

Standard Operating Procedure - Intrafetal digoxin as an adjuvant for dilation and evacuation at 20 to 24 weeks' gestation: a placebo-controlled, double-blinded randomized controlled trial.

**INTRAFETAL DIGOXIN AS AN ADJUVANT FOR DILATION AND EVACUATION
AT 20 TO 24 WEEKS' GESTATION: A PLACEBO-CONTROLLED, DOUBLE-
BLINDED RANDOMIZED CONTROLLED TRIAL**

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Standard Operating Procedures (SOPs)

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I. INTRODUCTION

These Standard Operating Procedures (SOPs) provide instruction for study staff conducting the research study “Intrafetal digoxin as an adjuvant for dilation and evacuation at 20 to 24 weeks' gestation: a placebo-controlled, double-blinded randomized controlled trial.” This study will investigate if the intrafetal injection of 1mg of Digoxin 16-24 hrs preoperatively decreases operative time for women undergoing dilation and evacuation (D&E) at 20-4 0/7 wks gestation compared to women who receiving a placebo injection. This study will take place at 4 sites. The sites and their Site Codes are listed below:

Site Code	Site
SF	Women's Options Center, San Francisco General Hospital, San Francisco, CA
LJ	Lovejoy Surgicenter, Portland, OR
LA	Family Planning Associates Women's Health, Los Angeles, CA
LB	Family Planning Associates Women's Health, Long Beach, CA

These SOPs contain detailed instructions for implementing the study protocol for each study participant, including instruction for each item on the study data collection forms and logs. This research study must be carried out exactly as described in the protocol and all study staff must follow the same procedures for data collection and completion of forms and logs. Study staff must read and understand the research protocol, study forms, and these SOPs before study enrollment begins.

These SOPs should be used as a reference over the course of this study to ensure that all study procedures are being conducted correctly. Questions about study conduct that are not answered in these SOPs should be directed to the site's Principal Investigator or to the site manager at the coordinating center

Project and site manager:

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The procedures set out in the study protocol are designed to ensure that study staff abide by good clinical practice (GCP) guidelines. GCP is an international quality standard defined by the International Conference on Harmonisation (ICH), which defines standards for clinical trials involving human subjects. At a minimum, each study staff member must have completed a human subjects protection course that has been approved by the study coordinating center.

Standard Operating Procedure - Intrafetal digoxin as an adjuvant for dilation and evacuation at 20 to 24 weeks' gestation: a placebo-controlled, double-blinded randomized controlled trial.

Study staff must also have attended a study training conducted by the coordinating center or received individual training in study procedures from an approved study staff member qualified to do so. Names of additions to study staff must be submitted to the coordinating center and approved by the overall Principal Investigator and applicable IRB before the new study staff may perform study procedures.

II. STUDY MATERIALS

The coordinating center will provide each site with the study materials listed below. If any supplies are beginning to run low, site staff are responsible for contacting the site manager to request replenishments. Please request replenishments with enough advance notice (about 2 weeks) so that enrollment will not be interrupted.

All study materials must be kept in a secure location accessible only to study staff. All study medications must be kept separate from the clinic's regular supply.

A. Study Binder

The Study Binder will include the following materials:

- FDA Study Protocol
- Data Collection Forms
- Standard Operating Procedures (SOPs)
- IRB-approved, stamped consent form
- HIPAA consent form
- Subject Bill of Rights
- Study staff log
- Protocol deviations log
- Payment log
- Adverse events log
- Protocol Updates
- Monitoring log
- IRB materials, including initial approval documentation, amendments, continuing reviews, corresponding approvals and correspondence

B. Forms:

Sites will be supplied with copies of each of the following forms:

- Form 1: Eligibility Screening and Baseline Data, Day 1
- Form 2: Dilator and Injection Data, Day 1
- Form 3: Arrival Data, Day 2
- Form 4: Intra-operative Data, Day 2
- Form 5: Post-operative Data, Day 2

