PROTOCOL TITLE:

Effect of immediate versus standard postpartum insertion of the contraceptive implant on breastfeeding outcomes

PRINCIPAL INVESTIGATOR:

Jamie Krashin, MD
OBGYN

ADMINISTRATIVE CONTACT:

Cassandra Darley

OBGYN

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REGULATORY FRAMEWORK:

Please indicate all that apply:

☐	DOD (Department of Defense)
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Is this a clinical trial under ICH-GCP E6? ☒ Yes ☐ No

If yes, please confirm that the research team is familiar with and agrees to comply with the investigator requirements cited in ICH-GCP E6. ☒ Yes ☐ No

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1. Objectives

1.1. We propose a non-inferiority randomized controlled trial (RCT) with a primary outcome of lactation continuation through 8 weeks postpartum comparing women receiving immediate (first 24 hours postpartum) versus standard (4-6 weeks postpartum) etonogestrel (ENG) implant insertion. Secondary outcomes include: number of days of postpartum bleeding, time to resumption of sexual activity, postpartum sexual function (measured by Female Sexual Function Index (FSFI) score), and postpartum mood as measured by Edinburgh Postnatal Depression Scale (EPDS) score. We will also measure breastfeeding exclusivity, factors effecting discontinuation of breastfeeding, timing of breast feeding discontinuation, satisfaction with postpartum contraceptive counseling, satisfaction with the contraceptive implant and satisfaction with bleeding pattern in the immediate and standard groups.

1.2. The contribution of the proposed research is to determine if immediate ENG implant insertion (within 24 hours) is non-inferior to standard insertion (4-6 weeks) postpartum. We hypothesize that inserting the ENG implant in the first 24 hours postpartum is not inferior to standard insertion at 4-6 week postpartum for breastfeeding continuation through 8 weeks postpartum.

1.2.1. Primary Objective 1: To compare continuation of lactation through eight weeks postpartum between women in the immediate versus standard group. Our hypothesis is that breastfeeding continuation at eight weeks postpartum is not inferior in women in the immediate insertion group of the ENG implant than in those with standard insertion. Our study is powered for this outcome.

1.3. Secondary Objectives: To compare number of days of postpartum bleeding, postpartum sexual function as measured by FSFI score, and postpartum mood as measured by EPDS score, time to resumption of sexual activity, exclusive breastfeeding method, factors associated with discontinuing breastfeeding, timing of breastfeeding discontinuation, patient satisfaction with postpartum contraception counseling and the implant and patient satisfaction with bleeding pattern between the immediate and standard insertion groups.

1.3.1. Secondary Objective 1: To compare the total number of days of postpartum bleeding in the immediate versus standard group at 2, 4, and 8 weeks postpartum . Our hypothesis is that number of days of bleeding in the immediate insertion group is not significantly different than the number of days of bleeding in the standard insertion group.

1.3.2. Secondary Objective 2: To compare postpartum sexual function as measured by Female Sexual Function Index (FSFI) score at 4, 8, and 12 weeks postpartum. Our hypothesis is that FSFI scores for the immediate insertion group are not significantly different than FSFI scores for the standard insertion group.

1.3.3. Secondary Objective 3: To compare postpartum mood as measured by EPDS score at 2, 4, and 8weeks postpartum. Our hypothesis is that EPDS scores for the immediate insertion group are not significantly different than EPDS scores for the standard insertion group.

1.3.4. Secondary Objectives 4: To compare exclusive breastfeeding through 6 months postpartum between the immediate versus the standard group.

1.3.5. Secondary Objective 5: To compare postpartum factors associated with discontinuing breastfeeding between the immediate versus the standard group.

1.3.6. Secondary Objective 6: To compare timing of breastfeeding discontinuation through 6 months postpartum between the immediate versus the standard group.

1.3.7. Secondary Objective 7: To compare participant satisfaction with postpartum contraception counseling in women enrolled in the study and in those women who opted not to enroll in the study.

1.3.8. Secondary Objective 8: To compare participant satisfaction with timing of ENG implant insertion between the immediate versus the standard group.

