... 15
6.2 Preparation/Handling/Storage/Accountability ..... 15
6.2.1 Acquisition and accountability ..... 15
6.2.2 Formulation, Appearance, Packaging, and Labeling ..... 15
6.2.3 Product Storage and Stability ..... 16
6.2.4 Preparation ..... 16
6.3 Measures to Minimize Bias: Randomization and Blinding ..... 16
6.4 Study Intervention Compliance ..... 16
6.5 Concomitant Therapy ..... 16
6.5.1 Rescue Medicine ..... 16
7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL ..... 16
7.1 Discontinuation of Study Intervention ..... 16
7.2 Participant Discontinuation/Withdrawal from the Study ..... 16
7.3 Lost to Follow-Up ..... 17
8 STUDY ASSESSMENTS AND PROCEDURES ..... 17
8.1 Feasibility Assessments ..... 17
8.2 Safety and Other Assessments ..... 18
8.3 Adverse Events and Serious Adverse Events ..... 19

8.3.1 Definition of Adverse Events (AE) 19
8.3.2 Definition of Serious Adverse Events (SAE) 19
8.3.3 Classification of an Adverse Event 19
8.3.4 Time Period and Frequency for Event Assessment and Follow-Up 20
8.3.5 Adverse Event Reporting 21
8.3.6 Serious Adverse Event Reporting 21
8.3.7 Reporting Events to Participants 21
8.3.8 Events of Special Interest 22
8.3.9 Reporting of Pregnancy 22
8.4 Unanticipated Problems 22
8.4.1 Definition of Unanticipated Problems (UP) 22
8.4.2 Unanticipated Problem Reporting 22
8.4.3 Reporting Unanticipated Problems to Participants 23
9 STATISTICAL CONSIDERATIONS 23
9.1 Research Hypotheses 23
9.2 Sample Size rationale 23
9.3 Populations for Analyses 23
9.4 Statistical Analyses 24
9.4.1 General Approach 24
9.4.2 Analysis of the Primary feasibility outcome variable(s) 24
9.4.3 Analysis of the Secondary outcome variable(s) 24
9.4.4 Safety Analyses 25
9.4.5 Baseline Descriptive Statistics 25
9.4.6 Planned Interim Analyses 25
9.4.7 Sub-Group Analyses 25
9.4.8 Tabulation of Individual participant Data 25
9.4.9 Exploratory Analyses 26
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 26
10.1 Regulatory, Ethical, and Study Oversight Considerations 26
10.1.1 Informed Consent Process 26
10.1.2 Study Discontinuation and Closure 26
10.1.3 Confidentiality and Privacy 27
10.1.4 Future Use of Stored Specimens and Data 27
10.1.5 Key Roles and Study Governance 27
10.1.6 Safety Oversight 28
10.1.7 Clinical Monitoring 28
10.1.8 Quality Assurance and Quality Control 28
10.1.9 Data Handling and Record Keeping 29
10.1.10 Protocol Deviations 29
10.1.11 Publication and Data Sharing Policy 30
10.1.12 Conflict of Interest Policy 30
10.2 Additional Considerations 30
10.3 Abbreviations 31
10.4 Protocol Amendment History 33
11 REFERENCES 34

## STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation **Good** Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

## 1 PROTOCOL SUMMARY

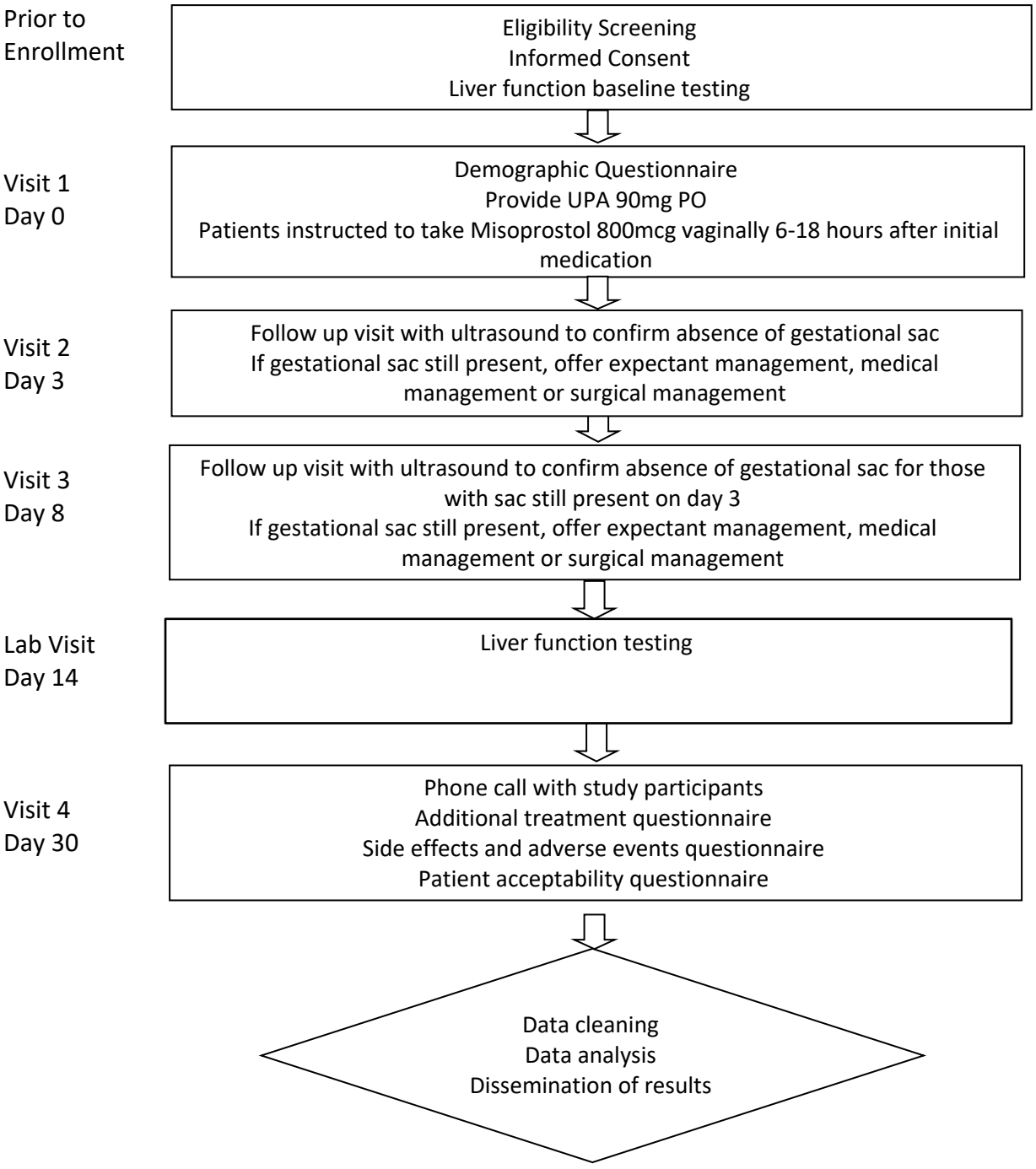
### 1.1 SYNOPSIS

| | |
|---|---|
| **Title:** | Ulipristal Acetate for use in early pregnancy loss: A Phase 2 pilot feasibility study |
| **Study Description:** | We investigate the feasibility of using 90mg ulipristal acetate, a selective progesterone receptor agonist, as an adjunct to 800mcg vaginal misoprostol for the medical management of early pregnancy loss. Patients will be followed to assess effective treatment of early pregnancy loss, additional interventions needed, side effects, adverse events and patient acceptability. |
| **Objectives:** | Primary Objective:<br>To assess if 90mg ulipristal acetate as an adjunct to 800mcg vaginal misoprostol is a feasible method for medical management of early pregnancy loss.<br>Secondary Objectives:<br>To evaluate if participants taking ulipristal acetate plus misoprostol achieve complete resolution of early pregnancy loss.<br>To investigate if patients using ulipristal acetate plus misoprostol have side effects or adverse events when used for early pregnancy loss.<br>To identify if patients find ulipristal acetate and misoprostol an acceptable treatment for early pregnancy loss. |
| **Outcomes:** | Primary Feasibility Outcome Variables:<br>- Recruitment<br>- Adherence<br>- Retention<br>Secondary Outcome Variables:<br>- Absence of gestational sac on transvaginal ultrasound following study intervention<br>- Side effects/adverse events following study intervention<br>- Patient acceptability of study intervention |

| | |
|---|---|
| **Study Population:** | Participants eligible for the study include women over age 18 presenting with a non-viable pregnancy between 5- and 12-weeks gestation or an anembryonic gestation and desiring medical management. Participants will be excluded if they are hemodynamically unstable, desire non-medical management, present with an incomplete or inevitable abortion, contraindication or allergy to the study medications, evidence of a viable intrauterine pregnancy, ectopic pregnancy or pregnancy with an IUD in place, evidence of a pelvic infection, anemia with a hemoglobin less than 9.5g/dL, known cardiovascular disease or known clotting or bleeding disorder. |
| **Phase:** | 2 |
| **Description of Sites/Facilities Enrolling Participants:** | All study activities will take place at University of North Carolina-Chapel Hill. Participants will be recruited from OBGYN clinics and the Emergency Department following diagnosis of early pregnancy loss on viability scan. All follow up study activities will take place at UNC Chapel Hill Family Planning Clinic. |
| **Description of Study Intervention:** | Ulipristal acetate is a selective progesterone receptor modulator that is currently FDA approved for the use of emergency contraception. Three 30mg tablets will be administered orally for a total dose of 90mg. Participants will be instructed to self-administer 800mcg of misoprostol 6 to 18 hours after receiving ulipristal acetate as per the standard of care for early pregnancy loss management. Participants will be followed for resolution of their early pregnancy loss. |
| **Study Duration:** | 2 years |
| **Participant Duration:** | 1 month |