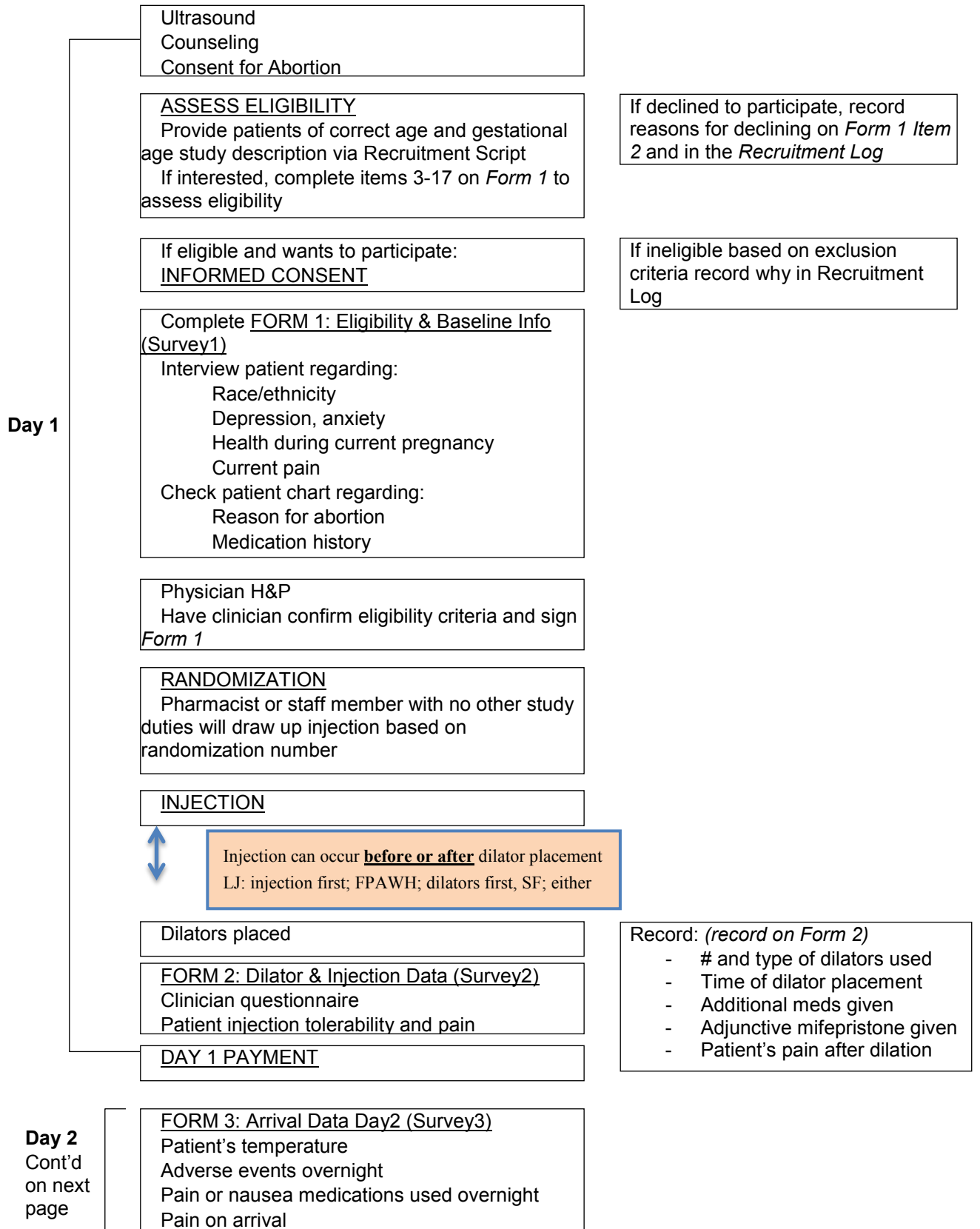
C. Study medication

D. Other site materials:

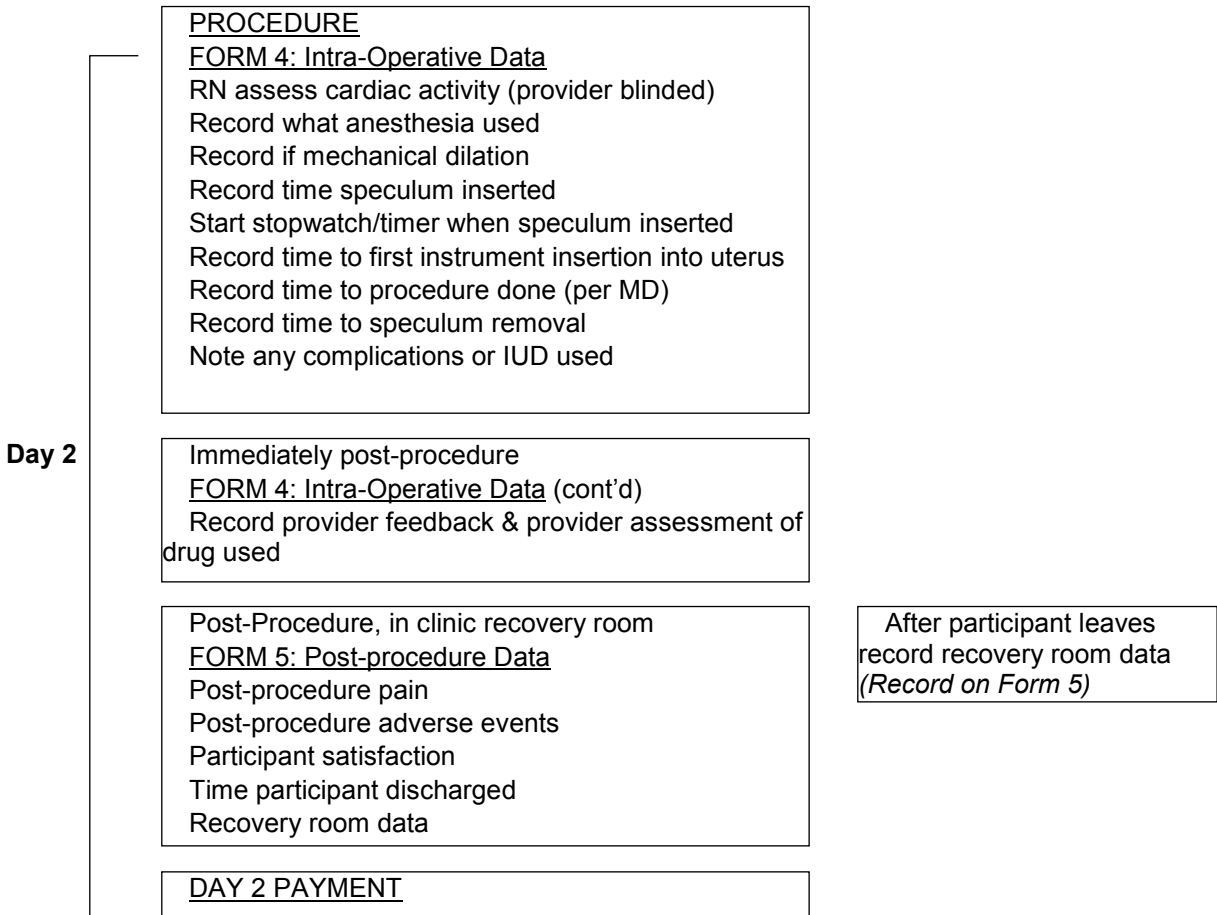
- Stopwatch
- Spinal Needles

- Cash Box
- Color Folders:
 - For sites recruiting multiple gestational age groups (SF and LJ) multi-color folders will be provided to help differentiate the colored folders:
 - RED folders: Gestational Age Group 1
 - [BPD is measuring 4.61-5.24cm check “Group 1”]
 - For participants who are in Group 1, materials should be placed in a Red folder in order to avoid confusion as to which group they are. For Lovejoy Surgicenter, randomization envelopes will also be marked with Red ink to correspond.
 - BLUE folders: Gestational Age Group 2
 - [BPD is measuring 5.25-5.88cm check “Group 2”]
 - For participants who are in Group 2, materials should be placed in a Blue folder in order to avoid confusion as to which group they are. For Lovejoy Surgicenter, randomization envelopes will also be marked with Blue ink to correspond.

• **III. FLOW DIAGRAM OF STUDY PROCEDURES**



Flow Diagram Continued



IV. ASSESSING STUDY ELIGIBILITY AND PARTICIPANT ENROLLMENT

A. Beginning the Screening Process

For the purposes of this study, a screened patient will be defined as one who was identified based on gestational age and procedure type (D&E), as being potentially eligible for the study and who was approached about study participation.

B. Assessing interest in study participation

Once staff have identified a patient who might be eligible, based on patient age, gestational age and procedure type, for study participation, study staff should approach the patient to gauge interest in participating in the study. Research staff should assess the patient's interest in study participation by describing the study using the following study description. This study description is also printed on the Recruitment Script Form. Please adapt as needed.

Digoxin RCT Recruitment Script

Digoxin RCT Recruitment Script

Hi my name is _____ and I am a researcher. I am working on a study that you are eligible for, is it okay if I tell you a little bit about it? It is totally optional, so after you hear about it, it will be up to you to decide if you're interested in being in the study.

The study is on a medication called digoxin. Digoxin is FDA approved to treat heart conditions, but it is often used before abortions to stop the fetal heart from beating. In some clinics, all women who are having an abortion after 20 weeks of gestation receive digoxin, and in some clinics they don't use this medication at all. Some doctors think that using digoxin helps to make the abortion procedure faster and easier, but we don't know this for sure. That is why we're studying digoxin; we want to know if using digoxin makes the abortion faster, easier and safer.

If you decide to be in the study it will involve some things today and some tomorrow. I will ask you some questions to make sure it's ok for you to be in the study, and then I would ask you a few questions about how you're feeling today. Today you will be having dilators placed, and if you are in the study, you will also receive an injection in your abdomen. The injection will either be digoxin, which is the medication that we're studying, or a placebo, which is salt water and doesn't do anything. The study drug will be injected into the fetus. After the injection, you would answer a few more questions. Then tomorrow we will give you a quick survey before your procedure,

collect some information during your procedure, and give you another quick survey while you're in the recovery room after your procedure. You will be paid \$100 in total over the two days as a thank you for your time.

If you choose not to participate in the study your care will not be affected in any way. You will/will not receive a digoxin injection today. (RA will tell them whether they will or will not receive digoxin depending on where they are having their abortion. SFGH: WILL NOT, FPAWH: WILL, Lovejoy: MAY OR MAY NOT depending on provider).

For patients who are interested in participating, they should proceed to eligibility screening (*Form 1*) and consenting.

For patients who were approached based on being recommended by clinic staff but declined to participate after hearing the Recruitment Script, their reason for declining should be recorded on *Form 1 (Item 2)* and logged in the Recruitment Log under the tab "Declined".

C. Assessing Inclusion Criteria

Once staff have identified a patient who might be eligible and is interested in study participation, study staff should use *Items 3-17 of Form 1* as a guide to assess inclusion and exclusion criteria.

Inclusion criteria: (*Items 3-7*)

- Female
- 18 years and older
- English-speaking
- Currently pregnant with singleton pregnancy
- Seeking pregnancy termination between 20 0/7 weeks and 24 0/7 weeks gestation
 - o Assessed via Biparietal Diameter on Day 1 between 4.61 and 5.88 mm by transabdominal ultrasound measurement.
- Medically eligible for outpatient Dilation & Evacuation procedure at clinical site
- Requiring only one day of dilators prior to D&E
- Able to give informed consent

If a patient meets all inclusion criteria on *Form 1* then study staff should proceed with assessing exclusion criteria.

D. Assessing Exclusion criteria

Following inclusion criteria assessment, patients who are still eligible should be screened for exclusion criteria. These are assessed using *Items 8-17 of Form 1*

Exclusion Criteria: *(Items 8-17 Form 1)*

- Reason for abortion is fetal demise
- Participant has contraindications to digoxin including but not limited to:
 - o Known allergy to digoxin
 - o Current cardiomyopathy or impaired systolic or diastolic function
 - o History of heart attack
 - o Current pericarditis
 - o Any cardiac rhythm abnormalities
 - o Current heart disease of any other type
 - o Current uncontrolled thyroid disease (hypothyroidism or hyperthyroidism uncontrolled by medication)
 - o Acute or chronic renal failure
 - o Autoimmune renal disease
- Participant requires more than one day of cervical preparation
- Participant diagnosed with placenta accreta, increta or percreta
- Participant diagnosed with preterm premature rupture of membranes (PPROM)
- Participant diagnosed with anhydramnios
- Participant has active bleeding or is hemodynamically unstable
- Participant has signs of chorioamnionitis or any clinical infection (fever >100.4°F)

Eligibility must be confirmed by a clinician or physician and must be documented using **Form 1: Eligibility Screening and Baseline Data, Day 1**. Detailed instructions for completing Form 1 can be found in the section V. A. of these SOPs.

Women must meet ALL eligibility (both inclusion and exclusion) criteria to be considered eligible for this study. If a woman does not meet eligibility criteria she cannot participate in this study.

If a woman does meet ALL eligibility criteria (both inclusion and exclusion) and wishes to participate in the study, she is ready to be consented. However, inform the patient that her eligibility is only confirmed when she sees the clinician, so there is the possibility of her being consented and later found ineligible for the study based on the clinician's recommendations.

E. Administering study informed consent

The study Informed Consent Form (ICF) and HIPAA Consent Form (HCF) must be completed for all study participants. These forms must be signed and dated by the participant and an IRB approved study staff before any study procedures may take place.

If a woman may be eligible for study participation and would like to participate in the study, she should be given an ICF and HCF to read and they should be explained to her. IF the woman cannot read the forms, then the forms should be read and explained to her. Study staff should ensure that the woman understands the requirements of the study protocol, the risks and benefits of the study participation, potential side effects and complications and the voluntary nature of the study participation. The woman should be given the opportunity to ask questions and to have them answered by the appropriate study staff.

If a woman agrees to participate in the study, she should sign and date the ICF and HCF. IRB-approved staff should also sign and date the ICF and HCF. Study staff should review the ICF and HCF to ensure that the patient has signed, the study staff has signed, and that both have written the correct date. If either the participant or study staff makes an error, she should cross out her mistake and clearly write the correction nearby. She should initial and date (MM/DD/YY) her correction.

The signed copies of the ICF and HCF should be kept by the study site. The patient should be offered copies of the ICF and HCF for her records. Furthermore ALL study participants should be given a copy of the Participant Bill of Rights.

Once the patient has signed the ICF and HCF, she is considered enrolled in the study. All enrolled participants should be asked to complete a records release form in the event that study staff need to request medical records from other institutions during the study period. After completion of the records release form, study staff should proceed with completing **Form 1: Eligibility and Baseline Info, Day 1**.

V. DATA COLLECTION

For this study, there are [5] data collection forms and an informed consent form. The [number] data collection forms are as follows:

- Form 1: Eligibility Screening Baseline Data, Day 1
- Form 2: Dilator and Injection Data, Day 1
- Form 3: Arrival Data, Day 2
- Form 4: Intra-operative Data, Day 2
- Form 5: Post-operative Data, Day 2

General Instructions for Data Collection Forms

1. All data collection forms should be completed thoroughly and carefully by an IRB-approved study staff using *black* ink. All five of the data collection forms should be completed for all study participants.
2. To make changes to a response on a data collection form, cross out the error using a single line, make the correction, and initial and date the change (MM/DD/YY)
3. All questions directed to patients should be read to the patient as printed on the data collection forms. Similarly, response choices for patient questions should be read as printed.
4. All questions assessing clinical information should be reviewed and confirmed by a clinician or physician.
5. All questions directed to a clinician or physician may be answered directly on the study for by the clinician/physician. Alternatively, study staff may read the question to the clinician/physician and record his or her response.
6. All forms should have the participant's enrollment ID, the date, and the signature of staff member filling out the form completed.

