The INTERRUPT Study

Intervention to End Recurrent Unscheduled bleeding Trial (INTERRUPT):
A randomized-controlled trial of ulipristal acetate
for unscheduled bleeding in etonogestrel implant users

Manual of Procedures

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[redacted]

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EXECUTIVE SUMMARY

INTRODUCTION

The subdermal etonogestrel (ENG) implant, a long-acting reversible contraceptive (LARC) method, is among the most effective forms of reversible contraception. As such, it is an important tool in the quest to reduce unintended pregnancy.[1] Despite its effectiveness, ENG implant users only account for a small proportion of women using LARC methods in the United States.[2,3] Previous studies have demonstrated that among women dissatisfied with their implant, the majority cite unpredictable and irregular bleeding as a primary reason.[4,5,6] Dissatisfaction with a contraceptive method can lead to discontinuation, which can put a woman at risk for unplanned pregnancy. Although irregular bleeding is a common side effect of all progestin-only contraceptives, there are significant gaps in our knowledge regarding the etiology of and effective therapies for unscheduled bleeding.[7] While several mechanisms have been proposed and several therapies have been studied, lack of convincing scientific evidence and possible contraindications to these therapies, demonstrate the need to investigate additional effective interventions. This project, through a double-blinded, randomized, placebo-controlled trial, will evaluate ulipristal acetate (UPA) as a potential therapy for irregular bleeding with the ENG implant. Women will be randomized to receive either 15mg of UPA daily for 7 days or placebo for the same duration.

OBJECTIVES

PRIMARY AIM

To evaluate the effectiveness of ulipristal acetate (15mg) in decreasing bleeding/spotting days due to the ENG implant over a 30-day period as compared to placebo.

SECONDARY AIMS (SA)

SA1: To evaluate bleeding cessation rates by day 10 following seven days of treatment with either ulipristal acetate or placebo.

SA2: To evaluate participant satisfaction with regards to bleeding pattern after use of ulipristal acetate.

SA3: To evaluate participant satisfaction with regards to medication side effects.

SA4: To evaluate effect, if any, of ulipristal acetate on ovulatory status.

KEY PEOPLE AND CONTACT INFORMATION

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PROTOCOL SUMMARY

TITLE

Intervention to End Recurrent Unscheduled bleeding Trial (INTERRUPT): A randomized-controlled trial of ulipristal acetate for unscheduled bleeding in etonogestrel implant users

INVESTIGATIONAL REVIEW BOARD INFORMATION

WUSM IRB #:	201612002
FDA IND#:	134150

CLINICAL TRIALS INFORMATION

ClinicalTrials.gov Identifier:	NCT03118297

OBJECTIVE

To date, no studies have been performed investigating ulipristal acetate for irregular bleeding with the subdermal etonogestrel (ENG) implant. We will perform a double-blinded, randomized, placebo-controlled trial to evaluate ulipristal acetate (UPA) as a potential therapy for irregular bleeding with the ENG implant. Women will be randomized to receive either 15mg of UPA daily for 7 days or placebo for the same duration. Specifically, the INTERRUPT study will answer the following questions:

1. Is UPA (15 mg) effective at decreasing bleeding/spotting days due to the ENG implant over a 30-day period as compared to placebo?
2. Is UPA effective at increasing bleeding cessation rates by day 10 following seven days of UPA (15mg) as compared to placebo?
3. Are participants satisfied with regards to bleeding patterns after use of UPA?
4. Are participants satisfied with regards to UPA side effects?
5. Is there an effect of UPA on ovulatory status?

POPULATION

104 reproductive age women 18-45 who have been using the contraceptive implant for more than 90 days and less than 3 years and have experienced more than 1 bleeding and/or spotting episode in a 24-day period.

STUDY SITE

Barnes Jewish Hospital and Washington University School of Medicine Obstetrics and Gynecology clinics, the Contraceptive Choice Center, Planned Parenthood of the St. Louis Region, and federally qualified health centers within the St. Louis region.

INTERVENTION

Participants will be randomized to a UPA, the experimental intervention, or to a placebo. After consent, participants will take 1 pill per day for 7 days, complete 30 daily text messages, and have follow-up at 1 week post-enrollment, 2 weeks post-enrollment, 3 weeks post-enrollment, and 4 weeks post-enrollment.

STUDY DURATION

We estimate a total of 12 months for recruitment and follow-up.

STUDY PARTICIPANT DURATION

Participants will be followed for 30 days.

INTRODUCTION, BACKGROUND, AND RATIONALE

The subdermal etonogestrel (ENG) implant, a long-acting reversible contraceptive (LARC) method, is among the most effective forms of reversible contraception and thus, an important tool in the quest to reduce unintended pregnancy.[1] However, despite overall increases in LARC use in the United States from 1.5% in 2002 to 7.2% in 2011,[2] and 11.6% most recently in 2015, implant use continues to make up only a small proportion of LARC use.[3] While evidence to explain the low uptake and continuation rates of the ENG implant is lacking, one potential reason is patient and provider concerns about changes to one's bleeding pattern. Irregular or unscheduled vaginal bleeding (*i.e.*, bleeding outside of one's normal period) is a known side effect of the ENG implant. Multiple studies have demonstrated that among women dissatisfied with their implant, the majority cite irregular and unpredictable bleeding as a primary reason.[4,5,6] A randomized controlled trial comparing ENG implant users to levonorgestrel intrauterine device (LNG-IUD) users demonstrated that only 33.6% of implant users were satisfied with their bleeding pattern at 12 months compared to 60.9% among LNG-IUD users.[1] Dissatisfaction with any contraceptive method can lead to discontinuation, which can put a woman at risk for unintended pregnancy.

