UC San Diego

Protocol: Early vs. Interval Postpartum IUD Insertion:
A Multi-Site Randomized Controlled Non-Inferiority Trial

Protocol Number: 172101

National Clinical Trial (ClinicalTrials.gov) Identifier Number: NCT03462758

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Funded by: Society of Family Planning

Version: 03.01.2018

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Early vs. Interval Postpartum IUD Insertion: A Multi-Site Randomized Controlled Non-Inferiority Trial
Study Description:	This is a randomized controlled non-inferiority trial comparing the expulsion rate of early postpartum IUDs (intrauterine devices) inserted between 2-4 weeks postpartum to the standard interval placement at 6-8 weeks postpartum
Objectives:	*Primary Objective:* Complete IUD expulsion at 6 months postpartum *Secondary Objectives*: Partial IUD expulsion at 6 months postpartum, IUD utilization, IUD removal, IUD perforation, pelvic infection, pain, vaginal bleeding, and user satisfaction at 6 months postpartum
Endpoints:	*Primary Endpoint:* Speculum and ultrasound evaluation *Secondary Endpoints:* Speculum, ultrasound and x-ray evaluation, self-reported outcomes (survey results)
Study Population:	Postpartum women who delivered an infant within the previous 10 days
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	Academic medical centers: the University of California, San Diego (UCSD); University of New Mexico (UNM); University of Illinois, Chicago (UIC); and Naval Medical Center, San Diego (NMCSD)
Description of Study Intervention:	Postpartum insertion of IUDs at 2-4 weeks after delivery vs. 6-8 weeks after delivery
Study Duration:	2 years
Participant Duration:	6 months (with optional 12-month participation offered)

2 INTRODUCTION

2.1 STUDY RATIONALE

Intrauterine devices (IUDs) provide highly effective contraception and are historically placed at the interval six-week PP visit for women who desire intrauterine contraception. Since ovulation can occur as early as 25 days postpartum, there is a risk that women could become pregnant between 4-6 weeks postpartum.
The early postpartum (EPP) period, 2-4 weeks postpartum, could be a convenient time for women to receive contraception, including IUDs. Women can't become pregnant in the first 25 days postpartum. The visit can be co-located with other health care visits, such as well baby visits, that occur in this time frame.
Offering women EPP IUDs may decrease the risk of undesired pregnancy and rapid repeat pregnancy.

2.2 BACKGROUND

Intrauterine devices (IUDs) provide highly effective contraception and are historically placed at the interval six-week postpartum visit for women who desire intrauterine contraception. Since ovulation can occur 25 days postpartum, there is a risk that women could become pregnant between 4-6 weeks postpartum.
Immediate postpartum (IPP) IUD placement, within 10 minutes of delivery, is safe and effective as well as convenient for providers and patients (ACOG, 2016). Despite the benefits of IPP IUD insertion, there are significant barriers to widespread implementation, most importantly a lack of reimbursement mechanisms and training. Although efforts are currently in place to increase access to IPP IUDs, they are developing slowly, and additional strategies are urgently needed to allow for flexibility and multiple options for provision of highly effective contraception in the postpartum period.
Both immediate and interval IUD insertion carry unique risks. IPP IUD insertion is associated with an increased risk of expulsion (IUD being pushed out of the uterus) with rates as high as 24-38% (Chen, 2011; Goldwaithe, 2017) compared to IUDs placed at 6 weeks PP 3-5% (Chen, 2011). However, interval IUD insertion at 6 weeks postpartum is associated with a small increase in the risk of uterine perforation (IUD going through the uterine wall), particularly among breastfeeding women (Heinemann, 2015) and there is a risk that women will become pregnant by 6 weeks postpartum leading to undesired pregnancies and rapid repeat pregnancies.
The early postpartum (EPP) period, 2-4 weeks postpartum, could be a convenient time for women to receive contraception, including IUDs. Women can't become pregnant in the first 25 days postpartum. The visit can be co-located with other health care visits, such as well baby visits, that occur in this time frame.
Three studies have shown that EPP IUD placement is feasible and acceptable (Baldwin 2016, Zerden 2017, Chen 2017). There were no perforations among participants in these studies and no complete expulsions. Partial IUD expulsion rates were low (2-5% at 6 months). However, these studies were not powered to determine IUD expulsion. The purpose of this study is to compare the expulsion rate of EPP IUDs inserted between 2-4 weeks postpartum to the standard placement timing at 6-8 weeks postpartum. This trial will provide a key piece of missing data that will allow women to be counseled appropriately about the benefits and risks of EPP IUD insertion and potentially allow women access to all methods of contraception, including the most effective methods of contraception, at time points earlier than the traditional six-week postpartum visit.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