The first form to be completed after signing the ICF is **Form 1: Eligibility Screening and Baseline Data, Day 1**.

A. Form 1: Eligibility Screening and Baseline Data, Day 1

Form 1 Overview

Form 1 is used to document study eligibility for patients who have signed the ICF. Thus included in the form is all the exclusion criteria for the study. It also records additional baseline clinical data and asks demographic questions of the participant.

Form 1 Detailed Instructions

1. Record the date that patient is screened for eligibility in the clinic. Dates should be recorded as month/date/year (MM/DD/YYYY)
2. If the woman wants to participate in the study, check “Yes” and proceed with consenting the participant. Once she is consented, complete the rest of Form 1. If she does not want to participate, check “No” and stop all study procedures.
 - a. If she does not want to participate, ask the woman her reason(s) for not wanting to participate and document her response on the line provided and in the Recruitment Log. If she does not wish to say, document “Declined to say” in the Recruitment Log.

Items 3-17, the Eligibility Checklist, document the patient’s eligibility for study participation. Eligibility must be confirmed by a clinician or physician, typically at the time of the clinician’s history taking with the patient. Complete items 3-17 even if the patient is found to be ineligible based on her responses prior to finishing question 17.

3. Check “Yes” if the patient is Age 18 or older. Check “No” if the patient is under age 18.
4. Check “Yes” if the patient is seeking pregnancy termination and is between 20w0d and 24w0d with a Biparietal diameter (BPD) of 4.61 to 5.88cm, inclusive, as assessed by ultrasound on enrollment day. Check “No” if the patient does not fit this criteria.
 - a. Patients with cranial defects must be between 20w0d and 24w0d by best estimate of gestational age AND BPD must also be within range above. If cranial defects preclude BPD measurement, use the best composite sonographic dating criteria available to ensure the patient is between 20w0d and 24w0d.

- b. For eligibility screening, record the gestation age that the patient or clinic staff provide. Once the patient has been consented, confirm the exact gestation age via BPD with the clinician.
5. Check "Yes" if the patient can speak English. Check "No" if the patient is not able to speak English.
6. Check "Yes" if the patient is carrying a singleton pregnancy (one fetus). Check "No" if the patient is carrying a multiple gestation pregnancy
7. Check "Yes" if the patient only required one day of dilator placement (aka dilators placed on the day prior to procedure). Check "No" if patient required dilator placement for longer than one day.
8. Indicate if the patient is incarcerated by checking "Yes" or "No"
9. Indicate if the patient is having active bleeding or if she is hemodynamically unstable at the time of eligibility assessment by checking "Yes" or "No".
10. Indicate if the patient has any signs of chorioamnionitis or a clinical infection, including if they have a fever $>100.4^{\circ}\text{F}$, at the time of eligibility assessment by checking "Yes" or "No".
11. Indicate if the patient has a known allergy to digoxin by checking "Yes" or "No".
12. Indicate if the patient has any contraindications to digoxin in their medical history by checking "Yes" or "No".
 - a. Inquire specifically about: current cardiomyopathy or impaired systolic or diastolic function, history of heart attack, current pericarditis, any cardiac rhythm abnormalities, current heart disease of any other type, current uncontrolled thyroid disease (hypothyroidism or hyperthyroidism uncontrolled by medication), acute or chronic renal failure, autoimmune renal diseases.
 - b. If the patient is unsure about her medical history with regards to any of the above listed criteria, record her response and confirm her medical history with the clinician after his or her assessment of the patient.
13. Indicate if the patient is presenting for her abortion procedure due to a known fetal demise (IUFD) by checking "Yes" or "No".

14. Indicate if the patient has previously participated in this study by checking "Yes" or "No".

15. Indicate if the patient has known preterm premature rupture of membranes (PPROM), defined as a rupture in the amniotic sac prior to labor at <37 wks gestation, by checking "Yes" or "No".

16. Indicate if the patient has been diagnosed with anhydramnios during this pregnancy by checking "Yes" or "No".

17. Indicate if the patient has been diagnosed with placenta accreta (including increta and percreta) during this pregnancy by checking "Yes" or "No".

18. Based on the answers to questions 3-17, ensure that the woman is eligible for the study. All checkmarks must be in the UNSHADED boxes for the patient to be considered eligible for study participation. If any checkmarks fall in the shaded area, then the patient is **not** eligible for study participation. If she is eligible for study participation, check "Yes" and proceed with consenting the patient. If she is not eligible for study participation, check "No" and stop all study procedures.
 - a. If the participant is not eligible, inform them of their ineligibility and reiterate that their planned abortion procedure will continue without study participation.

 - b. Document in the Screening Log the reason(s) for the participant's ineligibility.

 - c. If the participant is found eligible, remind the patient that her eligibility must be confirmed by the clinician for her to receive the injection. However, if she were to be found ineligible by the clinician she would still be compensated for her time.

19. If the study ICF and HCF have been signed by both the woman and an IRB-approved study staff member who was responsible for conducting the study consent process, check "Yes" and proceed with Form 1. If not, check "No", and stop all study procedures until the ICF and HCF are signed. A patient may only participate in the study if she has signed the ICF and HCF.

20. All study participants should be offered a copy of the ICF and HCF for their records. They should also receive a copy of the Participant Bill of

Rights. Note whether copies were offered to the patient by checking "Yes" or "No".

As noted above, a clinician or physician must assess and confirm study eligibility. The clinician or physician who was responsible for assessing study eligibility must print and sign his/her name on the designated lines below Question 20. This may be completed after the rest of Form 1 is completed as the clinician may not be able to assess the patient until immediately before the dilator placement. However, Form 1 should be completed and signed prior to any dilator placement or study medication injection begins.

If the answers to Q18-20 are all "Yes" then the participant should be given a study Enrollment ID. This Enrollment ID should be recorded in the header of all study forms. This Enrollment ID should also be recorded when completing the patient's entry in the electronic Enrollment Log. Detailed instructions for completion of the Enrollment Log can be found in Section VI. A.

Study Enrollment ID assignment

The Enrollment ID of each participant includes both the standard code for her study site and an individual numerical code specific to each participant. Once a participant is randomized to either the digoxin or placebo group she will also have a separate Randomization ID, discussed further in Section V.B. Site ID's are fixed per site as follows:

- Women's Options Center: SF
- Lovejoy Surgicenter: LJ
- FPAWH Los Angeles: LA
- FPAWH Long Beach: LB

Thus the first participant at Women's Options Center would have the Enrollment ID SF001 and each subsequent participant would have the next Enrollment ID in numerical order.

Women's Options Center, San Francisco CA	Lovejoy Surgicenter, Portland OR	FPAWH, Los Angeles CA	FPAWH, Long Beach CA
SF001	LJ001	LA001	LB001
SF002	LJ002	LA002	LB002
SF003	LJ003	LA003	LB003
SF004	LJ004	LA004	LB004

Once the patient has been assessed for eligibility, consented and assigned an enrollment number, complete Form 1 by asking the patient items 21-27.

21. Ask the patient how she would describe her race or ethnicity. Record her response by ticking the appropriate box. If the patient reports a race or ethnicity that is not on this list of response choices, tick the box for "Other" and write in her reported race/ethnicity on the line. If the patient declines to answer the question, tick "Decline to answer".
22. Read the prompt prior to asking the questions under item 22. For each question under item 22, read the question as:
 - a. Question a: "Over the last 2 weeks how often have you had little interest or pleasure in doing things" and read the 4 choices to the patient " Not at all," "Several days," "More than half the days," and "Nearly everyday". Tick the appropriate response.

- b. Question b: "Over the last 2 weeks how often have you been feeling down, depressed or hopeless" and read the 4 choices to the patient " Not at all," "Several days," "More than half the days," and "Nearly everyday". Tick the appropriate response.
- c. Question c: "Over the last 2 weeks how often have you had trouble falling or stay asleep, or sleeping too much" and read the 4 choices to the patient " Not at all," "Several days," "More than half the days," and "Nearly everyday". Tick the appropriate response.
- d. Question d: "Over the last 2 weeks how often have you been felt tired or had little energy" and read the 4 choices to the patient " Not at all," "Several days," "More than half the days," and "Nearly everyday". Tick the appropriate response.
- e. Question e: "Over the last 2 weeks how often have you had a pore appetite or been overeating" and read the 4 choices to the patient " Not at all," "Several days," "More than half the days," and "Nearly everyday". Tick the appropriate response.
- f. Question f: "Over the last 2 weeks how often have you been feeling bad about yourself, or that you are a failure or hae let yourself or your family down" and read the 4 choices to the patient " Not at all," "Several days," "More than half the days," and "Nearly everyday". Tick the appropriate response.
- g. Question g: "Over the last 2 weeks how often have you had trouble concentrating on things, such as reading the newspaper or watching tv" and read the 4 choices to the patient " Not at all," "Several days," "More than half the days," and "Nearly everyday". Tick the appropriate response.
- h. Question h: "Over the last 2 weeks how often have you been moving or speaking so slowly that other people have noticed, or had the opposite where you were so fidgety or restless that you have been moving around a lot more than usual" and read the 4 choices to the patient " Not at all," "Several days," "More than half the days," and "Nearly everyday". Tick the appropriate response.
- i. Question i: "Over the last 2 weeks how often have you had thoughts that you would be better off dead or of hurting yourself" and read the 4 choices to the patient " Not at all," "Several days,"

“More than half the days,” and “Nearly everyday”. Tick the appropriate response.

- i. NOTE: if the patient expresses suicidality and/or scores very highly on the PHQ9, please ensure that she has talked to another clinic staff member (counselor, RN, NP, MD) about this so that she can be referred to adequate resources.