Although irregular bleeding is a common side effect of all progestin-only contraceptives, including the ENG implant, there are significant gaps in our knowledge regarding the etiology of and effective therapies for unscheduled bleeding.[7] Previously studied therapies have shown mixed results with regards to efficacy. While several mechanisms have been proposed and therapies have been studied, lack of convincing scientific evidence, in addition to possible contraindications, demonstrates the need to investigate additional effective interventions.

Studies evaluating interventions for abnormal uterine bleeding in other clinical settings, such as from uterine leiomyoma, a provide insight into potential untested therapies for progestin-mediated bleeding. In prior studies, ulipristal acetate (UPA), a selective progesterone receptor modulator, has been shown to reduce bleeding symptoms associated with uterine leiomyoma, including decreasing or stopping excessive bleeding.[8,9,10,11,12] Amenorrhea was achieved for the majority of participants within the first ten days of UPA administration.[8] It has been shown to have mixed agonist/antagonist effects within endometrial and myometrial tissue. Uterine bleeding has been reduced or eliminated via antiproliferative effects. Progestin-associated irregular bleeding has been proposed to be secondary to a disruption in endometrial angiogenesis, therefore creating a fragile venous network.[13] UPA may displace local progestin to counteract this effect. Thus, this medication has demonstrated both biologic plausibility as well as clinically important outcomes.

To date, however, no studies have been performed investigating UPA for irregular bleeding with the ENG implant. Other studies assessing different therapies have been performed with mixed outcomes. In addition, some previously studied therapies are contraindicated in many women and/or are not easily obtainable medications. UPA is rarely contraindicated and is available in outpatient pharmacies. As such, the proposed research is designed to evaluate the effectiveness of UPA as a potential therapy for irregular bleeding with the ENG implant.

STUDY AIMS

PRIMARY AIM

To evaluate the effectiveness of ulipristal acetate (15mg) in decreasing bleeding/spotting days due to the ENG implant over a 30-day period as compared to placebo.

> ***Hypothesis:*** *UPA will decrease bleeding and spotting days in users of the ENG implant with unscheduled bleeding by 30% when compared to placebo as assessed by daily bleeding diaries.*

SECONDARY AIMS (SA)

SA1: To evaluate bleeding cessation rates by day 10 following seven days of treatment with either ulipristal acetate or placebo.

SA2: To evaluate participant satisfaction with regards to bleeding pattern after use of ulipristal acetate.

SA3: To evaluate participant satisfaction with regards to medication side effects.

SA4: To evaluate effect, if any, of ulipristal acetate on ovulatory status.

KEY STUDY MEASURES

PRIMARY AIM

1. Daily SMS text message bleeding diaries (Day 1 – Day 30)

SECONDARY AIMS

1. SMS text message bleeding diaries Day 1 – Day 10
2. Phone/in-person survey to assess satisfaction with bleeding pattern at 1, 2, 3, and 4 weeks post-study enrollment
3. Phone/in-person survey to assess satisfaction with medication side effects at 1, 2, 3, and 4 weeks post-study enrollment
4. Serum progesterone levels at baseline and at 1, 2, 3, and 4 weeks post-study enrollment

STUDY DESIGN

The INTERRUPT study is a single-site, double-blinded, randomized, placebo-controlled clinical trial. The total sample size for this study is 104. Of these participants, a subset will undergo weekly venipuncture to assess serum progesterone levels.

RANDOMIZATION SCHEME

A block randomization scheme will be created using a computerized random number generator. In order to keep the research team and participants blinded, assignment will be done by the pharmacy based on this randomization scheme. The pharmacy will make identical UPA and placebo capsules, dispensed as a labeled outpatient prescription after a participant is randomized. The randomization scheme will be generated by a random number table with an allocation ratio of 1:1 in blocks of four with a total of 52 participants in each group for a total sample size of 104.

DESCRIPTION OF METHODS

ULIPRISTAL ACETATE

UPA is a synthetic progesterone receptor modulator, shown to postpone follicular rupture and have mixed agonist/antagonist effects within uterine tissue. The U.S. Food and Drug Administration (FDA) approved Ulipristal acetate in August 2011 as an emergency contraceptive for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. In other countries, including Canada and Europe, UPA is indicated for the preoperative treatment (*e.g.*, reduction in size for less invasive procedure) and long-term management (*e.g.*, abnormal uterine bleeding) of symptomatic leiomyoma. The likely mechanism of action of UPA for decreasing or stopping progestin-associated excessive bleeding is the displacement of local progestin that counteracts endometrial angiogenesis. The recommended dose ranges from 5-10mg daily for up to three months at a time.

In the United States, UPA is only available in 30mg doses. To ensure feasibility and generalizability, participants will be given 15mg UPA doses, which would allow for splitting of the currently-available UPA tablet if the therapy proves beneficial.

Medication (UPA or placebo) will be taken for seven consecutive days. Participants will be instructed to begin their medication on the day of enrollment (*i.e.*, Day 0) and continue through Day 6.

BLEEDING DIARIES

Participants will completed 30 daily text message bleeding diaries that track medication compliance through Day 6 and any bleeding experienced during the study.