1. Loss of confidentiality: there is risk of stress, emotional distress, inconvenience, and possible loss of privacy associated with participating in a research study. There will be a need for medical record access to assess patient demographics and clinical outcomes. Most study data will be stored in the HIPAA-secure online REDCap database. Any printed study data (such as consent forms) will be secured in a locked cabinet/filebox, and only those directly involved in the study will have access to these including the investigators who will process the data. Data will only be saved under a secure file on a computer requiring a log-in password. Data will be shared between institutions and UCSD using REDCap, which is a secured HIPAA-compliant web application (*https://redcap.ucsd.edu*). NMCSD is not able to enter data directly into REDCap. NMCSD will, instead, use paper copies of all study instruments and share them via secure fax to UCSD; UCSD staff will enter data into REDCap. Once data is entered into REDCap, UCSD will shred the paper copies. Shared patient identifiers include: patient initials, date of service, baby delivery date. Consent will be obtained in the patient's private postpartum room, in the private clinical space where participant can ask questions without feelings of embarrassment or discomfort, and/or over the phone from a private office. The physical exam will be conducted in a private examination room.
2. IUD expulsion or uterine perforation risk: there is a risk that IUD expulsion and uterine perforation could be greater than in the study group (EPP) compared to the standard of care group. Currently available data suggest that the risk of expulsion and perforation will be less than or equal to the risk of expulsion and perforation associated with the standard of care. There have been over 200 women who have had documented EPP IUDs placed and the risks of expulsion have been low (<4%) and there have been no documented perforations (Baldwin 2016, Zerden 2017, Chen 2017). In addition, ultrasound studies have shown that approximately two-thirds of uterine involution occurs by 14 days PP which could be protective against expulsion (Belachew, 2012) In the EPP period the uterine wall is thicker than 6 weeks postpartum, which could be protective against perforation (Watanagara, 2015). The practice of inserting IUDs at this time is approved and considered to be a category 2 practice (benefits outweigh the risks) from the CDC Medical Eligibility Criteria (CDC, Medical Eligibility Criteria, 2016). However, the data on this practice are minimal and thus there are potential risks to IUD insertion at this time which is why this study is urgently needed.
   All patients will be informed of possible IUD expulsion and uterine perforation (known and unknown). Clinicians may also use ultrasound guidance for placement if they feel that ultrasound will mitigate the risk of expulsion or perforation. Participants will be assessed at a follow-up visit for IUD expulsion and uterine perforation. A study clinician will conduct a bimanual pelvic exam and a transvaginal ultrasound at this visit and provide any care clinically required to address any IUD side effects or complications.
3. There is a risk that an IUD could be placed when a woman is already pregnant. This is true only during the standard of care and it is a potential benefit of the EPP that women cannot yet be pregnant so soon after delivery (ovulation can't occur until at least 25 days postpartum). Any woman who is > 25 days postpartum who has an IUD placed will be assessed for the risk of new pregnancy (will be asked if she has had unprotected intercourse and will be assessed for lactational amenorrhea). If > 25 days postpartum and at risk for pregnancy, then a urine pregnancy test will be done prior to IUD placement and an IUD will not be placed if a urine pregnancy test is positive until new pregnancy has been excluded. A clinician will see the patient and evaluate whether the positive

pregnancy test represents a new pregnancy or residual positive pregnancy test from the recently delivered pregnancy.