23. Ask the patient to assess her pain currently on a scale of 0-10. Show her the 0-10 scale on Form 1 and read the question as printed on the Form. Ask her to select the appropriate box on the scale. Mark an “X” in the appropriate box, based on her response.
24. Ask the patient how acceptable this amount of pain was to her. Read the 5 response choices to the patient: “Very acceptable”, “Somewhat Acceptable”, “Somewhat Unacceptable”, or “Very Unacceptable”. Tick the appropriate response. If the patient is unable to answer the question, tick “Don’t know”.
25. Ask the patient if she is experiencing any nausea right now. If she is not experiencing nausea currently, circle “None” on the corresponding line. If she is experiencing nausea, ask her if it was mild, moderate, or severe and circle her response. If the woman would like the study staff to define mild, moderate or severe, read her the definitions below. These definitions are also printed directly on Form 1:

Mild: Symptoms were annoying but did not get in the way of your usual activities.

Moderate: Symptoms got in the way as you tried to do your usual activities but you were still able to do most of the things you needed to.

Severe: Symptoms stopped you from being able to do your usual activities.

26. Indicate whether the patient has experienced any nausea in the past week by checking “Yes” or “No”.
27. Indicate whether the patient has experienced any vomiting in the past week by checking “Yes” or “No”.

Items 28-37 can be completed by gathering information for the patient’s chart. Thus the patient interview is completed after Item 27 is completed, unless the

IRB-approved study staff is unable to access the patient's chart, in which case the staff can refer to the clinician or physician to complete items 28-37.

28. Record the patient's age in years.
29. Record the patient's BMI
30. Record the patient's Biparietal Diameter (BPD) as assessed by the ultrasound performed earlier in the participant's appointment on Day 1. Record the BPD in cm to two decimal places.
31. Record the patient's GA as charted in the clinic in weeks and days. Use the main gestational age that the clinic uses when documenting this patient.
32. Participants will be divided into two study groups based on gestational age. For participants whose BPD is measuring 4.61-5.24cm check "Group 1". For participants whose BPD measures 5.25-5.88cm, check "Group 2".
 - a. Note that FPA Women's Health locations in Los Angeles and Long Beach will only be recruiting patients for Group 1. Thus all patients enrolled in these sites should have BPD within 4.61-5.24cm, and should all be checked for Group 1.
33. This question assesses the patient's reason for her current abortion. This question should be completed in consultation with a counselor or with a clinician or physician. If the patient is having her abortion for a fetal anomaly or a pregnancy complication check "Anomaly/comp.". If the patient is having her abortion for any other reason, check "Other".
 - a. Patients with cranial defects must be between 20w0d and 24w0d by best estimate of gestational age AND BPD must also be within range above. If cranial defects preclude BPD measurement, use the best composite sonographic dating criteria available to ensure the patient is between 20w0d and 24w0d. If accurate dating is unable to be obtained, the patient is not eligible for the study.
 - b. Other kinds of fetal anomalies (non-cranial defects, see above a.) are otherwise eligible for the study.
34. Record the total number of times the patient has been pregnant, regardless of outcome. A multi-gestational pregnancy is 1 pregnancy. Include her current pregnancy in this total.

35. Record the total number of vaginal deliveries this patient has had. Delivery of a multi-gestational pregnancy is 1 delivery. Vaginal deliveries are considered deliveries occurring >20wks.
36. Record the total number of c-section deliveries this patient has had. Delivery of a multi-gestational pregnancy is 1 delivery.
37. Record the number of abortions the patient has had. An abortion is considered to be any elective termination of a pregnancy.
38. Record the number of miscarriages the patient has had.
39. Check any of the medical conditions listed that the patient has recorded in her chart. If there is a medical condition that the patient has or previously had that is not listed, check "Other" and write in the medical condition as it's listed in her chart.
 - a. NOTE: anxiety that is listed in the chart as a chronic condition (i.e. has been diagnosed by a healthcare professional and/or uses medication to manage) then this should be considered "psychiatric disease". If the chart notes that the patient is generally feeling anxious (for example, is feeling anxious about the abortion procedure), this does not need to be noted.

This is the end of **Form 1: Eligibility Screening and Baseline Data, Day 1.**

Upon completion of Form 1, study staff should:

- Review Form 1 for accuracy and completeness
- Make corrections as necessary. Date and initial all corrections.
- Sign both sides of the Form in the header (next to "Staff signature")
- Once clinician/physician has completed H&P with patient, confirm eligibility criteria with clinician/physician and have physician sign Form 1 under "Clinician signature)
- Proceed to Randomization, Drug Tracking Log, Drug Drawing**
- When patient is taken to room for dilator placement and injection, proceed to **Form 2: Dilator and Injection Data, Day 1**

B. Form 2: Dilator and Injection Data, Day 1

Form 2 Overview

Form 2 is used to document the injection of the study medication and dilator placement. It also assesses the pain felt by the patient during the dilator placement and injection. This form will be completed by IRB-approved study staff before and after the injection and during dilator placement. The staff member will survey both the provider and the participant while completing.

Injection and dilator order will vary by site. LOVEJOY: Injection will happen first, followed by dilator placement. FPAWH: Dilators will be placed first, followed by injection. SFGH: Order may vary.

The Injection Questionnaire and the Dilators Questionnaire should be asked and answered about the specific event to which they refer (injection or dilator placement). Please perform the questionnaires DIRECTLY after each event and clarify for the participant that the questions are referring to that event only.

Form 2 Detailed Instructions

Injection data on Form 2:

Write the participants Randomization ID in the box provided. The randomization ID contains the group assignment code 1 or 2 followed by the site specifier (1 for SF, 2 for LJ, 3 for LA, 4 for LB) and the patient-specific number (01, 02, 03). For example, a Group 1 participant from SF would have the Randomization ID 1-101.

Summary of Randomization IDs:

- First number = GA group (1= BPD 4.61-5.24cm, 2= BPD 5.25-5.88cm)
- Dash
- Second number = site (SFGH = 1, Lovejoy = 5-6, FPAWH Los Angeles = 3, FPAWH Long Beach = 4)
- Third and fourth numbers go in numerical order starting at 01 for each site and group

Women's Options Center, San Francisco CA		Lovejoy Surgicenter, Portland OR		FPAWH, Los Angeles CA	FPAWH, Long Beach CA
1-101	2-101	1-501	2-501	1-301	1-401
1-102	2-102	1-502	2-502	1-302	1-402
1-103	2-103	1-503	2-503	1-303	1-403
1-104	2-104	1-504	2-504	1-304	1-404

For FPA Women's Health locations, only participants in the first gestational age group 1 (BPD 4.61-5.24) are being recruited. Thus all randomization numbers will begin with "1-".

Blinded injection preparation and placement

Injection drug preparation and randomization protocol vary by site. See below for the protocols of each site:

SF: Women's Options Center

WHO draws up study medication:

- The RA will fax down a Pharmacy Order form to the ZSFG Pharmacy once the patient is enrolled.
- A pharmacist who is not involved with any other study procedures will draw up the study drug (digoxin or placebo) based on the randomization scheme.
- The pharmacist will then tube the labeled syringe (containing either digoxin or placebo) up to 6G.

Randomization protocol:

- The pharmacist will use the subject ID number located on the faxed Pharmacy Order form to look at the randomization guide to determine whether the patient will receive active drug (digoxin) or placebo.
- Once the injection is administered, the participant is considered randomized. Any participant who withdraws from the study prior to the injection is not randomized and the randomization number can be reused. The unused syringe will be disposed.

Drug Preparation

- Once the pharmacist determines whether the patient will receive digoxin or placebo he/she will do the following:
 - o If digoxin, the pharmacist will retrieve two ampules digoxin (500 mcg/2 mL concentration) from study binder in IVAC
 - o If placebo, the pharmacist will retrieve a 10 ml vial of 0.9% sodium chloride (use general IVAC stock)
- The pharmacist will aseptically draw up 4 mL of product into a 5 mL syringe
- The pharmacist will label the syringe using the pre-made labels found in the study binder and place the syringe in a protect-from-light bag.

LJ: Lovejoy Surgicenter

WHO draws up study medication:

- A Lovejoy Surgicenter nurse (RN) from the upstairs section of the center (clinical section) who is not part of the patient's further care will draw up after the patient is enrolled.

- The RA is responsible for informing the nurse of the patient and coordinating with the nurse so he/she can prepare the drug prior to the injection.
- The nurse who is responsible for drawing up the medication may change per participant as each nurse is assigned certain patients and not involved in the care of others. The nurse will be recruited to draw up medication only of the patients he/she is not otherwise caring for. If he/she is caring for a study participant, he/she may draw up the drug for another study participant but not for his/her participant patient.

Randomization protocol:

- Prior to the study starting, the coordinating center (UCSF) will send a randomization list that is developed to be consistent with the randomization schemes of the other sites.
- Using this randomization list, research assistants who are not otherwise related to the study (research assistants known to the clinic but in different departments or on different studies) will create envelopes that correspond to each randomization ID.
- Each envelope will be labeled with only a Randomization ID and inside the sealed envelope will be the drug randomization: "Placebo" or "Digoxin"
- This envelope is opened only by the nurse who will be drawing up the drug and the contents are not to be shown to anyone else.
- Once the envelope is opened, the participant is considered randomized. Any participant who withdraws from the study prior to envelope opening is not randomized and the envelope is replaced in the cabinet to be reused. Any envelope that is open is discarded even if the participant does not ultimately receive the injection and that randomization ID is not reusable.
- Thus it is important that the envelope be opened, and study drug drawn, as close to the injection as possible.
- Envelopes will be kept in a locked box in the clinic

Drug Preparation

- Once they have opened the envelope, the nurse responsible for drawing up the medication should prepare the injection syringe out of view of any other research or clinic staff. The drug may be prepared downstairs, where staff are not involved in clinical care, or anywhere that is not in the presence of any one else caring for the study participant.
- No drug containers other than the syringe containing the prepared medication should be brought into the procedure room during the injection to ensure blinding.

FPAWH – LA and LB sites:

WHO draws up study medication:

- A FPAWH medical assistant (MA) who is not part of the patient's medical care will draw up the study medication (digoxin or placebo) after the patient is enrolled.