## 1.2 SCHEMA

***UPA for EPL Flow Diagram***


Prior to Enrollment
Eligibility Screening
Informed Consent
Liver function baseline testing
Visit 1
Day 0
Demographic Questionnaire
Provide UPA 90mg PO
Patients instructed to take Misoprostol 800mcg vaginally 6-18 hours after initial medication
Visit 2
Day 3
Follow up visit with ultrasound to confirm absence of gestational sac
If gestational sac still present, offer expectant management, medical management or surgical management
Visit 3
Day 8
Follow up visit with ultrasound to confirm absence of gestational sac for those with sac still present on day 3
If gestational sac still present, offer expectant management, medical management or surgical management
Lab Visit
Day 14
Liver function testing
Visit 4
Day 30
Phone call with study participants
Additional treatment questionnaire
Side effects and adverse events questionnaire
Patient acceptability questionnaire
Data cleaning
Data analysis
Dissemination of results

## 1.3 SCHEDULE OF ACTIVITIES (SOA)

| Procedures | Screening Visit 1, Day 0 | Enrollment/Baseline Visit 1, Day 0 | At Home Day 0 | Study Visit 2 Day 3 +/- 1day | Study Visit 3 Day 8 +/- 1 day | Lab Testing Day 14 +/- 1 day | Study Visit 4 Day 30 +/- 7 days |
|---|---|---|---|---|---|---|---|
| Eligibility criteria | X | | | | | | |
| Informed consent | X | | | | | | |
| Demographics questionnaire | X | | | | | | |
| Administer UPA | | X | | | | | |
| Patient self-administers misoprostol | | | X | | | | |
| Physical exam | X | | | | | | |
| Vital signs | X | | | X | X | | |
| Hemoglobin and ABO/Rh testing | X | | | | | | |
| Liver function testing | X | | | | | X | |
| Adverse event review and evaluation | X | | | X | X | | X |
| Radiologic/Imaging assessment | X | | | X | X | | |
| Treatment success questionnaire completed by MD | | | | X | X | | |
| Offer additional intervention if needed if gestational sac still present | | | | X | X | | |
| Additional treatment questionnaire | | | | | | | X |
| Side effects and adverse events questionnaire | | | | X | X | | X |
| Patient acceptability questionnaire | | | | | | | X |

# 2 INTRODUCTION

## 2.1 STUDY RATIONALE

Early pregnancy loss affects approximately 10% of women throughout their reproductive lives [1]. Options for management of early pregnancy loss include expectant management, medical management, or surgical management. Data from two large randomized controlled trials suggests that pretreatment with mifepristone 200mg, a selective progesterone receptor modulator, prior to administration of misoprostol 800mcg increases effectiveness of medical management of early pregnancy loss and decreases the need for subsequent surgical management [2,3]. However, mifepristone is subject to regulations based on the FDA Risk Evaluation and Mitigation Strategy (REMS) restrictions that have remained in place for more than 20 years despite extensive safety data for mifepristone and evidence-based protocols for its use. Many OBGYN and non-OBGYN providers do not prescribe mifepristone due to these logistical barriers. Ulipristal acetate (UPA) is another selective progesterone receptor modulator that may allow for similar priming of the endometrium and sensitization of the myometrium to the prostaglandins to improve effectiveness of misoprostol in medical management of early pregnancy loss.

Ulipristal acetate is not subject to the FDA REMS restrictions and is available as a prescription medication through commercial pharmacies, with approximately 72% of pharmacies able to fill the prescription within 24 hours [4]. Thus, utilizing UPA plus misoprostol for early pregnancy loss may improve access to patients who otherwise may not be prescribed mifepristone. We propose a pilot feasibility study of UPA plus misoprostol for medical management of early pregnancy loss to assess if a larger clinical trial would be possible.

## 2.2 BACKGROUND

Early pregnancy loss (EPL), defined as a nonviable intrauterine pregnancy, occurs in approximately 10% of clinically recognized pregnancies [1]. Early pregnancy loss encompasses both anembryonic gestations (presence of an empty gestational sac without embryo or fetus, previously known as a "blighted ovum") and embryo or fetus without fetal cardiac activity before the 13$^{th}$ week of gestation [1]. Often, early pregnancy loss is diagnosed on viability ultrasound, and specific radiologic criteria have been laid out by the Society of Radiologists in Ultrasound Multispecialty Consensus Conference (so called "Doubilet criteria", see Appendix A) [5]. When faced with this diagnosis, women are offered expectant management, medical management, or surgical management to allow expulsion of the pregnancy. Misoprostol, a prostaglandin analogue, has long been the standard of care for medical management of EPL; however, recent randomized controlled trials of mifepristone use prior to misoprostol illustrated increased rates of pregnancy expulsion with medication alone and decreased need for surgical intervention to complete evacuation of the pregnancy [2,3]. As a selective progesterone receptor modulator (SPRM) with antagonist effects on the endometrium and myometrium, mifepristone increases uterine contractility and sensitizes the myometrium to prostaglandin use, allowing for a lower dose of misoprostol to cause uterine emptying and shorter time to pregnancy expulsion. Following treatment with mifepristone, endometrial cells exhibit an increase in decidual prostaglandin release and decreased activity of prostaglandin dehydrogenase to prevent metabolism of prostaglandins [6]. Further, mifepristone downregulates progesterone receptor signaling in the endometrium, prompting antiproliferative effects that halt secretory changes to the endometrium and decrease endometrial receptivity [7,8].

While mifepristone exhibits many benefits when used for EPL, availability of mifepristone is limited by the Risk Evaluation and Mitigation Strategy (REMS) FDA restrictions [9]. This program restricts mifepristone administration to certified providers, requires a patient agreement form to be signed prior to administration, and requires administration of the medication in the presence of the certified provider [10]. These restrictions have been in place since mifepristone was FDA-approved in 2000 despite excellent safety data and evidence-based protocols; even with extensive legislative appeals to remove the REMS restrictions [11]. Particularly as many women diagnosed with EPL are seen in non-OBGYN settings such as the emergency department or primary care, these restrictions often prevent patients from accessing appropriate evidence-based medical management. Indeed, in a large qualitative survey of primary care clinicians, two thirds of providers were unable to dispense mifepristone in their clinics for medication abortion or EPL care, with most citing logistical difficulties with the REMS restrictions and resistance from health center leadership as rationale [12]. Logistical barriers to prescribing mifepristone for medication abortion has also been well documented among both OBGYN and non-OBGYN providers [13,14].

Ulipristal acetate (UPA, Ella®) is another substituted steroid synthetic progesterone agonist/antagonist commonly used for emergency contraception with a similar molecular weight, structural formula, and molecular formula to mifepristone [15-17]. As a class, progesterone receptor modulators are utilized in

similar clinical scenarios ranging from contraception to treatment of fibroids, endometriosis, and other causes of heavy or irregular bleeding. In the normal menstrual cycle, progesterone from the corpus luteum transforms the proliferative endometrium to the secretory endometrium for implantation. In contrast, the presence of SPRMs causes the endometrium to undergo glandular dilation and antiproliferative effects [18]. Like other SPRMs, UPA induces changes in the endometrium including a significant increase in glandular dilation and architecture and decrease in endometrial thickness similar to the effects noted following administration of mifepristone [19,20]. UPA's effect on endometrial cells is also responsible for similar changes in receptivity markers when compared to mifepristone [21,22]. With the similarities between UPA and mifepristone, a recent pilot study investigated UPA in place of mifepristone for cervical preparation prior to dilation and evacuation for termination of pregnancy between 16- and 18-weeks' gestation and found that UPA was a feasible and acceptable alternative [23].

While mifepristone is an effective medication for EPL, prescribing restrictions limit the ability of patients to use this medication to increase the efficacy of medical management of EPL. Thus, alternative regimens are needed to increase access to effective medical management of EPL for women choosing medical management. Given similarities between UPA and mifepristone, we propose utilizing UPA prior to misoprostol for medical management of EPL. As no prior studies have investigated UPA for this use, we propose a pilot feasibility study of UPA plus misoprostol for medical management of EPL to inform a subsequent larger clinical trial if successful.