FOLLOW-UP SURVEYS

Weekly follow-up surveys will be conducted to assess participants' compliance with medication, experience of side-effects, as well as their satisfaction with their bleeding patterns at the end of weeks 1, 2, 3, and 4.

VENIPUNCTURE

A subset of participants (*i.e.*, 20 UPA, 20 placebo) will undergo weekly venipuncture to assess serum progesterone levels.

POTENTIAL BENEFITS AND RISKS

POTENTIAL BENEFITS

If UPA is effective, it will decrease the number of bleeding and/or spotting days or lead to amenorrhea. As a result, satisfaction with the contraceptive implant may increase. UPA, however, has not previously been studied as a therapy for unscheduled bleeding with the ENG implant.

POTENTIAL RISKS

Participants may experince one or more of the risks indicated below from their participation in this study. In addition, there may be other unknown risks, or risks that were not anticipated, associated with particiation in this study.

Participants are at risk of experiencing side effects of UPA and are listed below:

Common

- Breast tenderness

Less Common

- Headache
- Dizziness
- Hot flash
- Nausea
- Abdominal pain
- Weight gain
- Fluid retention

Rare

- Pregnancy
- Endometrial hyperplasia

There is some risk involved with blood draws. These possible complications include:

Common

- Discomfort
- Bruising

Rare

- Infection at site of blood draw

One risk of participating in this study is that confidential information about participants may be accidentailly disclosed.

STUDY PROCEDURES

RECRUITMENT

INTRODUCING THE PROJECT

The introduction process is designed as a brief encounter with potential participants to provide them with a general understanding of the study and to determine their level of interest in preparation for the eligibility screening process.

The INTERRUPT study is double blinded, randomized, placebo-controlled clinical trial. People who are using the ENG implant can enroll in the study in which they will be randomized to either receive either 1) 15mg UPA for 7 days or 2) 15mg placebo for the same duration.

The following key points should be included in the introduction:

- This is a research study to evaluate the effectiveness of UPA in reducing the number of bleeding or spotting days or ceasing bleeding with the ENG implant.
- Emphasize that the INTERRUPT study is a voluntary study.
- Inform them that their participation in the study will involve taking one pill per day for 7 days, a daily text message for 30 days to capture information about their bleeding pattern, 4 weekly follow-up surveys, one in-person visit, and 5 blood draws and 4 additional in-person visits for those participating in the progesterone subset.
- Study activities last for 30 days.
- Answer any questions that they might have.

If they are interested in the study, offer them the opportunity to be screened for eligibility. The screening process can be completed over the phone or in person during a clinic visit.

SCREENING

Screening for eligibility requires the completion of the screener form in RedCap.

SCREENER FORM

1. Read the screener consent script as written.
2. Ask if you can go over some questions to see if they are eligible.
3. If they decline, note the reason why they are not interested in screening.
4. If they are interested in screening, read every question as written and enter their answers directly into RedCap while talking with the patient.
5. If they are not eligible, research staff will inform them that they are not eligible, thank them for their time, mark the reason for ineligibility on the screener form, and retain the screening ID in RedCap records.
    a. It is our policy to not share ineligibility reasons with subjects. If asked, research staff should respond, "In order to keep study protocols confidential, we are unable to tell you the exact reason why you did not qualify for the study. Thank you for your time."
6. If they are eligible, explain the 5 main elements of the study:
    a. Enrollment: Enrollment will be a 45 minute – 1 hour appointment, which includes gathering contact information, completing a baseline survey, distribution of medication, and if participating in the progesterone subset, a blood draw.
    b. Bleeding Diaries: The bleeding diary is a daily text message survey that participants will complete for 30 days. Participants will be sent a daily text message with 2 questions about their bleeding patterns. During the first week, the text messages will include a question about medication compliance. Participants will need to respond daily to the text message. Responding to the text message will take no longer than 1-2 minutes.
    c. Follow-Up Surveys: Participants will complete 4 5-minute follow-up surveys every week. The follow-up surveys will be completed over the phone, with the exception of participants in the progesterone subset who will do so at each in-person study visit.
    d. Venipuncture Study Visits: Participants in the progesterone subset will have 4 in-person study visits after the enrollment visit. Each in-person study visit includes a follow-up survey and blood draw and will last approximately 15-20 minutes.
    e. Gift Cards:
        - Standard Subset:
            - $50 at completion of enrollment visit
            - $50 at completion of week 2 follow-up survey
            - $50 at completion of week 4 follow-up and exit surveys
        - Progesterone Subset:
            - $75 at completion of enrollment visit and successful blood draw
            - $25 at completion of week 1 follow-up survey and successful blood draw
            - $75 at completion of week 2 follow-up survey and successful blood draw
            - $25 at completion of week 3 follow-up survey and successful blood draw

    - $75 at completion of week 4 follow-up and exit surveys and successful blood draw

7. Ask if they would like to enroll in the INTERRUPT study. If yes, schedule their enrollment visit.

SCHEDULING ENROLLMENT APPOINTMENT

All participants will meet with the study coordinate to enroll in the study. Participants in the progesterone subset will also meet with the MA to give a blood sample.