- When the study medication is prepared, the MA will deliver the syringe on a tray to the nurse who is performing the injection.

Randomization protocol:

- Prior to the study starting, the coordinating center (UCSF) will send a randomization list that is developed to be consistent with the randomization schemes of the other sites.
- Once a patient is enrolled, the RA will inform the MA of the patient's randomization number and the MA will use the randomization list (contained in an envelope) to determine if placebo or digoxin should be drawn up. The MA who draws up the study drug is the only one who has access to this envelope.
- Once the injection is administered, the participant is considered randomized. Any participant who withdraws from the study prior to the injection is not randomized and the randomization number can be reused. The unused syringe will be disposed.

Drug Preparation

- Once the randomization list is viewed, the MA responsible for drawing up the medication should prepare the injection syringe out of view of any other research or clinic staff. The drug is usually prepared in the recovery room, where staff are not involved in clinical care, or anywhere that is not in the presence of any one else caring for the study participant.
- No drug containers other than the syringe containing the prepared medication should be brought into the procedure room during the injection to ensure blinding.

1. Record today's date. Dates should be recorded as month/day/year (MM/DD/YYYY)
2. Record pain medications given before injection and dilator placement.

--- FPAWH skip to dilator placement and then items 10-16. After question 16 return to item 3 and proceed with the rest of the form.---

3. Record whether the patient was randomized. If they received the blinded injection, check "Yes" indicating they were randomized. If they did not receive the blinded injection, check "No" indicating they were not randomized.
 - a. If they were not randomized, indicate the reason(s) for not randomizing the patient on the line provided.
 - b. For LJ: the patient is considered randomized if their envelope was opened even if they didn't receive the injection.

4. Print the last name of the clinician or physician administering the injection on the line provided.
5. Record the time that the injection was completed and circle "AM" or "PM". Record the time as standard time (12hr format), hh:mm. No stopwatch is needed. Injection is considered complete when all study medication has been administered.

Directly after the injection procedure is complete, ask the patient items 6-9.

6. Ask the patient to assess her pain specifically during her injection on a scale of 0-10. Show her the 0-10 scale on Form 2 and read the question as printed on the Form. Ask her to select the appropriate box on the scale. Mark an "X" in the appropriate box, based on her response.
7. Ask the patient how acceptable this amount of pain was to her. Read the 5 response choices to the patient: "Very acceptable", "Somewhat Acceptable", "Somewhat Unacceptable", or "Very Unacceptable". Tick the appropriate response. If the patient is unable to answer the question, tick "Don't know".
8. Ask the patient how the injection compared to her expectations prior to the procedure. Read her the 3 answer choices "Better than expected", "The same as expected", "Worse than expected" and tick the appropriate response. If the patient is unable to answer the question, tick "Don't know".
9. Ask the patient if she is experiencing any nausea right now. If she is not experiencing nausea currently, circle "None" on the corresponding line. If she is experiencing nausea, ask her if it was mild, moderate, or severe and circle her response. If the woman would like the study staff to define mild, moderate or severe, read her the definitions below. These definitions are also printed directly on Form 2:

Mild: Symptoms were annoying but did not get in the way of your usual activities.

Moderate: Symptoms got in the way as you tried to do your usual activities but you were still able to do most of the things you needed to.

Severe: Symptoms stopped you from being able to do your usual activities.

Osmotic dilator placement occurring during Form 2

Osmotic dilators should only be placed by clinicians specified in the Delegation of Authority Log.

Items 10-16 should be recorded by study staff during the dilator placement.

10. Record whether the dilators were placed in the patient's cervix prior to her study drug injection or after by checking "Before" and "After"
11. Record the number of Laminaria dilators and the number of Dilapan dilators successfully placed in the cervix.
12. Record the time that dilator placement was completed and circle "AM" or "PM". Record the time as standard time (hr format), hh:mm. No stopwatch is needed.
13. Indicate whether adjunctive mifepristone was given after dilator placement by checking "Yes" or "No".
14. Indicate whether the amniotic sac was ruptured during dilator placement by checking "Yes" or "No".

Once the dilator placement is complete, ask the patient questions 15-16, rating her pain during dilator placement. Ask these questions while the patient is still in the procedure room.

15. Ask the patient to assess her pain specifically during her dilator placement on a scale of 0-10. Show her the 0-10 scale on Form 2 and read the question as printed on the Form. Ask her to select the appropriate box on the scale. Mark an "X" in the appropriate box, based on her response.
16. Ask the patient how acceptable this amount of pain was to her. Read the 5 response choices to the patient: "Very acceptable", "Somewhat Acceptable", "Somewhat Unacceptable", or "Very Unacceptable". Tick the appropriate response. If the patient is unable to answer the question, tick "Don't know".

After the procedures are complete ask the clinician the following three questions. Make sure to ask these questions not in the presence of the patient (aka once the patient or clinician has left the procedure room).

17. Once the injection is complete, record where the administering clinician thinks the injection went by checking "Intra-amniotic", "Thorax", "Cardiac", "Extremity". If the physician responds with another location, check "Other".
18. Ask the clinician of their confidence in their response to Item 17 and record their response by checking "Confident" or "Not confident".
19. Ask clinician how difficult the injection was and record their response as "very easy", "somewhat easy", "somewhat difficult", or "very difficult".

This is the end of **Form 2: Dilator and Injection Data, Day 1**. Upon completion of Form 2, study staff should:

- Review Form 2 for accuracy and completeness
- Make corrections as necessary. Date and initial all corrections.
- Sign both sides of the Form in the header (next to "Staff signature")
- If Form 1 was not already completed, review patient's chart and complete any missing data from Form 1
- Ensure that the patient received \$50 payment and that this payment is logged in the Payment Log.
- The next data collection form to be completed will be **Form 3: Arrival Data, Day 2**. Form 3 must be completed when the patient arrives at the clinic on Day 2.

C. Form 3: Arrival Data, Day 2

Form 3 Overview

Form 3 is used to assess the patient's experience of any side effects or adverse events since she was last seen in the clinic on Day 1. Form 3 will also document any pain the patient is having currently. Form 3 should be completed when the patient arrives to clinic on Day 2.

Form 3 Detailed Instructions

1. Record today's date. Dates should be recorded as month/day/year (MM/DD/YYYY).
2. Take the patient's temperature as soon as possible after she arrives in the clinic. Record the patient's temperature in degrees Fahrenheit.
3. Ask the patient if she has experienced the following symptoms since she left clinic yesterday: Nausea, vomiting, chills, fever, dizziness. If she did not experience the symptom, circle "None" on the corresponding line. If she did experience the symptom, ask her if it was mild, moderate, or severe and circle her response. If the woman would like study staff to define mild, moderate, or severe, read her the definitions below. These definitions are also printed directly onto Form 3:

Mild: Symptoms were annoying but did not get in the way of your usual activities.

Moderate: Symptoms got in the way as you tried to do your usual activities but you were still able to do most of the things you needed to.

Severe: Symptoms stopped you from being able to do your usual activities.

4. Ask the patient if they took any narcotics for pain since leaving the clinic yesterday. If they need further examples, read the examples listed "Norco, tyco or T3, Percocet, Vicodin". If they have taken a narcotic since leaving the clinic yesterday, check "Yes" and print the medication name. If they haven't taken any narcotics, check "No".
5. Ask the patient if they took any other medication for pain since leaving the clinic yesterday. If they need further examples, read the examples listed

- “ibuprofen, tylenol”. If they have taken any other medications for pain since leaving the clinic yesterday, check “Yes” and print the medication name. If they haven’t taken any other medications, check “No”.
6. Ask the patient if they took any medication for nausea since leaving the clinic yesterday. If they have taken any medications for nausea since leaving the clinic yesterday, check “Yes” and print the medication name. If they haven’t taken any other medications, check “No”.
 7. Ask the patient if they called the clinic for any reason since leaving the clinic yesterday. If they have called the clinic check “Yes” and print the reason for their call. If they haven’t taken any other medications, check “No”.
 8. Ask the patient if they went to an Emergency Room or any other clinic for any reason since leaving the clinic yesterday. If they did go to an Emergency Room or another clinic check “Yes” and print the reason for their visit. If they haven’t taken any other medications, check “No”.
 9. Ask the patient what their bleeding has been like since leaving the clinic yesterday. Read them the question as printed followed by the following 4 responses: “No bleeding”, “Spotting or light bleeding only”, “Moderate bleeding (like a period)”, or “Heavy bleeding (heavier than a bleeding)”. Tick the appropriate response.
 10. Ask the patient if they noticed the fetus had stopped moving?. If they say yes, check “Yes” and record the approximate time they last felt fetal movement if they can remember. Record the time in 12hr format, as hh:mm and circle AM or PM. If they don’t remember, write “99:99”. If they have not felt any stop in fetal movement, check “No”.
 11. Ask the patient which medication they think they received yesterday. Check the appropriate response and write why they think they received that particular medication. If the participant cannot offer a guess of which medication she received check “Don’t Know”.
 12. Ask the patient to assess her pain currently on a scale of 0-10. Show her the 0-10 scale on Form 3 and read the question as printed on the Form. Ask her to select the appropriate box on the scale. Mark an “X” in the appropriate box, based on her response.
 13. Ask the patient how acceptable this amount of pain was to her. Read the 5 response choices to the patient: “Very acceptable”, “Somewhat

Acceptable", "Somewhat Unacceptable", or "Very Unacceptable". Tick the appropriate response. If the patient is unable to answer the question, tick "Don't know".

14. After the patient questionnaire is completed, refer to the patient's medical chart. Check "yes" or "no" to reflect whether misoprostol was given adjunctively.

- a. If checked "Yes", provide the time in HH:MM (12hr format) and circle AM or PM. Record the dose in *micrograms* and report the route of drug delivery by checking "Buccal", "Oral" or "Other". If choosing other record the route used.

15. Check "yes" or "no" to reflect whether the patient was given any other medications after arrival at the clinic and before the procedure (like ibuprofen, morphine, Zofran, Ativan, norco, etc).