## 2.3 RISK/BENEFIT ASSESSMENT

### 2.3.1 KNOWN POTENTIAL RISKS

Ulipristal acetate is a 30mg tablet progesterone receptor agonist/antagonist that was FDA approved for emergency contraception in 2010. Adverse events noted from an open-label multicenter trial and a randomized, single-blind multicenter trial include headache (18%), nausea (12%), and abdominal pain (12%). Other less common side effects include dysmenorrhea, fatigue and dizziness. Post marketing experience has also shown an increase in acne among users of the medication [16].

This study will be utilizing a dosage of UPA 90mg to most closely match the effects of mifepristone 200mg, which is the dosage studied for EPL based on a study of endometrial histology showing similar effects of UPA 100mg to mifepristone 200mg [2,19]. FDA approval indicated that experience with single dose equivalent of up to four times the standard UPA dose were administered to a limited number of subjects without any adverse reactions, suggesting that UPA 90mg may be used safely in this patient population [16]. In a pilot study of ulipristal acetate 90mg at the dose that would be used for this study, no significant adverse events were noted [23].

Additionally, there will be two blood draws required for the study to monitor liver function testing. Possible risks of these blood draws include mild risks of pain, bruising and fainting. These risks are infrequent, and all lab draws will be completed by clinic nurses or the study coordinator, who have been trained in phlebotomy.

Possible psychologic risks of the study include consequences of breach of confidentiality. All study materials will be kept solely with research staff. All medical care will be documented in the UNC EPIC system, which has safeguards to reduce the risk of confidentiality breaches.

Possible social risk includes the risk of stigmatization of UPA if used in the context of EPL. Just as mifepristone is known as the "abortion pill", making it less likely to be used in other settings, UPA may undergo similar stigmatization, which may change prescribing patterns of UPA.

Possible economic risks include loss of income and time for follow up appointments, as patients undergoing medication management of EPL generally are followed up with a phone call as opposed to an in-person appointment. Patients will be compensated for their travel time and will not have to pay for their follow up visits.

### 2.3.2 KNOWN POTENTIAL BENEFITS

There are no direct benefits to patients enrolling in this study. Participants will receive care for their EPL with appropriate follow up over the course of the study.

### 2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

While there are no direct benefits of UPA to study participants, UPA is very well tolerated with minimal side effects or adverse events noted from FDA pre-marketing and post marketing analysis. Further, all participants will also get misoprostol, which in clinical environments that do not prescribe mifepristone, is the standard of care for medical management of EPL.

Societally, demonstration of feasibility of UPA for EPL may improve access to effective medical management for EPL. While mifepristone has been shown to increase effectiveness of medical management of EPL and decrease need for additional intervention for pregnancy expulsion, challenges with access to mifepristone limit its use. Thus, if UPA were to be a feasible alternative to mifepristone pretreatment, patients desiring medical management of EPL would have an effective option for treatment that can be more easily obtained.

## 3 OBJECTIVES AND OUTCOMES

| OBJECTIVES | OUTCOMES | JUSTIFICATION FOR OUTCOMES |
|---|---|---|
| Primary | | |
| To assess whether it is feasible to study UPA plus misoprostol as an intervention for medical management of EPL for larger future studies. | Recruitment: number of participants in study/number of patients screened for participation<br><br>Adherence: number of participants adhering to study intervention (UPA + misoprostol vaginally after 6-18 hours)/number of participants in study<br><br>Retention: number of participants attending all study visits (day 0, 3/8, 30)/number of participants in study | Study outcomes of interest for feasibility based on outcomes of interest appropriate for pilot studies [24-26]. |
| Secondary | | |

| OBJECTIVES | OUTCOMES | JUSTIFICATION FOR OUTCOMES |
|---|---|---|
| To evaluate if participants taking UPA plus misoprostol achieve complete resolution of EPL. | Absence of gestational sac on transvaginal ultrasound examination on Day 3 follow up | Same outcome was used in randomized controlled trial of mifepristone plus misoprostol for early pregnancy loss to calculate effective intervention [2]. |
| To investigate if UPA plus misoprostol is associated with side effects or adverse events when used for EPL. | Participants self-report of side effects or adverse events following UPA and misoprostol. | Study outcomes of interest for feasibility based on outcomes of interest appropriate for pilot studies [24-26]. |
| To identify if UPA plus misoprostol is acceptable to patients for treatment for EPL. | Participants willing to use this combination of medication again for another early pregnancy loss or recommend this combination of medications to a friend. | |

# 4 STUDY DESIGN

## 4.1 OVERALL DESIGN

This is a phase 2 single site pilot study of UPA for use in medical management of early pregnancy loss. Our hypothesis is that UPA will be a feasible option for women desiring medical management. Specifically, we estimate that over 60% of participants screened for participation will enroll in the study (based on a recruitment rate of 75% in a prior study of mifepristone plus misoprostol for EPL) [2]. Additionally, we estimate that greater than 50% of participants will be able to adhere to the study protocol in taking UPA and misoprostol at the designated times and greater than 90% of participants will be able to complete follow up for the study. This is a pilot study with a small sample size and thus our secondary aims will only be for hypothesis generating activities, not hypothesis testing activities.

The study will be conducted at UNC Chapel Hill. Patients will be approached as a convenience sample from patients diagnosed with EPL on viability scan at UNC Chapel Hill OBGYN clinics and UNC Chapel Hill Emergency Department between 5- and 12-weeks' gestation desiring medical management. Participants will be provided counseling regarding their EPL by their OBGYN physician and subsequently screened for eligibility by a research coordinator. Based on prior data on recruitment in this setting and number of patients seen desiring medical management for EPL at UNC Chapel Hill, we anticipate 40 women will be eligible for participation and desire participation in the study after recruitment for 12 months.

After providing informed consent, participants will complete a demographic questionnaire and ensure that they have appropriate baseline lab work (hemoglobin, ABO/Rh status, liver function testing). Participants will all receive the study intervention of 90mg UPA and will be instructed to self-administer 800mcg misoprostol vaginally 6 to 18 hours after the study drug is administered. Self-administration of misoprostol is the standard of care for medical management of EPL. As all participants will receive the same intervention, no randomization or blinding will take place. Participants will receive an

appointment card with their follow up appointment date that also provides space for participants to document their misoprostol timing at home.

Follow up of medical management of EPL generally consists of confirmation of pregnancy expulsion by ultrasound examination or serial beta-hCG measurements in settings where ultrasound is not available [1]. There is no standard of care regarding specific intervals when ultrasonography or laboratory follow up assessment should take place. Study follow up schema for our study is based on participant follow up design from a similar study of mifepristone and misoprostol for EPL [2].

Participants will follow up with the UNC Family Planning Division for a transvaginal ultrasound on study day 3 to ensure expulsion of the gestational sac. Women generally experience cramping and vaginal bleeding 1 to 4 hours following misoprostol administration and pass their pregnancy within 24 hours of starting to bleed. Thus, follow up on day 3 will assess participants who are able to pass their pregnancy with a single dose of UPA and misoprostol.

For those who still have a pregnancy in the uterus, they will be offered an additional dose of 800mcg misoprostol, expectant management, or surgical management. Those who did not have expulsion of the pregnancy on day 3 and elect for an additional dose of misoprostol or expectant management will follow up with the UNC Family Planning Division for another transvaginal ultrasound on study day 8 to ensure expulsion of the gestational sac. As some studies of EPL assess for response 7 days after medication administration, we will be able to compare our data to similar studies through our day 8 follow up results [3]. Further, twenty-five to thirty percent of EPL will pass with expectant management alone one week after diagnosis [27].

Participants will be assessed for possible liver toxicity on study day 14 through a laboratory test of ALT, AST and total bilirubin.

All study participants will receive a phone call on study day 30 to what additional treatment patients needed for their early pregnancy loss, investigate any side effects or adverse events, and identify acceptability of the treatment. Most symptoms of bleeding and abdominal cramping following medical management of EPL occur in the first two to four weeks following medication administration; thus, 30 days is an adequate time to assess for side effects and acceptability of treatment while not being too remote from the time of the pregnancy passing.