- Try to schedule the enrollment appointment as soon as possible since the eligibility criteria for bothersome bleeding has a small window (*i.e.*, 24 days). If they are unable to enroll within a week, schedule the enrollment appointment and tell them that you will call the day before the appointment to re-screen them for eligibility.
- The enrollment process will take 45 minutes to 1 hour: 45 minutes for the study coordinator visit and 15 minutes for the blood draw.
- Schedule the enrollment visit in Office Tracker in the "DCR Studies" column.
- Send the participant a confirmation email that includes the date and time of their enrollment appointment, directions to the DCR, and a copy of the informed consent document.
- Call the day before the enrollment appointment to confirm.

ENROLLMENT

We will enroll 104 participants overall, 52 participants receiving UPA and 52 receiving placebo. Of these 104 participants, 40 will participate in the progesterone subset, 20 from each intervention group. Participation in this portion of the study will be voluntary and offered to all subjects until maximum enrollment for each group is met.

INCLUSION & EXCLUSION CRITERIA

Inclusion Criteria

- People age 18-45
- Implant placed >90 days and <3 years prior to enrollment
- Greater than 1 bleeding/spotting episode in a 24-day time period
- Willing to be abstinent or use condoms during the study period
- Willing to complete 30-day bleeding diary (via text)
- Ability to send/receive SMS text message
- Willing to be randomized to placebo or ulipristal acetate

Exclusion Criteria

- Non-English speaking
- Implant placed <90 days or >3 years prior to enrollment
- Contraindication to ulipristal acetate
- Inability or unwillingness to comply with medication protocol
- Inability or unwillingness to comply with bleeding diary
- Current breastfeeding

ENROLLMENT PACKET

The following materials are included in the INTERRUPT study packet:

- An orange 9x12 envelope
- 2 informed consent documents
- Prescription order form
- Bleeding diary answer key
- Tax office form
- Gift cards
- Serum Progesterone Standard Clinical Chemistry Form (if participating in the progesterone subset)

Study packets are stored in the top left drawer of the study coordinator's desk.

BASELINE ENROLLMENT

The enrollment process includes multiple activities from obtaining consent to providing the participant with a gift card for their time. This section will describe the process in detail and the associated forms that are completed during the enrollment appointment. The enrollment process for the INTERRUPT study must be done in-person.

Order of Enrollment Activities

1. Obtain Informed Consent
2. Complete & Fax Prescription Order Form
3. Collect Contact Information
4. Conduct Baseline Survey
5. Verify Text Messaging Service with Participant's Phone
6. Complete Post-Randomization Form
    a. Schedule First Phone Follow-Up Survey and/or Clinic Appointment
7. Blood draw from participants in progesterone subset
8. Distribute Medication
9. Complete Tax Office Form & Distribute Gift Cards
10. Wrap-Up

Informed Consent Process

The informed consent process is the most important step of the enrollment process. The informed consent provides the participant with written information regarding (1) study procedures and (2) responsibilities, costs, risks, benefits, and confidentiality related to participating in the study.

The participant provides their signature on the informed consent document, which has been approved by the Human Research Protection Office. This signature indicates they are fully aware of their rights and privileges as a study participant. The informed consent document must be completed in its entirety in order for the participant to move through the remaining steps of the enrollment process. The informed consent document can be read to the participant in its entirety or summarized using key points from each section. You will ask the participant if they would like it read to them in its entirety or summarized.

Steps to Take When Obtaining Informed Consent

- Give them a copy of the informed consent document to review
- Provide a brief explanation of the informed consent
- Explain that you will leave the room to give them 10 minutes (or more should they request it) to read the form before you return and go over the document together
- Once back in the room, offer to read the informed consent document verbatim or summarize the main points

- All study participants need to record their initials for two different statements
    - On page 2, those participating in the progesterone subset will initial, “Yes” in order to have their blood drawn. Participants in the standard subset will initial, “No.”
    - On page 7, all participants will initial “Yes” or “No” based on their preference for being contacted by email.
- When finished, the study coordinator must sign and date both the participant’s copy and their own copy
- The participant signs and dates the consent form
- Give the participant the informed consent form signed only by the coordinator
- The completed consent form with the participant’s signature goes in the enrollment packet

Prescription Order Form

The prescription order form will need to be faxed to the IDS pharmacy in order for the participant to be randomized to receive either UPA or placebo.

- Complete the prescription order form with the participant’s full name, date of birth, and known allergies
- Add the subject ID, which will be written with three digits (*e.g.*, 001)
- Write the correct date
- Fax the prescription order form, along with the signature page of the informed consent document, to the pharmacy
- Put the original prescription order form and the fax confirmation sheet in the study packet.

Contact Information Form

Contact information is obtained at the time of the enrollment for follow-up purposes. We obtain contact information of the participant and one close friend or relative, who will act as an alternate contact if we are unable to get in touch with the participant.

- Enter the information directly into RedCap

Baseline Questionnaire

The study coordinator administers the baseline questionnaire to every participant during the enrollment visit. They will ask the participant to respond to the baseline survey questions based on their experiences to date with their current implant. Below is the process to complete the baseline questionnaire:

- Complete the baseline survey in RedCap
- Open participant’s research file
- Click the “Date” button

- Administer the survey
- At the end of the survey, select "Complete" from the dropdown menu, click "Save", and tell the participant that they will receive a text message shortly

Verification of Text Message Service

Once the baseline questionnaire is completed, the participant will be automatically sent a text message from the text messaging service (Twilio) to verify that they able to receive the daily bleeding diaries. If they respond to the text message, a check mark will automatically appear next to the link for the "Text Verification" form in RedCap.