2. Background

2.1. Regarding primary objectives:

Counseling and provision of postpartum contraception is an integral component of comprehensive reproductive healthcare. A woman's preference for contraception is paramount; early initiation of postpartum contraception may assist in optimal birth spacing promoting the wellbeing of mother and baby (1). Equally important is the provision of appropriate support for breastfeeding (1). Exclusive breastfeeding for six months with continuation beyond one year of age is recommended by the American Academy of Pediatrics (AAP) (2), American Academy of Family Physicians (3), American College of Obstetricians and Gynecologists (ACOG) (4), and the World Health Organization (WHO) (5). In the United States, approximately 47% and 25% of women breastfeed exclusively at three and six months respectively, and 57% and 36% of women who supplement with formula continue breastfeeding at three and six months respectively (6).

Current recommendations advise against use of combined hormonal contraceptives in the first 4-6 weeks postpartum due to the hypercoagulable state of pregnancy and the high risk for thrombogenic events (7). Progestin-only hormonal contraceptive methods are considered appropriate for initiation in the postpartum period including the ENG subdermal implant, the levonorgestrel intrauterine device (LNG IUD), and the depot medroxyprogesterone acetate injection (8). However, because lactogenesis is precipitated by progesterone withdrawal after placental expulsion, early initiation of progestin-containing

contraception could theoretically decrease lactogenesis and breastfeeding continuation (9). Due to this theoretical concern, immediate postpartum use of progestin contraceptives by breastfeeding women is classified as Category 2 (benefits of use outweigh any theoretical or proven risks) the *United States Medical Eligibility Criteria for Contraceptive Use, 2016* (US MEC) (8). This classification balances the theoretical concern with a handful of reassuring studies. A University of New Mexico and University of Utah 2016 study found no differences in breastfeeding continuation and time to lactogenesis between groups randomized to immediate postpartum LNG IUD placement versus standard insertion at 4-6 weeks (10). In 2017 a Cochrane review evaluated three studies of immediate postpartum insertion of the ENG implant versus standard insertion; it was unable to determine a statistically significant effect of insertion timing on breastfeeding continuation rates (11). The literature on the implant and breastfeeding outcomes is limited by a small sample size and variable timing of implant initiation within the first 3 days postpartum in "immediate" allocation groups (12-13). Despite limitations, studies of progestin-only methods showed no differences in lactogenesis, infant growth, and lactation continuation (12-14). Additional studies with the implant are needed to precisely define postpartum initiation, better inform evidence-based contraceptives guidelines, and to assist in the provision of evidence-based counseling about the effects of immediate postpartum implant insertion.

Regarding secondary objectives:

When counseling women on their postpartum contraception options, it is important to address patient-centered outcomes that affect patient satisfaction with their contraceptive method and may affect continuation rates of highly effective contraception that they initially selected to support their reproductive goals. We have chosen bleeding pattern, mood and sexual function as the eight domains that we will assess and compare between the immediate and standard insertion groups as they are domains commonly perceived as affected negatively by contraceptives. In addition, we will measure breastfeeding discontinuation and reasons for discontinuation through 8 weeks postpartum. These are important outcomes in alignment with recommendations from several professional organizations and the WHO.

2.2. Regarding primary objectives:

A systematic review identified 50 studies of progestin-only contraception and breastfeeding (13). These studies can be divided into those that focus on breastfeeding performance (initiation, continuation, and exclusivity) and those that focus on infant health and growth. Fewer than ten studies focus on use of the contraceptive implant and breastfeeding performance, of which only two measure outcomes related to immediate insertion versus standard insertion (5,12). In Guttcheff et al., a RCT in healthy postpartum women was performed to evaluate time to lactogenesis stage II between early ENG implant insertion (1-3 days

postpartum (PP)) and standard insertion (4-8 weeks PP). The authors demonstrated that early insertion is non-inferior to standard insertion with a mean difference of 1.4 hours. In addition, no differences were found between the early insertion group and standard insertion group for incidence of lactation failure, breastfeeding, formula supplementation and breastfeeding continuation at 6 months. Bryant et al., studied immediate (before leaving the hospital) versus standard (at 6 weeks PP) insertion of the ENG implant in adolescent and young women age 14-24 years old. Their primary outcome was contraceptive use at six months. No difference was found in contraceptive use between the two groups at six months. The rate of lactation continuation at three and six months was higher in the immediate insertion group.