A detailed description of all study visits is provided below:

Visit 1 (Day 0):

- Participant is screened for eligibility by the study coordinator and offered admission to study if eligible
    - Review of radiologic imaging to confirm early pregnancy loss based on eligibility criteria
    - Review of physical exam findings and vital signs (heart rate, blood pressure, temperature) to ensure that patient is hemodynamically stable and not having an inevitable or incomplete abortion based on eligibility criteria
- Participant reviews and signs informed consent and HIPAA authorization form
- Participant completes paper baseline demographic questionnaire
- Participant will have hemoglobin, ABO/Rh status and liver function testing (ALT, AST, total bilirubin) if not already performed by primary OBGYN

- Participant takes 90mg ulipristal acetate with study team; given prescription for 800mcg misoprostol to take at home

Visit 2 (Day 3 ± 1 day):

- Participant returns to UNC Family Planning Clinic
- Participant has vital signs checked by RN at clinic
- Participant fills out questionnaire regarding bleeding symptoms and any side effects or adverse events after taking the ulipristal acetate and misoprostol, including reporting time and route of administration of misoprostol at home
- Participant has a transvaginal ultrasound completed by the principal investigator to ensure that the pregnancy has passed (no gestational sac visualized on ultrasound)
- If pregnancy is still in the uterus, patient will be offered surgical management, medical management (an additional dose of misoprostol 800mcg), or expectant management

Visit 3 (Day 8 ± 1 day):

- **Participant will only attend this visit if a gestational sac was still present on ultrasound on Visit 2 and patient opted for medical management or expectant management. If gestational sac is absent at Visit 2, participant will not need Visit 3. All participants will complete Visit 4.**
- Participant returns to UNC Family Planning Clinic
- Participant has vital signs checked by RN at clinic
- Participant fills out questionnaire regarding bleeding symptoms and any side effects or adverse events after taking the ulipristal acetate and misoprostol
- Participant has transvaginal ultrasound completed by the principal investigator to ensure that the pregnancy has passed (no gestational sac visualized on ultrasound)
- If pregnancy is still in the uterus, patient will be offered surgical management, medical management (if patient did not receive additional misoprostol at Visit 2), or expectant management
    - If patient has medical management or expectant management, patient will be followed with weekly transvaginal ultrasounds until pregnancy has passed. No study questionnaires will be administered at these visits. Patient may elect for surgical management at any follow up visit as per the standard of care.

Lab Visit (Day 14 ± 1 day):

- Participant will have liver function testing (ALT, AST, total bilirubin) performed at outpatient laboratory

Visit 4 (Day 30 ± 7 days):

- Participant will be called by the principal investigator to administer a follow up questionnaire about any additional treatments taken to help pass the pregnancy, any side effects experienced with the medication and participant acceptability

## 4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

As this is the first study utilizing UPA for this indication, a pilot feasibility study is warranted to ensure that patients are willing to take part in a research study of this kind, be adherent to the study protocol, monitor the effectiveness of the study medication for this use, and evaluate for any possible side effects or adverse events. As such, we will be employing a convenience sample of patients presenting with early pregnancy loss. No comparison group will be utilized.

### 4.3 JUSTIFICATION FOR DOSE

UPA 90mg will be utilized for this study based on multiple factors. As this is the first use of UPA for this indication, no prior dosage data is available. Safety of UPA has been well-documented at dosages over 90mg, both from the FDA package insert that notes a lack of adverse events at dosages up to four times the standard dose of UPA (thus up to 120mg) as well as from phase 1 dose determination studies that showed that a single dose of UPA up to 100mg was well tolerated [16, 28]. Further, similar endometrial changes have been noted between UPA 100mg and mifepristone 200mg, suggesting that UPA may be effective at a dose of approximately one half that of mifepristone [19]. In clinical practice, when mifepristone is used for emergency contraception, which is the FDA-approved indication for UPA, mifepristone most effective at doses of 25-50mg compared to UPA 30mg [29], again suggesting that mifepristone may be effective at between one to two times the dosage of UPA. Lastly, UPA 90mg was the dosage used when UPA was studied in place of mifepristone 200mg for cervical preparation prior to dilation and evacuation for termination of pregnancy between 16- and 18-weeks' gestation [23, https://clinicaltrials.gov/ct2/show/NCT03802149]. We further wanted a dosage of UPA that would be easily accessible based on the current packaging of UPA, which is in 30mg tablets for ease of use among participants. Given that mifepristone 200mg is used in early pregnancy loss, we propose a dose of UPA 90mg for this study. No dose adjustments will be made for UPA, although further study could examine the effectiveness of a lower dosage of UPA on pregnancy expulsion.

### 4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

## 5 STUDY POPULATION

### 5.1 INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. English or Spanish-speaking
4. Female, age 18 years or older
5. Ultrasound examination showing a non-viable intrauterine pregnancy between 5- and 12-weeks' gestation as indicated by the Doubilet criteria or anembryonic gestation [5], see Appendix A

### 5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Desire for non-medical management of early pregnancy loss (either expectant management or surgical management)
2. Hemodynamically unstable
3. Women with incomplete or inevitable abortion (due to high efficacy of misoprostol alone)
4. Contraindication or allergy to ulipristal acetate or misoprostol (glaucoma, mitral stenosis, sickle cell anemia, chronic glucocorticoid use)
5. Evidence of a viable intrauterine pregnancy, ectopic pregnancy, or pregnancy with IUD in place
6. Evidence of pelvic infection
7. Hemoglobin <9.5g/dL
8. Known cardiovascular disease (arrhythmia, cardiac failure, valvular disease, angina)
9. Known clotting or bleeding disorder, or on anticoagulation therapy
10. Use of the following medications that may influence metabolization of the study medications: barbituates, bosentan, carbamazepine, felbamate, griseofulvin, oxcarbazepine, phenytoin, rifampin, St. John's Wort, topiramate [16]
11. Use of CYP3A4 inhibitors within five elimination half-lives of ulipristal acetate
12. Chronic adrenal failure (risk of acute renal insufficiency)
13. Concurrent long-term corticosteroid therapy (risk of acute renal insufficiency)
14. Any history of underlying liver disorder, including hepatitis
15. Elevation of any or all liver enzymes (ALT, AST, total bilirubin) above the upper limit of normal (ULN) at baseline testing prior to enrollment
16. A family history of hepatitis or currently living with a person who has been given a diagnosis of hepatitis
17. A history of or currently working as a sex worker
18. A history of or currently using intravenous (IV) drugs
19. A self-reported history of alcohol dependency or abuse

Of note, exclusion criteria 1 and 2 will be evaluated by the OBGYN provider assessing the patient for EPL. No discussion of options for management of EPL will take place by the research team prior to inclusion in the study to avoid any potential bias towards medical management if the patient desires expectant or surgical management.

## 5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Abstain from intercourse until expulsion of gestational sac is noted via transvaginal ultrasonography

## 5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the study but are not administered the study intervention (ulipristal acetate) due to either participant withdrawal from the study or change in exclusion criteria following informed consent. A minimal set of information will be kept on all screen failure participants including eligibility screening checklist, informed consent documentation, demographic questionnaire (if completed), screen failure details and any severe adverse event (SAE). This information may be used in study reports, published materials, or to respond to regulatory authorities.

Additionally, a minimal set of information will be kept for patients screened for enrollment who do not meet eligibility criteria or who do not consent to participate in the study on the study screening register.

This information includes name, date of birth, referring physician, date of referral, date of contact with patient, and patient outcome (e.g. screen out, decline to participate, enroll in study). Following completion of enrollment of study participants, this information will be de-identified with just the number of patients in each outcome (screen out, decline to participate, enroll in study) for use in study reports, published materials, or to respond to regulatory authorities.

## 5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

We propose a convenience sample as this is a pilot feasibility study. We propose enrolling 40 patients in the study based on an average of two patients presenting with early pregnancy loss per week at viability ultrasounds at UNC Chapel Hill OBGYN clinics over a year of recruitment. We estimate that 100 patients will be diagnosed with EPL to enroll these 40 patients given prior recruitment rates from studying mifepristone and misoprostol for early pregnancy loss (800 EPL patients for a total of 300 participants) [2].

This will be a single site study at UNC Chapel Hill. Participants will be recruited from OBGYN clinics at their viability scan upon diagnosis of EPL. Recruitment will take place at UNC Chapel Hill OBGYN clinics and UNC Chapel Hill Emergency Department. To aid providers in recruitment efforts, the study coordinator and principal investigator will pre-screen patient visits at the UNC Chapel Hill OBGYN clinics to identify those patients presenting for an early pregnancy ultrasound based on their visit type. Providers at the UNC Chapel Hill OBGYN clinics will be notified via secure EPIC message which of their patients may be eligible for recruitment to the study if they are diagnosed with an early pregnancy loss on that ultrasound. No additional patient information will be obtained until after a diagnosis of early pregnancy loss has been confirmed and the patient has been referred to the study team from the primary medical team.

Once early pregnancy loss has been diagnosed on ultrasound, patients are referred back to their primary OBGYN provider for counseling on the diagnosis and discussion of management options, often on the same day as the ultrasound. Patients desiring medical management of EPL are referred to the GYN consultation team at UNC via a telephone call for more information regarding medical management and prescription of the requisite medications. The GYN consultation team will offer patients the standard of care of mifepristone and misoprostol versus admission into the study for ulipristal acetate and misoprostol. Patients interested in the study will then be approached by the research staff. Patients who initially elect for expectant management of their early pregnancy loss but desire medical management at a later date may be offered admission into the study as well within the first two weeks following diagnosis, as over 50% of patients will pass their pregnancy after two weeks following diagnosis [27].