- a. If checked "yes", please list the medications given.

This is the end of **Form 3: Arrival Data, Day 2**. Upon completion of Form 3, study staff should:

- Review Form 3 for accuracy and completeness
- Make corrections as necessary. Date and initial all corrections.
- Sign both sides of the Form in the header (next to "Staff signature")
- Proceed to **Form 4: Intra-operative Data, Day 2**, which must be completed during her abortion procedure.

D. Form 4: Intra-operative Data, Day 2

Form 4 Overview

Form 4 is used to document the initial pre-operative setup, procedure time, and details of the D&E procedure. Form 4 will also include the operating physician's assessment of procedure difficulty and his or her guess as to the study drug assignment. Questions from Form 4 should be completed in consultation with the operating physician. The operating physician must be listed on the Delegation of Authority Log as approved to perform the D&E.

Form 4 Detailed Instructions

1. Record today's date. Dates should be recorded as month/day/year (MM/DD/YYYY).
2. Print the last name of the clinician or physician performing the D&E on the line provided.
3. Record what anesthesia the patient received during their abortion procedure by checking the appropriate response.
 - a. Moderate sedation is defined as "a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained" per ASA guidelines
4. Prior to the MD placing their speculum and starting to the procedure, the RN assisting with ultrasound during the procedure will check for fetal presentation and cardiac activity using the ultrasound. **The MD is blinded and CANNOT know whether or not cardiac activity is present. The study RA must remain blinded to cardiac activity as well.** The MD must be turned around and not looking at the ultrasound. The RN may inform the MD about fetal presentation but will not say whether or not there was cardiac activity aloud.

A separate log, the Cardiac Activity Log, will be used to record cardiac activity. RN will record the subject's enrollment ID, the date, cardiac activity (yes, no, or unsure) and initials. The Cardiac Activity Log will be kept in an opaque folder, and the research assistant will remain blinded to the cardiac activity.

5. Based on the findings of the RN performing the ultrasound, record the fetal presentation by ticking "Cephalic", "Breech" or "Transverse". If the fetal presentation is not listed in the response choices, tick "Other" and write in the fetal presentation on the line provided.

After the RN is done viewing cardiac activity, it may be necessary for the clinician to view the ultrasound during the procedure. This is acceptable as necessary for the procedure, however the physician should avoid intentionally searching for cardiac activity to the degree that is possible.

6. Using a clock, record the time when the speculum is first placed in the vagina. Record the time as standard time (12hr format) **hh:mm**. Circle AM or PM as appropriate. ***Start the stopwatch at this time.***
7.
 - a. The initial amount of cervical dilation will be measured using Bierers or ring forceps. Record which instrument the clinician uses to measure cervical dilation by checking either "ring forceps" or "Bierer forceps". (*Preference is ring forceps*)
 - b. The clinician will place the Bierers or ring forceps into the internal os of the cervix and open them as far as possible. The research assistant will use a paper ruler to measure the distance between the handles and will record the distance in **millimeters** in the spot marked "distance between handles".
 - c. LATER when the clinician has finished using the instrument that was used to check the dilation (Bierers or ring forceps), the research assistant will open them to the same distance (using the ruler to match the distance between the handles to the original distance between the handles in mm) and keeping the handles at the original distance, will record the distance between the tips of the instrument in **millimeters** in the spot marked "distance between tips". *This should be done after the procedure is over when the clinician is no longer using this instrument.*
8. Record the time on the stopwatch when the first instrument enters the uterus. Record the time as seen on the stopwatch, hh:mm:ss. Do not reset or pause the stopwatch. *The first instrument could be Bierer forceps, a mechanical dilator, or the suction cannula.*
9. Indicate whether the physician had to mechanically dilate the cervix before beginning the procedure by checking "Yes" or "No".

10. Record the procedure end time on the stopwatch when the last instrument is removed from the uterus. Record the time as seen on the stopwatch, hh:mm:ss. Do not reset or pause the stopwatch.
11. Indicate whether bimanual massage, compression or uterus elevation to control bleeding following the abortion procedure by checking "Yes" or "No".
12. Indicate whether Monsel's solution or Silver Nitrate was used to stop any bleeding following the abortion procedure by checking "Yes" or "No".
13. If the patient is having an IUD contraceptive placed following her abortion procedure, check "Yes"
 - a. Record the time on the stopwatch when the IUD package was requested by the physician, with the format hh:mm:ss.
 - b. IF, following IUD placement, the strings are cut, record the time the strings are cut, with the format hh:mm:ss. If the IUD is left in place, move to item 13, leaving "Time to removal" empty.
 - c. IF, following IUD placement, the IUD is subsequently removed, record the time of removal, with the format hh:mm:ss. If the strings were never cut during the IUD placement, leave "Time to strings cut" empty.
 - d. If the patient did not have an IUD placed check "No".
 - e. Do not reset or pause the stopwatch
14. If the patient had a cervical laceration with repair during her abortion procedure check "Yes".
 - a. Record the time on the stopwatch when the cervical laceration repair begins, with the format hh:mm:ss.
 - b. Record the time on the stopwatch when the cervical laceration repair is finished, with the format hh:mm:ss
 - c. If the patient did not have a cervical laceration during her abortion procedure, check "No".

15. Record whether any uterotonics were used after the procedure, while the patient was still in the procedure room, by checking "Yes" and writing the name, dose and time administered (as indicated on the stopwatch in the format hh:mm:ss) or checking "No" if no uterotonics were used.
 - a. At Lovejoy and FPAWH sites, please record Pitocin (and the dose) as an intra-operative uterotonic. You can record the time of day given from the chart, and it will always be "prophylactic"
 - b. Record any uterotonics that are used in the procedure room, even if the speculum has been removed, on Form 4.
 - c. Record any uterotonics used once the patient has left the procedure room (once in the recovery room) on Form 5.

16. Once all the instruments are removed from the vagina, including the speculum and MD's fingers, stop the stopwatch and record the time in the format hh:mm:ss.

17. Record any complications that occurred during the procedure by checking the appropriate complication on the list provided.
 - a. If she experienced no complications check "None"
 - b. If she required placement of a Foley or Bakri for bleeding tamponade while still in OR after procedure, check "Foley/Bakri".
 - c. If she required vaginal packing room for hemostasis, check "Vag pack."
 - d. If she required an immediate blood transfusion (while in OR for procedure) check "Transfusion."
 - e. If she required a reaspiration of uterine contents after all instruments were removed from the vagina, but while she was still in the procedure room, check "Reaspiration-immediate".
 - f. If she experiences a uterine perforation during her procedure, check "Perforation".
 - g. If she experienced a complication that is not listed, check "Other" and write the complication on the line provided (ex. Major surgery). Receiving uterotonics does not qualify as a complication.

18. Record the estimated blood loss in milliliters.

19. For Site SF: Record the measured blood loss in milliliters, per clinic protocol

Once the physician has finished his or her work with the patient, ask them to complete items 21-24.

20. Ask the operating physician whether the patient's membranes were intact or if there was rupture of membranes prior to starting the D&E. Record their response by checking "Yes" or "No".
21. Ask the operating physician to assess the overall procedure difficulty. Tick the appropriate response: "Very easy", "Somewhat easy", "Somewhat difficult", "Very difficult".
22. Ask the operating physician their reasoning for their answer to item 22 and write their response on the line provided.
23. Ask the operating physician whether the blood loss during the procedure was "less than normal", "normal" or "more than normal" compared to his/her typical D&E procedure of similar gestational age.
24. Ask the operating physician whether they were concerned about the blood loss following the procedure. Record their response by checking "Yes" or "No".
25. Ask the operating physician to guess the patient's study assignment. Tick the box "Digoxin" or "Placebo" and write their reasoning on the line provided. If the operating physician is uncertain about the patient's study assignment tick "Don't know".
- a. If the physician guessed digoxin, ask whether they believed there was fetal demise prior to the procedure and ask how that demise affected the procedure. Record their response on the line provided.
26. Ask the operating physician if in general, not just during this current abortion procedure, whether they find it easier to do an abortion procedure when the fetus is demised. Check "Easier", "The Same", or "Harder" as appropriate.

This is the end of **Form 4: Intra-operative Data, Day 2**. Upon completion of Form 4, study staff should:

- Review Form 4 for accuracy and completeness

Standard Operating Procedure - Intrafetal digoxin as an adjuvant for dilation and evacuation at 20 to 24 weeks' gestation: a placebo-controlled, double-blinded randomized controlled trial.

- Make corrections as necessary. Date and initial all corrections.
- Sign both sides of the Form in the header (next to "Staff signature")
- The next data collection form to be completed will be **Form 5: Post-Operative Data, Day 2.**

E. Form 5: Post-Operative Data, Day 2.

Form 5 Overview

Form 5 is a survey of the patient's experiences after her abortion procedure, including her pain, side effects and satisfaction.

Form 5 Detailed Instructions

1. Record today's date. Dates should be recorded as month/day/year (MM/DD/YYYY).
2. Ask the patient to assess her pain currently on a scale of 0-10. Show her the 0-10 scale on Form 5 and read the question as printed on the Form. Ask her to select the appropriate box on the scale. Mark an "X" in the appropriate box, based on her response.
3. Ask the patient how acceptable this amount of pain was to her. Read the 5 response choices to the patient: "Very acceptable", "Somewhat Acceptable", "Somewhat Unacceptable", or "Very Unacceptable". Tick the appropriate response. If the patient is unable to answer the question, tick "Don't know".
4. Ask the patient if she has experienced the following symptoms since she left clinic yesterday: Nausea, vomiting, chills, fever, dizziness. If she did not experience the symptom, circle "None" on the corresponding line. If she did experience the symptom, ask her if it was mild, moderate, or severe and circle her response. If the woman would like study staff to define mild, moderate, or severe, read her the definitions below. These definitions are also printed directly onto Form 5:

Mild: Symptoms were annoying but did not get in the way of your usual activities.