2.3. *Regarding primary objectives:*

Prior studies lack specific data on timing of early postpartum implant use and the effect on breastfeeding. The contribution of the proposed research is to add to the limited literature on immediate postpartum contraception options and, specifically, to evaluate the impact of initiating ENG implants within the first 24 hours on breastfeeding continuation. The lack of precise timing for immediate postpartum progestin initiation was cited as an important research gap in the US MEC (8). Additionally, more and more state Medicaid programs are reimbursing for implant insertion prior to the hospital discharge (16). It is important to make sure that this increasing trend is supported by the best possible evidence.

Regarding secondary objectives:

1. Bleeding patterns: Irregular bleeding is the most common side effect noted by users of the ENG contraceptive implant. Limited evidence shows that this holds true in the postpartum period (17). In a retrospective cohort study of women who underwent immediate versus standard postpartum insertion of the implant, approximately one in five women requested discontinuation of use due to irregular bleeding, and this rate was not significantly different between the two groups (17). Evidence on the effect of immediate postpartum insertion of the ENG contraceptive implant on lochia is limited and mixed. An RCT of immediate versus standard postpartum insertion of the six-rod levonorgestrel implant showed significantly more total days of bleeding for the immediate insertion group (18), while a more recent Australian prospective cohort study demonstrated no lengthening of the duration of lochia (postpartum bleeding) with immediate insertion (19). We will measure postpartum bleeding patterns using periodic review of a patient bleeding diary that quantifies bleeding on a daily basis as “none”, “spotting”, “bleeding” or “heavy bleeding”. As patient dissatisfaction with irregular bleeding likely mediates discontinuation for this reason, we will also measure patient satisfaction with their bleeding pattern postpartum.

2. Postpartum mood changes: It is possible that postpartum use of an ENG implant may affect postpartum mood. In a retrospective study of adverse event reporting for ENG implant use, it was noted that postpartum depression was a commonly reported adverse event, and therefore may be associated with implant use in the postpartum period (20). In addition, in a secondary analysis study, use of the ENG implant in the postpartum period was associated with a higher risk of later antidepressant use compared to women with no hormonal contraceptive use (21). Women's perception of contraceptives' effect on their mood is a significant factor in contraception discontinuation (22). We hypothesize that timing of implant insertion will not increase postpartum depression related mood changes as measured by the EPDS. We will also assess patient perception of impact of ENG implant insertion on mood.

3. Postpartum sexual function: Effect of postpartum ENG implant use on postpartum sexual function is not well studied. However, in a 2016 study of impact of LARC use on sexual function (not in the postpartum period), it was noted that there was no objective change in sexual function with initiation of copper IUD, levonorgestrel IUDs or ENG implant (24). We hypothesize that this is also true in the postpartum period and that the effect of timing of ENG implant insertion will not affect postpartum sexual function as measured by the FSFI. The FSFI is a validated tool for assessing female sexual function that been used in the aforementioned studies, both in assessing LARC effects and in the postpartum period (25). Patient perceptions of the effect of their contraceptive on sexual experience may affect contraceptive continuation rates regardless of objective findings on sexual function. In a 2018 study of the impact of sexual function and perceived effect of contraceptive method on sexual experience on continuation rates of multiple LARCs, patients' perception of a negative impact of the contraceptive on sex life was the strongest predictor of discontinuation (26). We will assess patient centered perception of impact of ENG implant insertion on sexual function.