Thus, patients approached for participation will meet the following criteria:

- Diagnosed with early pregnancy loss or anembryonic gestation between 5- and 12-weeks' gestation on viability ultrasound at UNC Chapel Hill OBGYN clinics and UNC Chapel Hill Emergency Department
- Desire medical management of early pregnancy loss and are clinically stable to do so (not hemodynamically unstable or with active vaginal bleeding)
- Interested in learning more about the study from research team

To aid in recruitment efforts, flyers will be placed in each of the two recruitment locations and brochures will be offered to patients if they are considering admission to the study but need time to process their diagnosis. All flyers and brochures will have contact information for the study team so

patients can reach out to the research team directly. Provider flyers will also be placed in the provider workspaces at both recruitment locations and in the GYN workspace at UNC Chapel Hill where the GYN consultation team is based to provide detailed information on the study and eligibility requirements. All study materials will be written to an appropriate reading level to ensure comprehension among all potential participants.

All counseling on the diagnosis of early pregnancy loss and options for management of early pregnancy loss will take place prior to patient being approached by the research staff. Research staff will reach out to potential participants via telephone call to schedule an eligibility screening at the UNC Same Day Clinic. Research staff will then assess patients for study eligibility and proceed with study activities if the patients are eligible for participation.

Participants will enroll in the study once they are screened for inclusion and exclusion criteria from the study team and the study team has been able to review laboratory tests (hemoglobin, hepatic function tests) to ensure the patient is an appropriate candidate for enrollment. Patients will be offered enrollment into the study and then complete their baseline visit including the demographic questionnaire and administration of UPA.

Spanish-speaking patients make up a key demographic seeking OBGYN care at UNC Chapel Hill, with approximately 10% of individuals identifying as Latinx in the surrounding catchment area. As such, we will include Spanish speaking patients within our study population. All consent and data collection forms will be translated into Spanish for use with this patient population. Additionally, all patient interactions will take place with a Spanish-certified research staff member or with a certified Spanish interpreter (either in person or via telephone).

All women recruited to the study will be pregnant but have already been diagnosed with an early pregnancy loss and thus do not have any risks to an ongoing pregnancy by participating in the study. Participants will be offered psychological support for their loss as part of their standard care for early pregnancy loss. No other vulnerable patients will be included in the patient population including minors under 18 years of age, prisoners, or patients unable to provide informed consent.

UNC-Chapel Hill students and employees may seek OBGYN care at UNC-Chapel Hill and will not be excluded from the study. Any information regarding medical care for UNC-Chapel Hill students or employees will be documented appropriately in their medical charts, which are confidential from UNC-Chapel Hill faculty or employers. Additionally, as with all other patients, all research materials relating to the study will be kept confidential and will not be shared with UNC-Chapel Hill faculty or employers.

As part of the study, participants will receive compensated medical care for management of their EPL including no cost medication for the study intervention and follow up visit with transvaginal ultrasound to confirm resolution of the pregnancy. Subjects will also receive a gift card of USD $20 for their travel and time to their follow up visit(s) on day 3 and day 8, as often outside the context of this study these follow ups are completed via phone call. They will also receive parking vouchers to park at the UNC Chapel Hill campus for follow up. As this reimbursement is nominal, the risk for coercion is low. Further, all study procedures are in line with the standard of care for treatment of EPL at UNC such that patients do not risk receiving different care by completing the study.

# 6 STUDY INTERVENTION

## 6.1 STUDY INTERVENTION(S) ADMINISTRATION

### 6.1.1 STUDY INTERVENTION DESCRIPTION

The study intervention will involve administration of 90mg UPA (three 30mg oral tablets) followed by 800mcg misoprostol (four 200mcg tablets) vaginally 6 to 18 hours after.

- Information regarding UPA 30mg oral tablet is detailed in the full prescribing information from the FDA. Use of UPA for this purpose is being studied under an IND (pending).
- Information regarding misoprostol 200mcg tablet is detailed in the full prescribing information from the FDA. While the FDA approves misoprostol for treatment of gastric ulcers, the dose and route of 800mcg misoprostol vaginally for medication abortion or medication treatment of early pregnancy loss has been studied extensively and is the most successful regimen to date [30, 31].

### 6.1.2 DOSING AND ADMINISTRATION

Participants will be given 90mg UPA (three 30mg oral tablets) in the presence of research staff on baseline/enrollment visit 1 (day 0) after determining eligibility and giving informed consent. Patients will be prescribed 800mcg misoprostol (four 200mcg tablets) and instructed to self-administer misoprostol vaginally 6 to 18 hours after administration of UPA. Participants will be given oral medications to manage pain and symptoms during their EPL from their OBGYN provider prior to discharge home.

Medication timing of misoprostol administration will be based on post-hoc analysis of misoprostol administration following mifepristone for early pregnancy loss. These data suggest that patients have the highest likelihood of success when misoprostol is administered 7 to 20 hours after mifepristone [32]. Pharmacokinetic data suggest that peak concentrations of ulipristal acetate and its active metabolite are 0.9 hours and 1 hour respectively, compared to mifepristone that reaches peak concentrations after 90 minutes; thus we propose earlier times when compared with those recommended with mifepristone [16,17]. Further, extensive data has studied vaginal misoprostol 6 hours after mifepristone for medication abortion with good success [33].

If a gestational sac is still present on transvaginal ultrasound on visit 2 (day 3), expectant management, medical management or surgical management will be offered to patients. Patients desiring additional medical management will be instructed to administer 800mcg misoprostol vaginally or buccally within 24 hours of their appointment. Patients may not be eligible for additional dosage of misoprostol if they are hemodynamically unstable and necessitate urgent or emergent surgical intervention.

## 6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

### 6.2.1 ACQUISITION AND ACCOUNTABILITY

UPA 90mg will be dispensed by study coordinators at visit 1. Prescription for misoprostol will be sent to the UNC Chapel Hill pharmacy for patients to pick up prior to discharge.

### 6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

UPA tablets are supplied as 30mg white, round, curved tablets marked with “ella” on both sides. Three tablets will be administered to patients at one time. UPA is manufactured by Osny Pharma in France and is under license from Laboratoire HRA Pharma. UPA is distributed by Watson Pharma, Inc [16].

### 6.2.3 PRODUCT STORAGE AND STABILITY

UPA tablets are supplied in a PVC-PE-PVDC-aluminum blister. The medication should be stored at 68-77 degrees F and the blisters will be kept in the outer carton to protect from light [16].

### 6.2.4 PREPARATION

No further preparation of UPA is needed for the study intervention.

## 6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

As UPA has not been studied for this indication, we propose a pilot study without randomization or blinding to assess the feasibility and effectiveness of this intervention. Once feasibility has been demonstrated, a subsequent randomized controlled trial may be undertaken.

## 6.4 STUDY INTERVENTION COMPLIANCE

Patients will take UPA in the presence of study staff prior to discharge from visit 1. Participants will report the time that they self-administered misoprostol vaginally on their return for their day 3 transvaginal ultrasound.

## 6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Patients will be advised to not take certain medications that affect CYP450 metabolism pathways as detailed in exclusion criteria (5.2) as these medications may influence metabolism of UPA. Otherwise, no recording of concomitant medication therapy will be collected from patients.

### 6.5.1 RESCUE MEDICINE

Not applicable.

# 7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from taking UPA will constitute discontinuation from the study protocol and participants may receive any option of EPL management (expectant management, medical management, or surgical management) from their OBGYN. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment but before UPA administration, the investigator or qualified designee will evaluate if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

## 7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance

- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant presents for enrollment >2 weeks following diagnosis of early pregnancy loss as over 50% of participants will have complete miscarriage with expectant management alone at this time point [27].

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form but do not receive the study intervention may be replaced.

Participants who discontinue or withdraw from the study will not be replaced. Instead, additional enrollment will commence to reach the targeted sample size of 40 study participants.

### 7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 1 day and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

Similarly, the following actions will be taken if a participant fails to return for her laboratory visit (Day 14 ± 1 day):

- The site will attempt to contact the participant and reschedule the laboratory visit within 1 day and counsel the participant on the importance of maintaining the laboratory visit and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

## 8 STUDY ASSESSMENTS AND PROCEDURES

### 8.1 FEASIBILITY ASSESSMENTS

At the time of recruitment to the study, participants' medical charts will be utilized to confirm the diagnosis of early pregnancy loss by ultrasound diagnosis. A HIPAA authorization form will be obtained from patients at the time of enrollment into the study, as EPL care will be documented in the UNC EPIC electronic medical record as well as in the study documentation. Any adverse events noted in the UNC EPIC electronic medical record during the study follow up time that are not associated with a study visit will be abstracted into the study documentation to appropriately follow up adverse events.

Once study participants have been approached, administration of UPA should occur within 14 days of diagnosis of early pregnancy loss, as over 50% of patients will have completion of their miscarriage with expectant management alone 14 days after diagnosis of early pregnancy loss [27]. Following administration of ulipristal acetate 90mg PO, participants will place misoprostol 800mcg vaginally 6 to 18 hours after ulipristal acetate. Study participants will note the time of misoprostol administration on their appointment card and report the time of misoprostol administration at their subsequent visit to ensure adherence to the study protocol.