Moderate: Symptoms got in the way as you tried to do your usual activities but you were still able to do most of the things you needed to.

Severe: Symptoms stopped you from being able to do your usual activities.

5. Ask the patient how satisfied they are with their abortion procedure overall. Read the choices "Very satisfied", "Somewhat satisfied", ,

“Somewhat unsatisfied” and “Very unsatisfied”. Record their response by checking the appropriate box.

6. Ask the patient how satisfied they are with specifically their injection procedure overall. Read the choices “Very satisfied”, “Somewhat satisfied”, “Somewhat unsatisfied” and “Very unsatisfied”. Record their response by checking the appropriate box.
7. Ask the patient if she were to become pregnant in the future and need a second trimester abortion similar to her procedure today, would she prefer to get the digoxin injection or not have the injection. Record whether she would rather have the injection, not have the injection or not sure by checking the appropriate box. Record the reason for her response on the line provided.
8. Ask the patient if they would recommend the digoxin injection to other women having a second trimester abortion. Record whether she would recommend having the injection or not having the injection, or whether she is not sure, by checking the appropriate box. Record the reason for her response on the line provided.

Item 8 is the final question for the patient. Once she has completed the questionnaire, provide the patient with the remaining \$50 payment and log it in the Payment Log. At that point the patient has completed her participation in the study and is free to leave after she has been cleared for discharge by the clinic staff. The study staff should complete the rest of Form 5 by consulting the patient’s chart or clinic physicians.

9. Record whether any uterotonic medications were given to the patient in the recovery room following her abortion procedure. If she was given uterotonics, check “Yes” and record the name, dose and time given (in 12-hr standard format, hh:mm, and circle AM or PM appropriately). If no uterotonic medication was given check “No”.
10. Record the time the patient was discharged from the clinic. Record the time in standard format (12-hr format), hh:mm. Circle AM or PM as appropriate.
11. Record any post-procedure complications. These are complications that occurred AFTER the patient has been taken out of the OR immediately following the procedure.
 - a. If she experienced no complications check “None”

- b. If she required placement of a Foley or Bakri for bleeding tamponade and was taken back into the OR for placement, check "Foley/Bakri – brought back in OR".
- c. If she required vaginal packing room for hemostasis and was taken back into the OR for placement, check "Vag pack – back in OR."
- d. If she required an immediate blood transfusion after the procedure finished and patient was out of OR, check "Transfusion – post-procedure."
- e. If she required a Uterine Artery Embolization (UAE), check "Embolization."
- f. If she required a reaspiration of uterine contents after leaving the procedure room (has to return to procedure room, OR or get admitted to hospital), check "Reaspiration- Brought back to OR".
- g. If she is admitted to a hospital following her procedure, check "Admission to hospital".
- h. If she experienced any other post-procedure complication that is not listed, check "Other" and write the complication on the line provided (ex. Major surgery). Receiving uterotonics does not qualify as a complication.

This is the end of **Form 5: Post-operative Data, Day 2**. Upon completion of Form 5, study staff should:

- Review Form 5 for accuracy and completeness
- Make corrections as necessary. Date and initial all corrections.
- Sign both sides of the Form in the header (next to "Staff signature")
- Ensure that the subject received the \$50 payment and that this was logged in the Payment Log.

This is the end of the data collection.

VI. STUDY LOGS

A. Recruitment and Enrollment Log

The Recruitment and Enrollment Logs are electronic files used to record the progress of the study participants. Each site will have its own R&E Log and will email the updated R&E log to the coordinating site *every week*. The title of the R&E document should be changed to reflect the appropriate week before it is sent to the coordinating site (e.g. Enrollment Log_LJ_12.7.16 -> Enrollment Log_LJ_12.14.16).

Recruitment Log

The Recruitment log is used to record the total number of possible participants at each clinic and the number who were actually approached. It also monitors their reason for declining participation and ineligibility. In the first column, Column A, the weeks are listed. Each row corresponds to a single recruitment day, or Day 1. Record the date of that Day 1 in Column B next to the week.

- Based on the clinic schedule, which differs per site, periodically update the recruitment log with the number of patients who come to clinic for D&E as the day goes on.
 - Recruitment days (Day 1) are as follows:
 - SF: Tuesdays, Thursdays
 - LB: Mondays
 - LA: Wednesdays, (possibly Fridays)
 - LJ: Monday, Tuesday, Wednesday, Thursday
- Not approached: Based off of how many patients present to the clinic by the end of each recruitment day, record how many were not approached under "NOT Approached". In the next column, record the reason they were not approached for the study. Reasons for not approaching include:
 - Being found ineligible prior to approaching: wrong gestational age (BPD <4.61 or >5.88; also at FPAWH if they were >5.24); under 18 years old, non-English or Spanish speaking; if it was a multiple gestation pregnancy; if they're incarcerated; per clinical judgment, when a nurse, physician or other clinic staff requests that the patient not be approached (i.e. mentally unstable, emotional, etc) though reason may not always be provided.
 - For LJ and both FPAWH sites: Spanish-speaking patients are not being recruited so indicate this an appropriate reason.
 - Missed the opportunity to approach the patient: RA was not available/with another participant; clinic flow was too busy.
 - Recruitment limits: maximum number of participants were enrolled for the day so no further patients approached; for SF or LJ, RA was only recruiting for one of the two gestational age groups and the

- participant was in the gestational age group that was not being recruited that day.
- Other: please write in parentheses what the reason for not approaching the patient.
 - Approached: record the *number* of participants that you approached. Each patient approached should have a corresponding data Form 1. Verify at the end of each day that the number of Form 1's completed matches the number "approached" recorded.
 - Declined: record the *number* of patients who declined to participate after you approached them about the study. For each participant that declines, ask the patient why they do not wish to participate. Record the reason(s) they provide for declining in the following column, separating each reason by a comma (ex: "don't want extra injection, don't want to spend extra time on study"). This response should also be documented on Form 1.
 - Determined ineligible after being approached: Based on their responses to Form 1 record the reason(s) the participant was found ineligible after being approached. These should also be recorded on Form 1. Ask the participant all of the eligibility questions regardless of eligibility status.
 - Enrolled: Record the number of participants enrolled for the day. Record the Enrollment ID of each participant enrolled under "Enrollment Numbers" column, separating each ID by a comma (SF001, SF002).
 - Randomized: Record the number of participants randomized for the day. If a participant was enrolled but not randomized (i.e. if # Enrolled ≠ # Randomized for the week) record the reason(s) for not being randomized, with each reason being separated by commas. The reason for not being randomized should also be recorded on Form 2. Reasons for not being randomized include ROM with dilator placement; patient withdrew from study before randomization; physician unable to complete injection; adverse event precludes patient completing study.

Enrollment Log

The enrollment log is used to track the progress of participants recruited for the study. In Column A, each row corresponds to a single participant.

- Date: Record the date that the participant was enrolled (Day 1)
- Enrollment ID: Record the participants Enrollment ID.

- **Randomized?**: Record whether the participant was randomized or not. If they were not randomized, record the reason(s), with each reason separated by a comma. The reason for not being randomized should also be recorded on Form 2. Reasons for not being randomized include ROM with dilator placement; patient withdrew from study before randomization; physician unable to complete injection.
- **Randomization ID**: if the participant was randomized, record their Randomization ID
- **Discontinued from study**: Record whether the participant discontinued from the study at any point prior to study completion after receiving an enrollment ID by writing "Yes" or "No". If the participant did discontinue, record the reason for their discontinuation by writing the number corresponding to their reason, with each number separated by a comma. If the participant withdraws voluntarily from the study, ask the participant if the research team still has permission to access their medical chart and record their response.

B. Protocol deviations log

Protocol deviations are any deviation from the IRB-approved protocol that are not approved prospectively by the IRB. Major protocol deviations are deviations from the protocol that have the potential to negatively impact subject safety, the integrity of study data, or a subject's willingness to participate in the study. Minor protocol deviations are deviations that do not have the potential to negatively impact subjects, their willingness to participate or data integrity.

All protocol deviations must be reported to the coordinating center within 72 hours of the site PI learning of the event.

Protocol deviations must be recorded on the Protocol Deviations Logs as follows:

- Record the Site ID (SF, LJ, LA, LB) in the designated space at the top of each page of the Protocol Deviations Log
- **Enrollment ID**: Record the patient's assigned Enrollment ID
- **Date the deviation discovered**: Write the date that the deviation was discovered by study staff. Dates should be recorded as month/day/year (MM/DD/YYYY).
- **Date the deviation occurred**: Write the date that the deviation actually occurred, even if it is not the same date as the day it was discovered. Dates should be recorded as month/day/year (MM/DD/YYYY).

- Description of deviation: Briefly describe what happened in the protocol deviation.

C. Payment Log

The Payment Log is meant to assist sites in documenting payment transactions with study participants. This log should be updated each time payment is given to a study participant. The Payment Log should be completed as follows:

- Record the Site ID (SF, LJ, LA, LB) in the designated space at the top of each page of the Payment Log
- Date: Write the date that payment is given to the study participant. Dates should be recorded as month/day/year (MM/DD/YYYY).
- Study Day: Record the number of the study day on which payment was given. Day 1 is the day the patient was enrolled in the study. In most cases, \$50 will be given on Study Day 1 and \$50 will be given on Study Day 2.
- Enrollment ID: Record the patient's assigned Enrollment ID
- Amount: Record the amount given to the patient that day
- Study staff initials: The study staff who gave the money to the study participant should initial the Payment Log.

Participants will receive their payment as cash or gift card. Cash will be kept in a locked safe box at each study site.

D. Adverse events log

Adverse events are any illness, pain or complication that occurred within the duration of the study. These may be expected (listed in Section VIII) or unexpected and may or may not be related to the study participation. Each Adverse Event should be recorded on its own line even if it is related to another event (e.g. nausea & vomiting are two distinct AE's and should be recorded individually). For each adverse event record:

- Enrollment ID: Record the patient's assigned Enrollment ID
 - If the same AE occurs for different patients (e.g. two patients both experience nausea) record this as two different AE's.