4. Postpartum exclusive breastfeeding through 6 months postpartum: Receiving only breast milk is known as exclusive breastfeeding (EBF). AAP and WHO promote EBF for the first six month of life of infants because it provides multiple health benefits to babies and to the mother (1,5). Nationally, 46.9 % and 24.9%of women exclusively breastfeed at 3 and 6 months, respectively; in New Mexico 53.0% and 27.6% breastfeed exclusively at 3 and 6 months, respectively (6). Since this data does not provide information about the mothers who use contraception and how many of the exclusively breastfeed, we will assess this information.

5. Factors associated with breastfeeding discontinuation: As mentioned previously, EBF is recommended for 6 months postpartum by the AAP and WHO. It is important to identify and acknowledge these factors to work and plan for counseling and initiatives to improve the length of lactation period. These factors can vary depending of society, culture and even mother's perception. Li et al reported the most common reasons for breastfeeding discontinuation during the first year postpartum were mothers' perception that their infant was not satisfied by breast milk alone and concerns about lactation and nutrition issue. In addition, mothers reported nipple biting and perceived infant loss of interest in breastfeeding (27). Odom et al, found in their study that factors such as difficulties with lactation, infant nutrition and weight, effort to pumping milk, among many others, play an important role in the decision making for lactation cessation (28). With this study, we aim to assess the reason for discontinuation in the mothers who use the implant as a contraceptive method.

6. Satisfaction with postpartum contraception counseling: The American College of Obstetricians and Gynecologists (ACOG) stated in Committee Opinion number 736: Optimizing Postpartum Care that as part of comprehensive postpartum care acknowledging women's reproductive life plan is of vital importance for decision making regarding contraception (1). We aim to explore by a survey how women perceived the counseling: if she understood the counseling and received enough information and time to make a decision about contraceptive choice. This might help to understand women's perception of counseling about postpartum contraception and may be helpful in improving current counseling.

7. Satisfaction with timing of contraceptive implant insertion: Early initiation of a contraceptive method has been recommended as an alternative by ACOG (1). This is because it has been proven that many women miss or do not have a postpartum follow up visit and it is more convenient for women to initiate a method early. When a contraceptive method is started in the postpartum period, it contributes to birth spacing, and maternal and infant wellbeing. We look to understand the satisfaction with having an implant inserted early vs having it inserted in the standard time.

3. Study Design

3.1. This RCT will be performed at the University of New Mexico Hospitalits affiliated clinics and the University of Utah and its affiliated clinics. The study design was chosen as the gold standard for determining cause and effect; it is methodologically strong and feasible for our research questions. RCTs minimize bias such as that related to treatment assignment (e.g., selection bias and confounding).

The two study groups will include women randomized to immediate (within 24 hours postpartum) versus standard (4-6 weeks postpartum) ENG implant insertion. The primary study endpoint is any breastfeeding at eight weeks postpartum; we will also measure breastfeeding continuation at 2, 4, 8, 12 and 24 weeks postpartum. Participants will be pregnant women 13 years old and older, who desire the ENG implant as a postpartum contraceptive and are willing to be randomized to immediate implant insertion (within 24 hours postpartum) versus standard insertion (4-6 weeks postpartum). A total of 150 participants, 75 in each group, will be enrolled to ensure adequate power to determine the primary outcomes, after anticipated loss to follow up.

4. Inclusion and Exclusion Criteria

4.1. Potential participants may be identified in the following locations/timeframes: 1) antenatal clinics, 2) visits to OB-Triage 2) on admission to L&D for delivery not in active labor or 4) during the first postpartum hours in the Ob-Gyn ward of the UNM Hospital and University of Utah Hospital.