Patients will return to clinic on day 3 for a transvaginal ultrasound to confirm absence of a gestational sac. Transvaginal ultrasound will be performed by an obstetrician/gynecologist (fellow or attending) in the UNC Family Planning Clinic to confirm absence of the gestational sac. These physicians have training in transvaginal ultrasound in early pregnancy. If participants are still noted to have a pregnancy in the uterus, they will be offered expectant management, medical management with an additional dose of 800mcg misoprostol, or surgical management with manual or electric uterine aspiration based on gestational age. Those patients with a pregnancy still in the uterus will return to clinic again on day 8 for an additional transvaginal ultrasound and again be offered options if pregnancy is still present. All patients will receive a phone call 30 days following misoprostol administration to assess for additional treatments needed, side effects, adverse events, and patient acceptability.

## 8.2 SAFETY AND OTHER ASSESSMENTS

At the time of diagnosis of EPL, the research coordinator will utilize the medical chart to review ultrasound images to confirm the diagnosis. Research personnel will then complete an eligibility questionnaire based on the inclusion and exclusion criteria as laid out above (5.1). Participants must be hemodynamically stable to take part in the study, which will be assessed by the OBGYN provider assessing the patient for their diagnosis.

On day 3 follow up, participants will provide information regarding the time and route they took their misoprostol medication to ensure compliance with the study activities. Patients will be informed in real time regarding their follow up transvaginal ultrasound results at their follow up visits, as they will be able to decide how they want to proceed with management (expectant management, additional medical management with second dose of misoprostol, or surgical management) if ultrasound still confirms the presence of an intrauterine pregnancy. Similarly, any patients who necessitated any additional care as part of their treatment of EPL (e.g. genetic studies on products of conception, infectious disease testing) will have those results shared in the standard manner for all patients seeking care with the Family Planning Division. Participants will report all adverse events (both pregnancy and non-pregnancy related) at each clinical visit.

During the two weeks post-treatment period, if women develop fatigue, malaise, abdominal pain or jaundice, a workup for liver injury should be performed. All patients with elevated LFTs (ALT, AST or total bilirubin) will be followed until resolution. For patients whose LFTs have not returned to normal within

one month, these patients will be referred to a specialist (e.g. hepatologist) for further workup and treatment if necessary.

The study sponsor will evaluate the first 20 patients for their post-treatment LFTs prior to expanding enrollment to the subsequent 20 patients.

Patients identified to have more severe medical adverse events or side effects will be advised to contact the UNC Family Planning Division. Based on the symptomatology and severity, patients will be instructed to seek care through the emergency department/urgent care or through the Family Planning Clinic. All medical adverse events or side effects will be managed based on the standard of care.

## 8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

### 8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

### 8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### 8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

#### 8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

#### 8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment.

The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

#### 8.3.3.3 EXPECTEDNESS

The study sponsor will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

### 8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study sponsor will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All participants in the study will have notation on their UNC EPIC chart to alert the research staff if the patient is seen for any possible adverse event. Patients will be assessed for adverse events at their telephone follow up 30 days after study intervention. Solicited information on adverse events will include increased bleeding requiring hospital admission or blood transfusion and infection requiring hospital admission or IV antibiotics. All other adverse events will be identified based on unsolicited questioning during this telephone visit.

### 8.3.5 ADVERSE EVENT REPORTING

Adverse event reporting by patient self-report will take place at each study visit, both in person and via telephone. Additionally, any adverse event that happens between study visits for which the participant seeks care at UNC Chapel Hill will be abstracted from the UNC EPIC electronic medical record. All adverse events will be recorded on case report forms (CRF) and will be reviewed by the principal investigator and mentor. Case report forms should be documented within 24 hours of the event, and review of the case report forms will occur on a weekly basis.

Likely mild medication side effects as detailed for UPA include headache (18%), nausea (12%), abdominal pain (12%). Other infrequent mild side effects include dysmenorrhea, fatigue and dizziness [14]. All patients may experience pain and discomfort during the process of pregnancy expulsion; however, this pain and discomfort are not different than what a patient would experience not in the study. Assessment of adverse events will include symptoms possibly related to the study medication and pregnancy expulsion, but will also include any additional adverse events experienced by the study participants.

### 8.3.6 SERIOUS ADVERSE EVENT REPORTING

Based on prior studies of mifepristone and misoprostol, the rate of severe adverse event in this population is extremely low (approximately 1%). The study clinician will immediately report to the sponsor any serious adverse event, whether the adverse event is considered study intervention related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study outcomes that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

Upon the first severe adverse event that occurs among study participants, the study will be stopped temporarily until review of the event by the UNC IRB. Following review of the severe adverse event, a decision will be made if the entire study will need to be stopped prematurely or if it is safe to continue the study.

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor identifies that the information qualifies for reporting.

Any serious liver injury case consistent with Hy’s law will be reported as an expedited report to the FDA.

### 8.3.7 REPORTING EVENTS TO PARTICIPANTS

Participants will be notified at an aggregate level about any AEs or SAEs affecting >5% of the study population.

### 8.3.8 EVENTS OF SPECIAL INTEREST

There are no additional events of special interest beyond those that have already been described.

### 8.3.9 REPORTING OF PREGNANCY

As patients are being admitted to the study with early pregnancy loss, no new pregnancies will be assessed during the study period.

## 8.4 UNANTICIPATED PROBLEMS

### 8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

### 8.4.2 UNANTICIPATED PROBLEM REPORTING

Research personnel will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the study sponsor within 7 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor within 30 days of the investigator becoming aware of the problem.

- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 7 days of the IRB's receipt of the report of the problem from the investigator.

### 8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable.

## 9 STATISTICAL CONSIDERATIONS

### 9.1 RESEARCH HYPOTHESES

- Primary Outcome Variable(s):
  - Feasibility:
    - Recruitment: >60% participants screened for participation enrolled in study
    - Adherence: >50% participants took study medications at the appropriate time and route
    - Retention: >90% participants had complete follow up for all study visits
- Secondary Outcome Variable(s): This is a pilot study with a small sample size and thus our secondary aims will only be for hypothesis generating activities, not hypothesis testing activities.

### 9.2 SAMPLE SIZE RATIONALE

As this is a feasibility pilot study, no formal power calculation is required. We anticipate recruiting a convenience sample of 40 participants over the course of 12 months recruitment based on prior information from UNC Chapel Hill where approximately two patients with EPL are diagnosed per week at our two study locations after accounting for eligibility criteria and desire participation in the study. We estimate that of the approximately 100 patients diagnosed with EPL over the year, 40 patients will enroll given prior recruitment rates from studying mifepristone and misoprostol for early pregnancy loss (800 EPL patients for a total of 300 participants) [2].

### 9.3 POPULATIONS FOR ANALYSES

As no randomization will take place in this analysis, all participants will be analyzed as part of the same population using univariate statistics. For the primary endpoint of feasibility, all patients screened for study participation will be included in the sample size. For the secondary endpoints of resolution of EPL, side effects/adverse events and patient acceptability, only participants adherent to study medication and completing all study visits will be analyzed. A sensitivity analysis will be conducted for the secondary endpoints that will include all participants enrolled in the study population for which data is available, regardless of adherence to study medication or completion of all study visits.

Patient disposition in the study will be reported, including the following:

- Number (%) of patients screened for study participation
- Number (%) of patients enrolled in study population
- Number (%) of participants adherent to study medication (UPA + misoprostol after 6 to 18 hours)
- Number (%) of participants non-adherent to study medication (any other route or timing of taking study medications)
- Number (%) of participants completing all study visits (day 0, day 3/8, day 30)

- Number (%) of participants completing some of study visits

Patient disposition will be reported as a flow chart and in tabular format in any future study communication and manuscript.

## 9.4 STATISTICAL ANALYSES

### 9.4.1 GENERAL APPROACH

Continuous variables will be summarized using mean and standard deviation or median and range depending on the distribution and categorical variables will be described as frequency and percentage. All statistics will be reported with 95% confidence intervals. Where applicable, missing data will be reported as an individual category. As this is a pilot feasibility study with a small sample size, no formal statistical testing will be completed. The principal investigator will be responsible for all data management and data analysis. Statistical calculations will be performed in Stata 15.1.

### 9.4.2 ANALYSIS OF THE PRIMARY FEASIBILITY OUTCOME VARIABLE(S)

- Recruitment (%): number of participants in study/number of patients screened for participation
- Adherence (%): number of participants adhering to study intervention (UPA + misoprostol vaginally after 6 to 18 hours)/number of participants in study
- Retention (%): number of participants attending all study visits (day 0, 3/8, 30)/number of participants in study

### 9.4.3 ANALYSIS OF THE SECONDARY OUTCOME VARIABLE(S)

- Resolution of EPL
    - Binomial outcome: Absence of gestational sac on transvaginal ultrasound examination on Day 3 follow up
    - Binomial outcome: Need for additional dose of misoprostol within 30 days of treatment
    - Binomial outcome: Need for uterine aspiration within 30 days of treatment
- Side Effects/Adverse Events
    - Side Effects Binomial Outcomes (N, %)
        - Fatigue
        - Headache
        - Dizziness or lightheadedness
        - Chills
        - Nausea
        - Diarrhea
        - Vomiting
        - Severe cramping
        - Fever
        - Other
    - Adverse Events Binomial Outcomes (N, %)
        - Excess bleeding requiring blood transfusion
        - Pelvic infection requiring antibiotics
- Patient Acceptability
    - Likert Scale Ordinal Outcomes (Median, Counts)

- Would you use this combination of medications again if you had another early pregnancy loss?
- Would you recommend this combination of medications to a friend with early pregnancy loss?
- If it was possible to take the first medication at home (versus in clinic), would you be more or less likely to use this combination of medications again?
- If it were possible to take the first medication at a different time (versus during your appointment), would you be more or less likely to use this combination of medications again?