- Randomization ID: Record the patient's assigned Randomization ID if they were randomized
- Event Description or Diagnosis: Record a brief description of the illness or complication. Whenever possible include a medical diagnosis if available.
- Date Onset: Record the date the adverse event was first noticed
- Date Resolved: Record the date the AE resolved. If the AE is ongoing, write "Ongoing"
- SAE: Report whether the AE reported is considered a SAE (criteria for SAE's covered in Section VIII) by checking "Yes" or "No". If checked "Yes" follow SAE reporting protocol elaborated in Section VIII of this SOP.
- AE Severity: Report the severity of the AE using the following numerical code: Mild=1, Moderate=2, Severe=3. Definitions for each are provided below:

Mild: Symptoms were annoying but did not get in the way of your usual activities.

Moderate: Symptoms got in the way as you tried to do your usual activities but you were still able to do most of the things you needed to.

Severe: Symptoms stopped you from being able to do your usual activities.

- AE Outcome: Record the outcome of the AE by writing "1" if the AE recovered/resolved, "2" if the AE is ongoing, "3" if the AE resulted in the death of the participant, and "4" if the AE outcome is unknown.
- Relation to Study Drug: Record whether the study clinician believes that the AE is related to the study drug by recording "1" if the clinician believes the event to be unrelated, "2" if it is unlikely related, "3" if it is possibly related, "4" if it is probably related, or "5" if it is definitely related.
- Treatment Needed: Record whether any treatment was required for the AE by writing "1" for no treatment, "2" for medication treatment and "3" for Non-drug treatment. Specify the medication or non-drug treatment on the lines provided on the AE log below the chart.

E. Participant log

This is a master subject list specific to each site. This log is not sent to the coordinating center but rather remains in a locked cabinet or on a secure server at each study site. The log contains the Enrollment ID, Name and MRN. If the log is being kept electronically on a secure server, check "Electronic" on the top of the page and write the location/name of the file in the line provided.

F. Monitoring log

The Monitoring Log is a record of when site managers monitor the data at a particular site. These visits will occur as needed, with site managers traveling to the site to correlate completed forms with original copies and medical chart data at the site. Each site will have a Site Monitoring Log in their Study Binder, to be completed by the site manager from the coordinating center as follows.

- Record Site ID: (SF, LJ, LA, LB) in the designated space at the top of each page of the Payment Log
- Name of Monitor: Record the name of the site manager from the coordinating center completing the monitoring
- Monitor Date: Record date of monitor. If monitoring occurred over multiple days, put range of dates (MM/DD/YYYY-MM/DD/YYYY).
- Description: Record a brief description what was monitored on this occasion.

The coordinating center will also have a Master Monitoring Log of all the monitoring that has occurred at any of the sites.

G. Drug accountability log

This is to be filled out by RA each time a drug is requested and drawn up. Keep track of the date, the randomization id number, and whether the drug was used or thrown away.

VII: INFORMATION EXCHANGE WITH THE COORDINATING CENTER

A. Sending data collection forms

Unless otherwise arranged, each site should send completed data collection forms to the coordinating center on a weekly basis every Friday. This includes Forms 1-5 for each study patient. Study staff should ensure that all forms are complete, accurate and legible. **Original copies of all data collection forms (Forms 1-5) should be kept at the study site.** These photocopies should be kept in a secure location for 5 years.

In order to send the forms, please scan or fax the original copies of all data collection forms.

- In order to scan the forms please email them to: Chiara.corbetta-rastelli@ucsf.edu

B. Queries

The coordinating center will send data queries to the site study coordinators at each site as needed, with an average response time of 14 days following data collection forms being sent. These queries will be based on submitted data collection forms. Queries will be sent via email. Site study coordinators should ensure that queries are addressed appropriately and responses are sent to the coordinating center in a timely manner. Responses should be sent from the site to the coordinating center via email.

C. Sending Logs to the Coordinating Center

Study sites should send the following Logs to the coordinating center in the time frame indicated:

- Adverse Events Log: Send a copy to the coordinating center on a weekly basis. This log can be scanned/emailed (chiara.corbetta-rastelli@ucsf.edu). If no adverse events have occurred during that week, site study staff should email chiara.corbetta-rastelli@ucsf.edu to report that no adverse events occurred during the preceding week.

D. Protocol Updates

Protocol updates will be emailed to site investigators by the principal investigator or the site managers as they become available. A copy of each update should be printed and placed in the site's Study Binder. The coordinating center will keep a Master Protocol Updates Log of every update that is issued. A copy of this log can be requested at any time by a site as well.

E. Delegation of Authority Log

The Delegation of Authority Log provides a list of the various study tasks and responsibilities and the person(s) approved to complete these tasks. For each study responsibility, either an individual is listed by name or a category is described (RN's, midwives, residents, etc). Only someone listed by name or falling into a listed category can perform the study responsibility.

VIII. SERIOUS ADVERSE EVENTS

An adverse event is any unfavorable medical occurrence in a study participant, including any abnormal sign, symptom or disease that is temporally associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

A serious adverse event (SAE) is an event that:

- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a permanent or serious disability
- Results in a congenital abnormality
- Results in death

Important medical events that may not result in death, be immediately life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an Emergency Room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Reporting SAEs

All SAEs, whether or not there is a probable relationship with the study drug or with the study procedures, must be reported by the site investigator to their coordinating center site manager within 24hrs of his/her becoming aware of the SAE. Coordinating center staff will report SAEs promptly to NEIRB and the IDMC. Sites using their own IRB must additionally report the SAE to their IRB (FPAWH in Long Beach and Los Angeles should report any SAE's to the Coordinating center. Lovejoy clinic should report any SAE's to both the Coordinating Center and their own IRB). Site investigators must also report all SAEs occurring up to two weeks after the participant is discharged from the study IF the event is thought to be related or possibly/probably related to the study.

Reporting of a SAE can be done by phone or email. When reporting a SAE to the coordinating center, the site investigator should refer to the subject by her Enrollment ID to protect patient privacy. Sites will work with the coordinating center to complete the Serious Adverse Event Reporting Form after this initial contact is made to report the SAE.

Principal investigator: Jennifer Kerns, MD, MPH. Jennifer.Kerns@UCSF.edu
510-502-4340

Research manager:

Chiara Corbetta-Rastelli
Chiara.Corbetta-Rastelli@UCSF.edu
Cell: (314) 387-3575

Assessing AEs

Monitoring for and documentation of adverse events related to the cervical dilation, medication injection and/or D&E of study participants, whether anticipated or unanticipated, is the responsibility of the site investigator, who will maintain oversight of the site's adverse events, but she may delegate collection of information related to this function to the site's research coordinator.

Possible adverse events related to the medication injection include those below.

- Injection site pain or bruising
- Nausea and vomiting
 - o Only report in AE log if patient reports severe nausea or vomiting, patient treated with more than one anti-emetic agent (ex. Zofran and Compazine), or patient treated with multiple doses of anti-emetic agent (ex. Patient given 3 doses of Zofran for nausea).
- Out of hospital delivery
- Bradycardia
- Endometritis, sepsis

Possible adverse events related to the D&E include those below. None of the risks listed below would be solely due to the study procedures but are rather potential adverse events that may be related to standard D&E or anesthesia/analgesia/uterotonic agents that accompany the D&E.

- Hemorrhage
 - o Requiring intrauterine tamponade (with Foley, Bakri, packing)
 - o Requiring transfusion
 - o Requiring embolization
- Uterine re-evacuation (for retained tissue, hematometra, bleeding)
- Endometritis, sepsis
- Cervical laceration requiring stitches
- Uterine perforation
- Abdominal surgery (laparoscopy, laparotomy, hysterectomy)

- Transfer to the hospital for any indication (even if the subject is not admitted)
- Allergic reaction/hypersensitivity/anaphylactic shock
- Vasovagal episode
- Syncope
- Anesthesia complications
- Cardiopulmonary arrest

These adverse events should be documented on Form #2 if they occur on Day 1 and Form #4 if they occur on Day 2 for acute events and Form #5 for delayed events and on the Adverse Event Log. The Adverse Event Log will include an assessment of whether the adverse event is unrelated, possibly/probably related, or related to the study medications. A copy of the Adverse Event Log should be sent from each site to the coordinating on a weekly basis. Any adverse events that is unexpected (not on list above) and related or possibly/probably related must be reported to the coordinating center within 5 working days or 7 calendar days of the date the site investigator first becomes aware of them. The principal investigator will review these adverse events at bi-weekly research meetings at the coordinating center.

IX. Detailed Data Analysis Plan

Efficacy endpoints

Primary endpoint: comparison of D&E operative time between two study arms (digoxin injection vs placebo injection)

Secondary endpoints: comparison of ease of procedure, achievement of fetal demise, and procedure complications between two study arms (digoxin injection vs placebo injection).

Safety endpoints

The Data and Safety Monitoring Board will provide recommendations about starting, continuing and stopping the study. Safety evaluations will monitor for statistically significant higher complication rates than complication rates for clinic in procedures of same gestational duration and for adverse events. The DSMB will meet to determine criteria for interim analysis and for stopping the trial.

Statistical analysis

For primary outcome analysis, we will use an intention-to-treat analysis and compare median procedure time using a paired *t* test. To control for site, we will conduct a regression with site as the single factor. In the event that any potential confounders are not balanced by randomization, we will control for those in the analysis. Controlling for site will not necessitate an increase in our sample size. We will do descriptive analyses of secondary outcomes using chi-square and *t* tests where appropriate.

Sample size

Sample size was calculated for the primary outcome of procedure time. In order to detect at least a 3-minute difference in procedure time between groups with 80% power and alpha of 0.05 (using a 2-way test), we would need 172 patients, or 86 per arm. Loss to follow up only would occur if a subject was randomized, received the injection and dilators, then failed to return for her procedure. In order to account for this rare but possible situation, we intend to enroll a total sample of N=180 subjects.