Post Randomization Form

While the participant is completing the text message verification, complete the form through the gift card information. Once the participant has completed the text message verification:

- Complete the tax office form (on paper)
- Schedule the participant's first follow-up, either in person or over the phone
    - Schedule the first follow-up within 7 days of their baseline enrollment visit
    - For in-person follow-up visits:
        - Schedule a 15-minute appointment under the "DCR Studies" column in Office Tracker
- Explain the bleeding diaries
    - Review bleeding questions the participant will receive by text message
    - Review the process to submit responses to the daily text message

(Blood Draw for Participants in the Progesterone Subset)

We must have a successful blood draw at baseline. If unable to get a blood draw at baseline push enrollment back by one week.

- Escort the participant to the blood draw room.
- Label one Tiger top serum gel tube with "INTERRUPT" and the participant's study ID #
- Let the MA know the participant is ready for their blood draw.
- Ideally, fill ¾ full. Invert tube gently 5 times.
- Complete the Serum Progesterone Standard Clinical Chemistry Form and place in a specimen bag along with the vial
- Take the sample to Core Lab within 2 hours of the draw time
- If you are unable to do so, the sample must be processed in the lab
    - Place the blood tubes in the test tube holder in the lab
    - Allow blood to clot 30 minutes in an upright position at room temperature.
    - Process the Tiger top serum gel tube per the instructions in "Specimen Processing"

Distribution of Medication

Give the participant their 7-day supply of pills and have them take the first dose in the consultation room. Instruct the participation that they will continue to take 1 pill per day for the following 6 days.

Gift Cards

The participant is offered $50.00 (standard subset)/$75 (Progesterone subset) in Target gift cards for their time and effort at the end of the enrollment visit. Prior to giving the participant their gift cards, complete the Tax Office form with the following information:

- Write “Enrollment” in the box above the place for the participant’s name
- Participant’s name
- Date gift cards were given
- Participant’s social security number (SSN)
    - The study coordinator must ask the participant if they would like to provide their SSN, however, providing it is voluntary for the participant.
    - If the participant provides their SSN, write it on the form. If they do not, write “Declined” where the SSN would have been written.
- Write each gift card’s number and access code on the top right corner of the form

Wrap-Up

- Remind the participant of the date of their first follow-up and that they will receive their first text message the next morning at 10:00am.
- Thank the participant for participating in the study
- Put completed study packet in the study coordinator’s desk

FOLLOW-UP AND RETENTION

FOLLOW-UP PHONE SURVEYS – STANDARD SUBSET

Follow-up surveys occur at scheduled times during the 30-day study period for each participant. When participants enroll, we will collect contact information which includes the participant's cell phone number, home address, email address, and the phone number of one alternative contact. Participants are contacted by their preferred contact method. If, after 2 attempted calls, the participant cannot be reached or does not call back, email contact is attempted. If the participant has still not responded, their alternate contact provided at enrollment will be called.

Administer Follow-Up Survey

Before beginning the follow-up survey, have the participant confirm their date of birth, verify their mailing address, and tell them the following:

- Everything will remain confidential;
- Participating in the study is voluntary, so if there is a question they do not feel comfortable answering, let the study coordinator know and they can move on; and
- If at any point they have any questions or need something repeated, to please let the study coordinator know.

The study coordinator will ask the participant to respond to the questions based on their experiences over the last week (*i.e.*, since their enrollment appointment or last follow-up survey). Below is the process to complete the weekly follow-up survey:

- Complete the follow-up survey in RedCap
- Open participant's research file
- On the "Participant Information" form:
    - Confirm participant's date of birth and mailing address; make changes as needed
    - Write the date and result of the contact (*e.g.*, completed week 1 follow-up, left message on unidentified voicemail)
- Open the form for the appropriate follow-up survey (*e.g.*, "Follow-Up Survey Week 1")
    - Click the "Date" button
    - Administer the survey
    - At the end of the survey, select "Complete" from the dropdown menu, click "Save"

Schedule Next Follow-Up Survey

- Schedule their next follow-up survey within 7 days
- During the enrollment visit and at the end of each follow-up survey, the participant will schedule a date and time at which they would like to be called for the next survey. The study coordinator will send the participant a confirmation email with the date and time agreed upon.

If the participant's schedule allows, schedule their Week 4 follow-up survey on the day or of within a day or two after their last bleeding diary so that they can complete their last follow-up survey and exit survey at the same time. If their schedule does not allow, schedule a separate date and time to complete their exit survey over the phone.

Gift Cards

The participant is offered a $50 in gift cards after the completion of their Week 2 and Week 4 follow-up & exit surveys. Prior to giving the participant their gift cards, complete the Tax Office form with the following information:

- Write for which week the gift cards were given (*e.g.*, "Week 2") in the box above the place for the participant's name
- Participant's name
- Date gift cards were given
- Participant's social security number (SSN)
    - The study coordinator must ask the participant if they would like to provide their SSN, however, providing it is voluntary for the participant.
    - If the participant provides their SSN, write it on the form. If they do not, write "Declined" where the SSN would have been written.
- Write each gift card's number and access code on the top right corner of the form

FOLLOW-UP CLINIC VISITS – PROGESTERONE SUBSET

Participants will undergo weekly venipuncture for a total of five blood draws over the 30 days of the study; one at the baseline visit and then weekly for four weeks. *Please Note: A participant can remain in study if there is a failed blood draw at a follow-up visit or a participant missed a weekly blood draw.* Complete the following tasks at the weekly follow-up visit:

Determine the order of activities of the follow-up visit.