### 9.4.4 SAFETY ANALYSES

AEs will be reported by frequency and percentage of participants presenting with the outcomes. Specific side effects and adverse events of interest are listed with secondary outcomes (9.4.3). All other side effects and adverse events outside of those listed in 9.4.3 will also be reported by frequency and percentage. Other AEs will be reported by severity of the adverse events (mild, moderate or severe) and related or not related to the study protocol. AEs will be grouped by Medical Dictionary for Regulatory Activity (MedDRA) System Organ Class (SOC).

### 9.4.5 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics will be reported for patient demographics based on the demographic questionnaire collected at the time of participant enrollment into the study. As there is only one study group, no statistical comparisons will be made. The following demographic information will be collected:

- Age (mean, SD)
- Race/ethnicity (N, %)
- Education (N, %)
- Marital status (N, %)
- Insurance type (N, %)
- Gravidity (median, IQR)
- Parity (median, IQR)
- Vaginal deliveries (median, IQR)
- Cesarean deliveries (median, IQR)
- Living children (N, %)
- Previous miscarriage (N, %)
- Previous abortion (N, %)
- Gestational age (mean, SD)

### 9.4.6 PLANNED INTERIM ANALYSES

Given the small size and short duration of the study, no interim analysis will be completed.

### 9.4.7 SUB-GROUP ANALYSES

Given the small sample size and lack of randomization, no sub-group analysis will be performed.

### 9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

All data will be aggregated for the purpose of reporting results from the study. No individual patient data will be listed.

#### 9.4.9 EXPLORATORY ANALYSES

No additional exploratory analyses will be completed.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

### 10.1.1 INFORMED CONSENT PROCESS

#### 10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol (Appendix A – Informed Consent).

#### 10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

### 10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants

- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- A life-threatening medical situation with determined study procedure causality
- Persistent or significant incapacity as a result of study drug(s) or procedure(s)
- A study participant with hepatic enzyme elevation greater than 3 times the upper limit of normal seen on laboratory testing on day 14

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

### 10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, research personnel, and the sponsor and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in a 21 CFR Part 11-compliant database through UNC. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. At the end of the study, all study databases will be disposed of 2 years following study termination.

### 10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

No future use of any data related to this study will be conducted.

### 10.1.5 KEY ROLES AND STUDY GOVERNANCE

| **Principal Investigator** | **Mentor** |
|---|---|
| Jill Melissa Hagey, MD MPH | Amy Bryant, MD MSCR |
| University of North Carolina, Chapel Hill | University of North Carolina, Chapel Hill |

| | |
|---|---|
| 101 Manning Drive<br>Chapel Hill, NC 27514 | 101 Manning Drive<br>Chapel Hill, NC 27514 |
| 919-966-5280 | |
| *jill.hagey@unchealth.unc.edu* | *amy_bryant@med.unc.edu* |

### 10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a medical monitor with appropriate expertise given the small number of participants in the study. The medical monitor should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The medical monitor will review this project at least semiannually to assess safety and efficacy data of the study. At this time, each data element that the medical monitor needs to assess will be clearly defined. The medical monitor will provide its input to the study sponsor and study team.

### 10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

On-site monitoring will occur for initial assessment and training of sites prior to study participant enrollment. The principal investigator will provide an overview of study activities and participant eligibility criteria to all OBGYN clinical staff at UNC Chapel Hill during a weekly departmental meeting. The principal investigator will also provide an overview of study activities to all key clinical staff members who may come in contact with study participants at the sites for patient recruitment as well as at UNC Chapel Hill Family Planning Clinic where follow up visits will take place. Targeted data verification will be performed by the principal investigator for the first 10 participants approached for recruitment to the study (approximately 10%) to ensure appropriate data collection from the research coordinator. As possible, most transvaginal ultrasounds will be performed by the principal investigator to ensure consistency between imaging findings. Of those not performed by the principal investigator, 20% will be randomly reviewed.

Independent audits will not be conducted.

### 10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the 21 CFR Part 11-compliant database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

### 10.1.9 DATA HANDLING AND RECORD KEEPING

#### 10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the research personnel at the site under the supervision of the principal investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed via paper and pencil and then transcribed into an electronic 21 CFR Part 11-compliant database to ensure accurate interpretation of data. All patient questionnaires will require an answer to each question with an option to select “Prefer not to answer” to improve data completeness. “Prefer not to answer” will be coded as “99” to denote this value during data analysis. All provider questionnaires will be filled out by consistent study staff, with enrollment visits completed by the study coordinator and all follow up visits completed by the principal investigator.

A data “codebook” will be created for each question of the source documents to ensure that all data is being entered into the electronic database in the same way.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the same 21 CFR Part 11-compliant data capture system provided by UNC. Any missing data from the clinical data abstracted from the EPIC chart will be denoted as “Missing” and will be coded as “98” to denote this value during data analysis. Any missing data will be reviewed in the EPIC chart by the principal investigator to ensure that this data value is not present.

The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

#### 10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

### 10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the UNC IRB. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

### 10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 2 years after the completion of the primary outcome by contacting the principal investigator.

### 10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the UNC IRB has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

## 10.2 ADDITIONAL CONSIDERATIONS

None

## 10.3 ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| CFR | Code of Federal Regulations |
| CMP | Clinical Monitoring Plan |
| COC | Certificate of Confidentiality |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | Case Report Form |
| DCC | Data Coordinating Center |
| DHHS | Department of Health and Human Services |
| DSMB | Data Safety Monitoring Board |
| DRE | Disease-Related Event |
| EC | Ethics Committee |
| EPL | Early Pregnancy Loss |
| eCRF | Electronic Case Report Forms |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FFR | Federal Financial Report |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practices |
| GMP | Good Manufacturing Practices |
| HIPAA | Health Insurance Portability and Accountability Act |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IND | Investigational New Drug Application |
| IRB | Institutional Review Board |
| ISM | Independent Safety Monitor |
| ISO | International Organization for Standardization |
| ITT | Intention-To-Treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MOP | Manual of Procedures |
| MSDS | Material Safety Data Sheet |
| NCT | National Clinical Trial |
| NIH | National Institutes of Health |
| NIH IC | NIH Institute or Center |
| OHRP | Office for Human Research Protections |
| PI | Principal Investigator |
| QA | Quality Assurance |
| QC | Quality Control |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |

| | |
|---|---|
| SMC | Safety Monitoring Committee |
| SOA | Schedule of Activities |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| UP | Unanticipated Problem |
| UPA | Ulipristal Acetate |
| US | United States |

## 10.4 PROTOCOL AMENDMENT HISTORY

| Version | Date | Description of Change | Brief Rationale |
|---|---|---|---|
| 1.0 | 24 Aug 2021 | Initial protocol | |
| 2.0 | 20 Sept 2021 | Updated protocol per SRC comments | |
| 3.0 | 3 Dec 2021 | Updated protocol per FDA IND comments | |
| 4.0 | 10 Jan 2022 | Updated protocol per FDA IND comments | |
| 5.0 | 15 Feb 2022 | Updated protocol per IRB comments | |
| 6.0 | 3 Mar 2022 | IRB Modification | |
| 7.0 | 22 Apr 2022 | IRB Modification | |
| 8.0 | 2 June 2022 | IRB Modification | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