2.3.2 KNOWN POTENTIAL BENEFITS

Patients may not experience a direct benefit from participation in this study. However, this study will help determine if IUDs can be provided during the early postpartum period with low expulsion rates and high patient satisfaction rates. There may be a benefit to women in the EPP group to avoid unplanned early repeat pregnancies.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The potential benefit of early postpartum contraception (the potential for decreased unwanted pregnancies, possible decrease in expulsion, and possible decrease in perforation) outweighs the potential risks of increase in expulsion and/or uterine perforation.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine if the risk of complete expulsion of EPP IUDs is non-inferior to interval PP IUDs	Diagnosis of IUD expulsion by speculum and ultrasound exam at 6 months postpartum. Expulsion defined as no IUD within the uterus by ultrasound or x-ray.	We propose that greater than or equal to a 6% difference in expulsion at 6 months postpartum between the two arms is clinically meaningful (6% non-inferiority margin).
Secondary		
To assess the proportion of participants utilizing the IUD at 6 months	Transvaginal and speculum exam to confirm presence of the IUD at 6 months.	From a public health perspective, the duration of IUD use is important for pregnancy prevention.
To determine if the risk of partial expulsion of EPP IUDs is non-inferior to interval PP IUDs	Diagnosis of IUD expulsion by speculum and ultrasound exam at 6 months postpartum. Partial expulsion defined as IUD protruding from the external cervical os on speculum exam or any part of the IUD seen below the internal cervical os on transvaginal ultrasound.	We propose that greater than or equal to a 6% difference in partial expulsion and perforation at 6 months postpartum between the two arms is clinically meaningful (6% non-inferiority margin).
Tertiary/Exploratory		
To assess the risk of perforation after EPP IUD compared to interval postpartum IUDs	IUD not visible in uterus on transvaginal ultrasound, but visible on pelvic x-ray at 6 months.	

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a multi-site, two-arm, non-blinded randomized controlled non-inferiority trial that includes 6 months of participation from enrollment to final follow-up.

Hypothesis: We hypothesize that the EPP IUD expulsion rate at 6 months postpartum will be lower than the reported expulsion rate for IPP IUDs (24%) and non-inferior at a 6% margin to the expulsion rate for interval postpartum IUDs (previously reported at 3-5%).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Traditionally, IUDs are placed at 6-8 weeks postpartum, therefore the standard of care will serve as the control condition. We are using a 6% non-inferiority assuming a 4% expulsions rate in the interval group according to prior research. This difference is presumed to be clinically meaningful.

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study after she has completed all phases of the study including the last visit at 6 months postpartum or the optional 12-month postpartum phone call.

5 STUDY POPULATION

Postpartum women delivering a baby at one of the 4 study sites are eligible: University of California, San Diego (UCSD); University of New Mexico (UNM); University of Illinois, Chicago (UIC), and the Naval Medical Center, San Diego (NMCSD). 404 women will be enrolled between the 4 different study sites. Participants will be screened for eligibility according to the below criteria using a screening checklist. If eligible and interested in participating, a consent form will be signed.

5.1 INCLUSION CRITERIA

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

1) Gave birth less than or equal to 10 days ago
2) Desires to use an IUD for contraception (either copper or levonorgestrel-containing)
3) Willing and able to sign an informed consent
4) Willing to comply with the study protocol
5) Age greater than or equal to 18 years
6) English or Spanish speaking

5.2 EXCLUSION CRITERIA

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

1) Uterine anomaly or leiomyomata which would not allow placement of an IUD
2) Desire for repeat pregnancy in less than 6 months
3) Evidence of intra-uterine infection (chorioamnionitis or postpartum endometritis) treated with antibiotics
4) Ruptured uterus at the time of delivery

5) Received a postpartum tubal ligation or immediate postpartum IUD or implant at delivery
6) Incarcerated women or women with significant cognitive impairment prohibiting consent
7) 4th degree perineal laceration at delivery
8) Any medical contraindication to IUD per the US CDC Medical Eligibility Criteria
9) Any suspicion of new pregnancy

5.3 SCREEN FAILURES

For individuals who do not meet the criteria for participation in this trial (screen failure) due to not meeting eligibility requirements, the reason will be documented. Potential participants who decline participation will be noted and counted as well. No identifying information will be collected from screen failures.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION

Control: IUD placed 6-8 weeks postpartum (standard of care, interval placement)
Intervention: IUD placed 2-4 weeks postpartum (early postpartum placement, EPP)

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Participants will be randomized to receiving EPP or Interval IUD placement by chance with a computer-generated randomization scheme in alternating blocks of 4 and 6 stratified by IUD type and site. The group assignment will be in opaque sealed envelope that will be opened by the research assistant. The participant will not be blinded to the group assignment.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

If a participant chooses not to move forward with placement of an IUD, she will remain in the study under observation. Remaining study procedures should be completed as indicated by the study protocol. Reasons for choosing another method of contraception will be documented and the participant followed for the study duration of 6-12 months.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants may withdraw voluntarily from the study at any time. The PI or study team will not withdraw anyone from the study without specific request from the participant. Medical care will be provided by the patient's clinician as standard of care in the case of study withdrawal. Research participants who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