- Check on MA's availability when the participant arrives for her appointment
- If MA is not busy, begin the appointment with the blood draw and then follow-up with bleeding diary review and follow-up survey
- If MA is busy, begin the appointment with the bleeding diary review and follow-up survey and then the blood draw

Bleeding Diary Review

- Review responses to the daily text messages in RedCap.
- If any responses are missing, ask the participant to verbally recall her bleeding patterns on the missed days.
- Enter her responses directly into RedCap

Administer Follow-Up Survey

The study coordinator will ask the participant to respond to the questions based on their experiences since their last appointment. Below is the process to complete the weekly follow-up survey:

- Complete the follow-up survey in RedCap
- Open participant's research file
- Open the form for the appropriate follow-up survey (*e.g.*, Follow-Up Survey Week 1)
    - Click the "Date" button
    - Administer the survey
    - At the end of the survey, select "Complete" from the dropdown menu, click "Save".

Schedule Next Follow-Up Visit

- Schedule their next follow-up appointment within 7 days of their previous follow-up appointment
- Schedule a 15-minute appointment under the "DCR Studies" column in Office Tracker
- Send the participant a confirmation email with the date and time of their next follow-up visit.

If the participant's schedule allows, schedule their Week 4 follow-up appointment on the day or of within a day or two after their last bleeding diary so that they can complete their last follow-up survey

and exit survey at this visit. If their schedule does not allow, schedule a date and time to complete their exit survey over the phone.

Blood Draw

- Escort the participant to the blood draw room.
- Label one Tiger top serum gel tube with "INTERRUPT" and the participant's study ID #
- Let the MA know the participant is ready for their blood draw.
- Ideally, fill ¾ full. Invert tube gently 5 times.
- Complete the Serum Progesterone Standard Clinical Chemistry Form and place in a specimen bag along with the vial
- Take the sample to Core Lab within 2 hours of the draw time
- If you are unable to do so, the sample must be processed in the lab
    - Place the blood tubes in the test tube holder in the lab
    - Allow blood to clot 30 minutes in an upright position at room temperature.
    - Process the Tiger top serum gel tube per the instructions in "Specimen Processing"

Gift Cards

Participants are offered a $25 gift card after the 1st and 3rd follow-up clinic visits and $75 in gift cards after the 2nd and 4th follow-up clinic visit for their time and effort at the end of each follow-up visit. Prior to giving the participant their gift cards, complete the Tax Office form with the following information:

- Write for which week the gift cards were given (*e.g.*, "Week 1") in the box above the place for the participant's name
- Participant's name
- Date gift cards were given
- Participant's social security number (SSN)
    - The coordinator must ask if the participant if they would like to provide their SSN, but providing it is voluntary for the participant.
    - If the participant provides their SSN, write it on the form. If they do not, write "Declined" in the same place.
- Write each gift card's number and access code on the top right corner

SPECIMEN PROCESSING

For participants in the Progesterone subset, there is one sample that will need to be processed: progesterone serum. The blood sample can be processed by the Core Lab or at the DCR lab. Record specimen information and test results on the "Specimen Tracking" form in the RedCap database.

CORE LAB PROCESSES BLOOD SAMPLES

- Store the blood collection tube at room temperature prior to drop off at the Core Lab
- Drop off labeled tiger top test tube along with the requisition form within two hours of the blood draw at the Core Lab.
    - Samples can be dropped off between 8:00am and 4:30pm.
- If your schedule does not allow you to drop off samples within two hours of the blood draw or if the lab will be closed, you must process the blood at the DCR lab.

PROCESS BLOOD SAMPLES AT THE DCR

The blood collection tube must be stored at room temperature at least 30 minutes but no longer than two hours after the blood draw.

- Process blood in the DCR Lab within two hours of collection
- Place the tiger top tube in the centrifuge; make sure the centrifuge is balanced
    - Centrifuge Settings:
        - **Time: 10 minutes, Temperature: 25C, Speed: 1300 RCF**
- Store the processed sample in the tiger top test tube in the DCR refrigerator (if storing overnight) or the subzero freezer (if storing over the weekend)
    - Drop off sample with requisition form at the Core lab, 6th floor, Wohl Building

TEXTING PROTOCOL

RedCap has the capability to send SMS text messages to survey respondents buy using a third party web service name Twilio (www.twilio.com). To use this feature, you must have a Twilio.com user account that is funded with some money (since there is a cost for each phone call made and for each SMS message sent). Once your REDCap project is connected to your Twilio account by entering your Twilio account credentials on your REDCap project's Project Setup page, you can then configure how you want to use Twilio in your project.

IMPLEMENT BLEEDING DIARY

RedCap will only send SMS messages to participant if the following information has been entered in their RedCap research file:

- Participant's cell phone number on the "Participant Information" form
- Interview date on the "Baseline Survey" form
- "Yes" is selected for the question "Is the participant ready to receive their daily text message?" and "Complete" is selected on the "Post Randomization" form

Participants will be sent text messages to complete the daily bleeding diary each day at 10:00am. If a participant does not complete the diary within 6 hours, a reminder text message will be sent. The bleeding diary can only be completed via SMS message the same day an invitation is sent. Once outside this window, bleeding diaries must be completed with the study coordinator over the phone.