## 11 REFERENCES

1. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 200: Early Pregnancy Loss. Obstet Gynecol. 2018 Nov;132(5):e197-e207.
2. Schreiber CA, Creinin MD, Atrio J, Sonalkar S, Ratcliffe SJ, Barnhart KT. Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss. N Engl J Med. 2018 Jun 7;378(23):2161-2170.
3. Chu JJ, Devall AJ, Beeson LE, Hardy P, Cheed V, Sun Y, Roberts TE, Ogwulu CO, Williams E, Jones LL, La Fontaine Papadopoulos JH, Bender-Atik R, Brewin J, Hinshaw K, Choudhary M, Ahmed A, Naftalin J, Nunes N, Oliver A, Izzat F, Bhatia K, Hassan I, Jeve Y, Hamilton J, Deb S, Bottomley C, Ross J, Watkins L, Underwood M, Cheong Y, Kumar CS, Gupta P, Small R, Pringle S, Hodge F, Shahid A, Gallos ID, Horne AW, Quenby S, Coomarasamy A. Mifepristone and misoprostol versus misoprostol alone for the management of missed miscarriage (MifeMiso): a randomised, double-blind, placebo-controlled trial. Lancet. 2020 Sep 12;396(10253):770-778.
4. Shigesato M, Elia J, Tschann M, Bullock H, Hurwitz E, Wu YY, Salcedo J. Pharmacy access to Ulipristal acetate in major cities throughout the United States. Contraception. 2018 Mar;97(3):264-269.
5. Doubilet PM, Benson CB, Bourne T, Blaivas M; Society of Radiologists in Ultrasound Multispecialty Panel on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy, Barnhart KT, Benacerraf BR, Brown DL, Filly RA, Fox JC, Goldstein SR, Kendall JL, Lyons EA, Porter MB, Pretorius DH, Timor-Tritsch IE. Diagnostic criteria for nonviable pregnancy early in the first trimester. N Engl J Med. 2013 Oct 10;369(15):1443-51.
6. Gemzell-Danielsson K, Bygdeman M, Aronsson A. Studies on uterine contractility following mifepristone and various routes of misoprostol. Contraception. 2006 Jul;74(1):31-5.
7. Cameron ST, Critchley HO, Buckley CH, Kelly RW, Baird DT. Effect of two antiprogestins (mifepristone and onapristone) on endometrial factors of potential importance for implantation. Fertil Steril. 1997 Jun;67(6):1046-53.
8. Swahn ML, Bygdeman M, Cekan S, Xing S, Masironi B, Johannisson E. The effect of RU 486 administered during the early luteal phase on bleeding pattern, hormonal parameters and endometrium. Hum Reprod. 1990 May;5(4):402-8.
9. Mifeprex REMS Study Group, Raymond EG, Blanchard K, Blumenthal PD, Cleland K, Foster AM, Gold M, Grossman D, Pendergast MK, Westhoff CL, Winikoff B. Sixteen Years of Overregulation: Time to Unburden Mifeprex. N Engl J Med. 2017 Feb 23;376(8):790-794.
10. FDA. Approved Risk Evaluation and Mitigation Strategies (REMS). Mifepristone Summary. *https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390* Accessed 29 July 2021.
11. Cleland K, Smith N. Aligning mifepristone regulation with evidence: driving policy change using 15 years of excellent safety data. Contraception. 2015 Sep;92(3):179-81.
12. Srinivasulu S, Yavari R, Brubaker L, Riker L, Prine L, Rubin SE. US clinicians' perspectives on how mifepristone regulations affect access to medication abortion and early pregnancy loss care in primary care. Contraception. 2021 Jul;104(1):92-97.
13. Grossman D, Grindlay K, Altshuler AL, Schulkin J. Induced Abortion Provision Among a National Sample of Obstetrician-Gynecologists. Obstet Gynecol. 2019 Mar;133(3):477-483.
14. Patel P, Narayana S, Thill Z, Gold M, Paul A. Family Physicians' Role in Simplifying Medication Abortion During the COVID-19 Pandemic. J Am Board Fam Med. 2021 Feb;34(Suppl):S33-S36.

15. Gemzell-Danielsson K, Berger C, P G L L. Emergency contraception -- mechanisms of action. Contraception. 2013 Mar;87(3):300-8.
16. FDA. Ella (ulipristal acetate) tablet. 2010. Full prescribing information.
17. FDA. Mifeprex (mifepristone) tablet. 2016. Full prescribing information.
18. Horne FM, Blithe DL. Progesterone receptor modulators and the endometrium: changes and consequences. Hum Reprod Update. 2007 Nov-Dec;13(6):567-80.
19. Stratton P, Levens ED, Hartog B, Piquion J, Wei Q, Merino M, Nieman LK. Endometrial effects of a single early luteal dose of the selective progesterone receptor modulator CDB-2914. Fertil Steril. 2010 Apr;93(6):2035-41.
20. Whitaker LH, Murray AA, Matthews R, Shaw G, Williams AR, Saunders PT, Critchley HO. Selective progesterone receptor modulator (SPRM) ulipristal acetate (UPA) and its effects on the human endometrium. Hum Reprod. 2017 Mar 1;32(3):531-543.
21. Berger C, Boggavarapu NR, Menezes J, Lalitkumar PG, Gemzell-Danielsson K. Effects of ulipristal acetate on human embryo attachment and endometrial cell gene expression in an in vitro co-culture system. Hum Reprod. 2015 Apr;30(4):800-11.
22. Boggavarapu NR, Berger C, von Grothusen C, Menezes J, Gemzell-Danielsson K, Lalitkumar PG. Effects of low doses of mifepristone on human embryo implantation process in a three-dimensional human endometrial in vitro co-culture system. Contraception. 2016 Aug;94(2):143-51.
23. Peterson S. Cervical preparation using ulipristal acetate in second trimester surgical abortions. Society of Family Planning Fellowship Research. *https://societyfp.org/awarded_grants/sfprf19-05/* Accessed 5 July 2021.
24. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, Robson R, Thabane M, Giangregorio L, Goldsmith CH. A tutorial on pilot studies: the what, why and how. BMC Med Res Methodol. 2010 Jan 6;10:1.
25. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract. 2004 May;10(2):307-12.
26. Arain M, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? A review of current practice and editorial policy. BMC Med Res Methodol. 2010 Jul 16;10:67.
27. Luise C, Jermy K, May C, Costello G, Collins WP, Bourne TH. Outcome of expectant management of spontaneous first trimester miscarriage: observational study. BMJ. 2002 Apr 13;324(7342):873-5.
28. Stratton P, Hartog B, Hajizadeh N, Piquion J, Sutherland D, Merino M, Lee YJ, Nieman LK. A single mid-follicular dose of CDB-2914, a new antiprogestin, inhibits folliculogenesis and endometrial differentiation in normally cycling women. Hum Reprod. 2000 May;15(5):1092-9.
29. Shen J, Che Y, Showell E, Chen K, Cheng L. Interventions for emergency contraception. Cochrane Database of Systematic Reviews 2019, Issue 1. Art. No.: CD001324.
30. FDA. Misoprostol (Cytotec) tablet. 2009. Full prescribing information.
31. Lemmers M, Verschoor MAC, Kim BV, Hickey M, Vazquez JC, Mol BMJ, Neilson JP. Medical treatment for early fetal death (less than 24 weeks). Cochrane Database of Systematic Reviews. 2019, Issue 6. Art. No.: CD002253.
32. Flynn AN, Roe AH, Koelper N, McAllister A, Sammel MD, Schreiber CA. Timing and efficacy of mifepristone pretreatment for medical management of early pregnancy loss. Contraception. 2021 Jun;103(6):404-407.

33. Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA; MOD Study Trial Group. A randomized comparison of misoprostol 6 to 8 hours versus 24 hours after mifepristone for abortion. Obstet Gynecol. 2004 May;103(5 Pt 1):851-9.
34. Zhang J, Gilles JM, Barnhart K, Creinin MD, Westhoff C, Frederick MM; National Institute of Child Health Human Development (NICHD) Management of Early Pregnancy Failure Trial. A comparison of medical management with misoprostol and surgical management for early pregnancy failure. N Engl J Med. 2005 Aug 25;353(8):761-9.
35. Small B, Millard CEF, Kisanga EP, Burman A, Anam A, Flannery C, Al-Hendy A, Whirledge S. The Selective Progesterone Receptor Modulator Ulipristal Acetate Inhibits the Activity of the Glucocorticoid Receptor. J Clin Endocrinol Metab. 2020 Mar 1;105(3):716–34.

APPENDIX A: DOUBILET CRITERIA [5]

**Table 2. Guidelines for Transvaginal Ultrasonographic Diagnosis of Pregnancy Failure in a Woman with an Intrauterine Pregnancy of Uncertain Viability.***

| Findings Diagnostic of Pregnancy Failure | Findings Suspicious for, but Not Diagnostic of, Pregnancy Failure† |
|---|---|
| Crown–rump length of ≥7 mm and no heartbeat | Crown–rump length of <7 mm and no heartbeat |
| Mean sac diameter of ≥25 mm and no embryo | Mean sac diameter of 16–24 mm and no embryo |
| Absence of embryo with heartbeat ≥2 wk after a scan that showed a gestational sac without a yolk sac | Absence of embryo with heartbeat 7–13 days after a scan that showed a gestational sac without a yolk sac |
| Absence of embryo with heartbeat ≥11 days after a scan that showed a gestational sac with a yolk sac | Absence of embryo with heartbeat 7–10 days after a scan that showed a gestational sac with a yolk sac |
| | Absence of embryo ≥6 wk after last menstrual period |
| | Empty amnion (amnion seen adjacent to yolk sac, with no visible embryo) |
| | Enlarged yolk sac (>7 mm) |
| | Small gestational sac in relation to the size of the embryo (<5 mm difference between mean sac diameter and crown–rump length) |

* Criteria are from the Society of Radiologists in Ultrasound Multispecialty Consensus Conference on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy, October 2012.
† When there are findings suspicious for pregnancy failure, follow-up ultrasonography at 7 to 10 days to assess the pregnancy for viability is generally appropriate.