7.3 LOST TO FOLLOW-UP

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

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

- The sites will attempt to contact the participant and reschedule the missed visit within one week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant, including 3 telephone calls or texts. These contact attempts should be documented in the participant's study file.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

a. Admission/Enrollment Procedure

All women in the 4 study health centers are educated about postpartum contraception during antenatal care. All postpartum women who do not receive an IPP IUD or tubal ligation will be asked if they are interested in the IUD for contraception while on the postpartum floor. If they plan to choose an IUD they will be asked for verbal assent to be pre-screened for the study. If a woman gives verbal consent to be pre-screened, a research assistant will administer the Pre-Participation Questionnaire/Eligibility Checklist. Women who meet inclusion criteria, meet no exclusionary criteria, and want to participate, will be formally consented to participate in the study. Signed informed consent forms will be collected. Subjects will be given copies of the consent document and a copy of the "Experimental Subject's Bill of Rights," and a HIPAA Authorization form for medical data to be released for research purposes. Enrolled participants will then be randomized to EPP or Interval PP IUD placement within 10 days of delivery. The Research Assistant (RA) will open the sealed envelope with the appropriate randomization envelope for the assigned participant number to unblind the participant to her assigned group. Participant numbers are assigned sequentially by each site. Participants will then be asked to complete the Baseline questionnaire.

For women who believe they want an IUD postpartum but are unsure whether or not they would like to be part of the study, study staff will provide them with our contact information, an informed consent form, a Subject's Bill of Rights, and a HIPAA Authorization form for medical data to be released for research purposes. If they decide they are interested in participating while they are still in the hospital, the RA will go to their postpartum floor within 24 hours and will pre-screen/enroll as outlined above. For interested women who are being discharged from the hospital, staff will ask them to call us to discuss the study. Over the phone, the RA will ask for verbal consent to pre-screen for the study. If a woman gives verbal consent to be pre-screened, the RA will administer the Pre-Participation Questionnaire/Eligibility Checklist. For women who meet inclusion criteria, meet no exclusionary criteria, and want to participate, the RA will review the Informed Consent and HIPAA Authorization forms and then ask the woman to sign the forms and bring the signed copies to their first study visit. The woman will be officially enrolled in the study at that point. The RA will then open the randomization envelope and schedule the first study visit at either 2 weeks or 6 weeks postpartum once the consent is

signed. The RA will administer the Enrollment Survey either over the phone or in person before the first research visit.

b. Two Week Postpartum Visit
All women randomized to EPP will be scheduled to have an IUD placement visit with their designated prenatal care provider **between 14 and 28 days**. Women will be scheduled to see a nurse midwife or physician based on their obstetrical history and prenatal care. IUDs will be placed by the patient's usual prenatal provider or any provider that the patient would normally be referred to for IUD placement. Whether ultrasound guidance is used for placement will be at the discretion of the clinician. Participants will be compensated with a $20 gift card for their time and participation after completing the IUD Insertion survey. If a patient in the interval group is seen by her provider at 2 weeks postpartum for other reasons an IUD will not be placed at that visit. Providers will be compensated with a $5 gift card for their time completing a brief questionnaire for every patient seen at 2 weeks who is participating in the study.

c. Six Week Postpartum Visit
All women will be scheduled to have a routine postpartum visit with their designated prenatal care provider **between 42-56 days postpartum** according to the standard of care at the health centers. Women will be scheduled to see a nurse midwife or physician based on their obstetrical history and prenatal care. Women in the interval group will be assessed for IUD placement at this visit per the standard of care at the center. IUDs will be placed by the patient's usual prenatal provider or any provider that the patient would normally be referred to for IUD placement. Whether ultrasound guidance is used for placement will be at the discretion of the clinician. Participants will be compensated with a $20 gift card for their time and participation. Participants will be asked to complete either the insertion visit questionnaire or the string check questionnaire depending on their assignment group. Providers will be compensated with a $5 gift card for their time completing a brief questionnaire for every patient seen at six weeks postpartum.