MONITOR BLEEDING DIARIES

It is very important to collect bleeding information on a weekly basis. Study staff will monitor bleeding diaries of research participants for completeness. Bleeding diaries need to be completed within 72 hours.

The study coordinator will monitor compliance with bleeding diaries daily. If participant missed any days between enrollment or follow-ups, the study coordinator will follow-up with the participant and complete the missing days.

For participants in the progesterone subset, the study coordinator will monitor show rates for weekly follow-up visits. If a participant missed their follow-up visit, call them at the end of the week to complete missing bleeding diaries by phone.

STATISTICAL CONSIDERATIONS

SAMPLE SIZE

Fifty-two participants will be enrolled per arm, for a total of 104 patients. Previous studies evaluating interventions for implant bleeding have defined a clinically significant difference as a decrease in bleeding/spotting days by20-40%.[22,23] Therefore, our effect size will be a 30% decrease in the amount of bleeding/spotting days. The sample size calculation used for this study assumes a standard deviation of 10, an alpha of 0.05, power of 80%, and accounting for 15% drop-out. This standard deviation is based on a previous study that found the standard deviation for the mean number of bleeding/spotting days to be approximately +/-10 days.[22]

STATISTICAL METHODS

Demographics will be presented with descriptive statistics stratified by randomization group. Student t tests, chi-square, and Fisher Exact tests will be used, where appropriate, to compare characteristics of participants receiving ulipristal acetate to those receiving placebo. For the primary outcome, mean number of bleeding days in the 30 days following intervention, if normally distributed, we will use a t-test. If not normally distributed, the Mann-Whitney U test will be employed. These tests will also be employed for our secondary outcomes of bleeding pattern satisfaction, medication side-effect satisfaction, and contraceptive efficacy. For the secondary outcome regarding cessation of bleeding by day 10, as this outcome is dichotomous, we will use a Chi-square test (or Fisher Exact test, if appropriate).

MISSING DATA

Missing data rates and patterns will be assessed twice weekly by the data manager and remedial measures, including re-abstraction of data and retraining of staff, will be used as needed to minimize missing data.

ETHICAL CONSIDERATIONS

INSTITUTIONAL REVIEW BOARD

Washington University School of Medicine in St. Louis, MO, has applied for and been approved through the Washington University School of Medicine's Institutional Review Board (IRB) office (protocol number #201612002).

INFORMED CONSENT

All participants will be introduced to the study and will be screened for eligibility based on the previously listed inclusion and exclusion criteria. If interested and eligible, potential participants will be given an informed consent form to read and review. Research personnel will then explain the study to the potential participant, outline key risks, benefits, and alternatives (including not participating), and then have participants sign the informed consent form. A copy will be given to the participant and a copy will be kept in the participant's research file.

PARTICIPANT CONFIDENTIALITY

After the informed consent has been signed, each subject will be entered into the enrollment database and be assigned a unique subject identification number. No two subjects will have the same subject identification number. This subject identification number will identify the subject throughout the study and will be used for all source documents, data collection forms, and bleeding diaries. The subject identification number will be held confidential so far as permitted by law. Investigative site staff and, under certain circumstances, the FDA and IRB, will be able to inspect and have access to the subject identification number and the confidential data to which it is linked. Any publication or presentation of data will not contain any identifiable subject information.

SAFETY REPORTS

ADVERSE EVENTS

There are few side effects of UPA and LNG-IUS. These are listed in the protocol and informed consent form. Most side effects resolve spontaneously. Anticipated events means reactions to treatment previously observed that may require medical intervention but are not serious in nature. All adverse events that occur will be recorded in the Source Documents. Adverse Events occurring will be captured and followed until the condition resolves, stabilizes, or is otherwise explained, or the subject is lost to follow-up. Subjects will be instructed that they may contact the PI or study coordinator at any time throughout the course of the study. The Investigator will review each event and assess its relationship to UPA (not related, unlikely, possible, probable, and highly probable). The following definitions will be used for rating relationship to the investigational device:

1. Not related – The event is clearly related to other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject.
2. Unlikely – The event was most likely produced by other factors such as the subject's clinical state, therapeutic interventions, or a concomitant medication administered to the subject; and does not follow a known response pattern to the investigational device.
3. Possible – The event follows a reasonable temporal sequence from the time of investigational device administration; and/or follows a known response pattern to the study treatments, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject.
4. Probable – The event follows a reasonable temporal sequence from the time of investigational device administration, follows a known response pattern to the investigational device, and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject.
5. Highly Probable – The event follows a reasonable temporal sequence from the time of investigational device administration, follows a known response pattern to the investigational device, and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject. The event occurs immediately following investigational device administration, improves on stopping the

investigational device, or reappears on repeat exposure. Each adverse event reported will be graded on a 3-point severity scale. The following definitions for rating severity will be used:

6. Mild – easily tolerated, causing minimal discomfort, and not interfering with normal everyday activities.
7. Moderate – sufficiently discomforting to interfere with everyday activities.
8. Severe – incapacitating and/or preventing normal everyday activities.

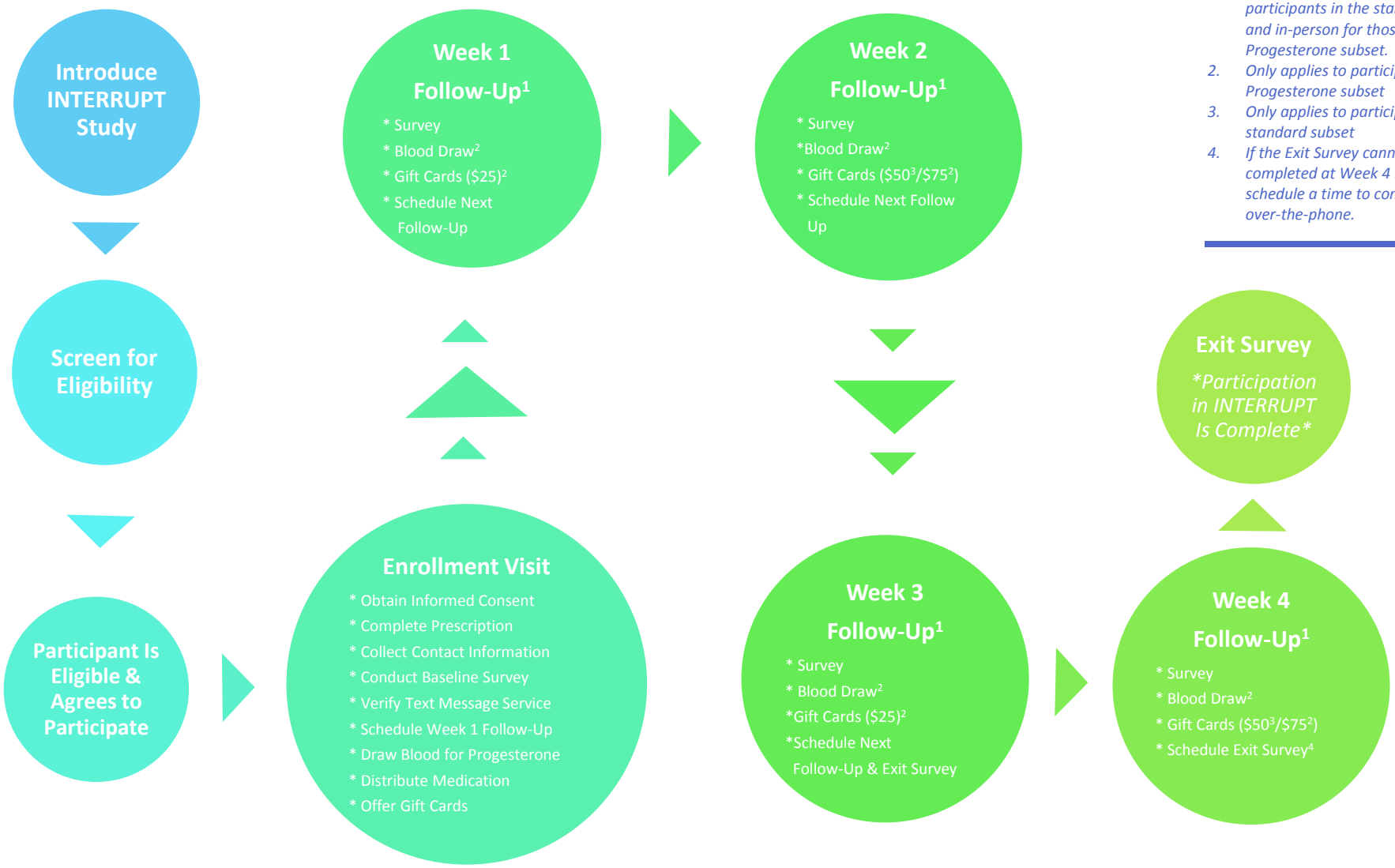
SERIOUS ADVERSE EVENTS

A serious adverse event is any adverse device experience that results in any of the following outcomes: death, life-threatening adverse device experience, in-patient hospitalization or prolongation of hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may or may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse device experience when, based upon appropriate medical judgment, they may jeopardize the subject or subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition. If any of the above adverse events are serious as defined by the FDA Code of Federal Regulations (CFR), Title 21, special procedures will be followed. All serious adverse events will be reported within 24 hours of acknowledgment to the Washington University in St. Louis coordinating center, whether or not the serious events are deemed treatment-related. All serious event reporting will adhere to 21 CFR part 812 and the IRB will be notified accordingly. Adverse events, whether serious or non-serious, will be followed until the condition is resolved, stabilized, or otherwise explained, or the subject is lost to follow-up. Adverse events will be captured up to one week after a subject completes the study and where appropriate, medical tests and examinations will be performed to document the resolution of event(s). Outcomes may be classified as resolved, improved, unchanged, worse, fatal, or unknown (lost to follow-up). Following the resolution of any study-associated adverse events there will be no further reports for that subject.

INVESTIGATOR MONITORING

Data will be collected at weekly follow-up appointments and phone follow-up surveys with regards to any side effects experienced during the study medication period. Serum levels of progesterone will also be monitored to assess contraceptive efficacy in a subset of patients. All of this data will be reviewed weekly.

STUDY FLOWCHART



1. *Visit will be over-the-phone for participants in the standard subset and in-person for those in the Progesterone subset.*
2. *Only applies to participants in the Progesterone subset*
3. *Only applies to participants in the standard subset*
4. *If the Exit Survey cannot be completed at Week 4 Follow-Up, schedule a time to complete it over-the-phone.*

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