D. Optional String Check Visit:

Whether a follow-up string check visit is scheduled after six weeks will be at the discretion of the clinician according to standard practice of the clinic. String checks are not recommended by the CDC but are common practice. If a string check is scheduled by the clinician at any time (according to their personal practice or participant needs) then the participant will be asked to complete the string check questionnaire at that time.

e. Six Month Follow Up Visit

All women will be scheduled for a 6-month follow up study visit to assess for IUD expulsion, perforation, pregnancy, IUD removals and acceptability. A study clinician will conduct a bimanual pelvic exam, a speculum exam, and a transvaginal ultrasound at this visit. Women will also be asked to complete the 6-month study questionnaire and will be compensated with a $20 gift card for their time and participation. The clinician will attempt to stay blinded to the participant's group assignment by not reviewing the medical chart prior to the visit.

f. 12 Month Optional Follow Up Call

During baseline survey data collection, all women will be asked if they consent to a 12-month follow up phone call to assess for IUD expulsion, perforation, pregnancy, IUD removals and acceptability.

8.2 SAFETY AND OTHER ASSESSMENTS

We will convene a Data Safety and Monitoring Board (DSMB) to review adverse events if any of the following occur:

- At the midpoint of enrollment
- If there is 1/3rd the expected enrollment at 6 months
- More than four serious adverse events at any time deemed definitely, probably, or potentially related to the intervention
- Rate of any serious adverse events is greater than 1% (including blood transfusion, hospitalization related to IUD, surgery related to IUD, death, IUD perforation, venous thromboembolism)

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

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

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

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

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

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

OR

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (DE challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

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

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

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

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

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

All adverse events will be reported to all three IRBs in a timely fashion (UCSD, UNM, UIC, and NMCSD) regardless of where the adverse event occurred. The on-site PI at each site will be responsible for monitoring adverse events and report any adverse events to each PI who will, in turn, report to their associated IRB. The management of information that is relevant to the protection of participants including adverse events, UPRs, protocol violations/deviations, interim results and protocol modifications will be the responsibility of each local PI at each site (Dr. Averbach- UCSD, Dr. Hofler - UNM, Dr. Stortz – NMCSD, Dr. Hinz – UIC).

8.3.6 SERIOUS ADVERSE EVENT REPORTING

All serious adverse events will be reported to all three IRBs in a timely fashion (UCSD, UNM UIC, and NMCSD) regardless of where the adverse event occurred. The on-site PI at each site will be responsible for monitoring adverse events and report any adverse events to each PI who will, in turn, report to their associated IRB.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

The IRB at each site will provide guidance to PIs on informing participants regarding AEs and SAEs as needed.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

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

8.4.2 UNANTICIPATED PROBLEM REPORTING

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

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

To satisfy the requirement for prompt reporting, UPs will be reported to the IRB within reasonable timing of the investigator becoming aware of the problem.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

The IRB at each site will provide guidance to PIs on informing participants regarding UPs as needed.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint: Complete expulsion of IUDs placed in the early postpartum is non-inferior to IUDs placed at the standard interval time, assuming a 6% non-inferiority margin.

- Secondary Efficacy Endpoints:
    - The proportion of participants utilizing the IUD at 6 months postpartum will be greater in the EPP group compared to the interval group.
    - Partial expulsion of IUDs placed in the early postpartum is non-inferior to IUDs placed at the standard interval time, assuming a 6% non-inferiority margin.
    - There will not be a clinically or statistically significant difference in the proportion of participants diagnosed with a pelvic infection.
    - Proportion of participants agreeing or strongly agreeing that they are satisfied with the IUD, and the timing of IUD placement, will be similar between groups.

9.2 SAMPLE SIZE DETERMINATION

We hypothesize that EPP IUD expulsion will be non-inferior to interval insertion. We propose that greater than or equal to a 6% difference in expulsion at 6 months postpartum between the two arms is clinically meaningful (6% non-inferiority margin). Therefore, we estimate that 404 women will be needed [202 in each arm] to achieve an 80% power to detect a difference of 6% in expulsion at 6 months at a significance level of .05 (two-sided alpha), assuming a 15% loss to follow up and that 5% of IUDs would not be placed after randomization (due to patient preference or new medical contraindication or inability to place the IUDs) and assuming a 4% expulsion rate in the interval group. We estimate that enrolling 404 patients allows us to achieve an 80% power to detect a difference of 6% or more between groups with a 1-sided type 1 error of 0.25%.

9.3 POPULATIONS FOR ANALYSES

The following datasets will be utilized for analysis:

- Intention-to-Treat Analysis Dataset: All participants randomized with known outcomes at the 6 month follow up visit*.
- Modified Intention-to-Treat Analysis Dataset: Participants who received an IUD within 6 months of delivery with known outcomes at the 6 month follow up visit*.
- Per-Protocol Analysis Dataset: Participants who received an IUD within the specified timeframe as designated by their group assignment with known outcomes at the 6 month follow up visit (14-28 days in the early group and 42-56 days in the interval group)*.

*participants known to have an IUD outcome by ultrasonography, pelvic examination, or a contact up to 240 days postpartum will be included.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Our primary outcome, the proportion of women with complete IUD expulsion at 6 months after delivery in the two groups, will be compared in the modified intention-to-treat (MITT) cohort using the Wald test. Women who change their mind about receiving the IUD after randomization, choose to receive the IUD after 6 months, or women who choose not to participate in the study any time after randomization, will be excluded from analysis for the MITT analysis. In addition, we will present a per-protocol analysis. The per-protocol analysis will include women who received their treatment according to the timeframe in which they were randomized. For the early IUD insertion group, per-protocol analysis will include women with documented receipt of the IUD insertion between 14 and 28 days postpartum. For the interval IUD insertion group, the per-protocol analysis will include only women with documented receipt of a postpartum IUD between 42-56 days postpartum. In both the MITT and per-protocol analyses IUD expulsion rates will be compared using the 2-sided test of noninferiority. If the CI for the risk difference does not cross the prespecified 6% margin, noninferiority will be confirmed.

We will consider imputing missing data. However, if one group had no or few expulsion outcomes the model may not converge.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Partial IUD expulsion and perforation will be analyzed with the same methods as the primary outcome. IUD discontinuation over the six-month study period will also be analyzed using survival analysis. Data will be censored either (1) at the last date of contact if a participant is lost to follow up or (2) time of IUD removal. The Log-rank test will be used for an unadjusted comparison of the two survival functions. This will be presented graphically using Kaplan-Meier curves.

For other secondary outcomes, normally distributed, continuous variables will be compared using Student's t-tests as appropriate. The Mann-Whitney U test will be used to compare other continuous variables that are not normally distributed. Proportions will be compared using chi-square tests. For small cell sizes, Fisher's exact test will be used as appropriate.

9.4.4 SAFETY ANALYSES

AEs and SAEs will be recorded by the study team when they become aware. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be presented in a table.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics such as demographic information (age, education level, race, ethnicity and employment status) will be collected. At the time of enrollment, questions will also be asked about pregnancy history, past use of contraception, breastfeeding status and future fertility desires. Means and proportions of respondents in each of the two groups will be compared to assess for success of randomization.

9.4.6 PLANNED INTERIM ANALYSES

Interim analyses will be carried out only when the conditions to convene a DSMB are met.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 STUDY DISCONTINUATION AND CLOSURE

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

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and/or IRB.

10.1.2 STUDY GOVERNANCE

The name and contact information of the Principal Investigator:

Sarah Averbach, MD, MAS, Associate Professor
University of California, San Diego
9500 Gilman Drive, La Jolla, CA, 92093
858-329-4464
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10.1.3 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including statistics and clinical. Members of the DSMB will be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet if the study meets the pre-specified conditions described in section 8.2. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the research team and IRBs as required.

10.1.4 CLINICAL MONITORING

Data verification will take place every 6 months by site PIs, who will report to the study PI at UCSD. This will ensure data completeness and monitor safety of participants.

10.1.5 DATA HANDLING AND RECORD KEEPING

10.1.5.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

10.1.5.2 STUDY RECORDS RETENTION

Study documents will be retained for 2 years after the formal completion of the study.

10.1.6 PROTOCOL DEVIATIONS

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

11 REFERENCES

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12 ABBREVIATIONS

AE	Adverse Event
DSMB	Data Safety and Monitoring Board
EPP	Early Postpartum
IRB	Institutional Review Board
IUD	Intrauterine Device
IPP	Immediate Postpartum
MITT	Modified Intention-To-Treat
NMCSD	Naval Medical Center, San Diego
N/A	Not applicable
OHRP	The Office for Human Research Protections
PI	Principal Investigator
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
UCSD	University of California, San Diego
UIC	University of Illinois, Chicago
UNM	University of New Mexico