- When women decide on an implant as a postpartum contraceptive in any of these venues, the PCP (Ob-Gyn, Family Medicine physicians/residents and midwives) may discuss the patient's interest in hearing about the study and may contact the research coordinator by a message in the EMR or by phone or in person to let her know that the patient is interested in hearing about the study.
- Additionally, the research coordinator will review antenatal clinic, OB Triage and inpatient (L&D and postpartum) lists to assess patients' contraceptive plan through review of the EMR.
- If the patient expresses interest, the research coordinator and/or a study co-investigator will explain the study, screen the patient for eligibility and obtain informed consent.
    - *Note: Hepatitis C will not be considered an exclusion criterion. Mothers with Hepatitis C can breastfeed per the Centers for Disease Control and Prevention. However, HCV is spread by infected blood. Therefore, if the HCV-positive mothers'nipples and/or surrounding areola are cracked and bleeding, she should stop nursing temporarily. To maintain her milk supply while not breastfeeding, she can express and discard her breast milk until her nipples are healed. Once her nipples are no longer cracked or bleeding, the HCV-positive mother may fully resume breastfeeding. If we identify a mother with hepatitis C, we will assess through follow up questionnaires when they stopped breastfeeding, if they continued to express milk during the period of no lactation and when they restarted lactation.*
    - *Note: We will continue enrollment in the study for all women regardless of the infants' status; we will perform a secondary sub-group analysis of women/infants with complications in order to improve the ability to generalize from the study.*

We request a waiver of HIPAA for screening/recruitment purposes.

4.2. Inclusion Criteria

- Pregnant women or women who have delivered vaginally and by cesarean section within 22 hours (2 hour window will allow for implant insertion by 24 hours postpartum)
- Aged 13 and older
- English or Spanish speakers
- Deliver an infant at UNM or Utah Hospital at ≥ 37 weeks gestational age
- Intend to breastfeed
- Desire the implant as a method for contraception
- Agree to randomization
- Must have a working phone (study questions to be answered through phone calls or accessed electronically by a link sent through email or text message)

Exclusion Criteria

- Under age 13
- History of breast cancer (screen by past medical history)
- History of undiagnosed vaginal bleeding (screen by past medical history)
- Head trauma that affected pituitary function (screen by past medical history)
- Prolactin insufficiency (screen by past medical history)
- Previous lactation failure (defined as no lactation within 5 days postpartum)
- Any contraindication to lactation/implant use including diseases transmittable by breast milk (screen by past medical history)
- Liver dysfunction (screen by past medical history)
- Use of drugs that inhibit lactation (screen by medical history)
- Sensitivity to the components of the ENG implant (screen by past medical history)
- Contraindications to use the implant by the (US MEC) (screen by past medical history)
- Active labor
- Delivery at < 37 weeks gestational age

There is a description of different inclusion/exclusion criteria between the sites. UNM Is recruiting minors under age 18 and over the age of 13, and the University of Utah is not recruiting minors. This is the only difference in the protocols.

4.3. This study will include pregnant adolescent and adult women. This study will not recruit adults who are unable to consent or women who are incarcerated.

4.4. This study will recruit women who can speak and read English and/or Spanish fluently.

5. Number of Subjects

5.1 NA

5.2. This is a multi-site study. Through the University of New Mexico Hospital, its affiliated clinics and the University of Utah and its affiliated clinics. We will recruit up to 200 participants between both study sites.

5.3. Up to 200 participants will be enrolled, with a goal of 75 in each group, to ensure adequate power to determine the primary outcome, after anticipated loss to follow up.

This study is a non-inferiority trial designed to demonstrate that immediate postpartum insertion of the ENG implant is non-inferior to standard ENG implant insertion with respect to the proportion of women who discontinue breastfeeding by 8 weeks after delivery. Discontinuation of breastfeeding under the current treatment, standard insertion, is expected to be 30% based on previous studies (10, 15). To achieve 80% power with a 1-sided Type 1 error of 5% utilizing the Z test (unpooled), 62 participants are required in each group for a total of 124. Accounting for expected loss to follow up of 20%, the total number of participants required is 149, rounded to 150. We intend to enroll up to 200 participants due to unanticipated loss to follow up, so this should ensure that we have enough data for data analysis.

6. Study Timelines

6.1. The estimated total of duration of the study is 18 months. Participants will be followed for 24 weeks (please see timeline below and further specific details on data collection in Section 12). Enrollment is estimated to start at the beginning of 2019. All participants will be recruited within a one-year time frame. The research project will conclude once all enrolled participants have been followed for 6 months and completed the questionnaires. Primary analyses will begin once all study participant complete the 8 weeks follow-up to accomplish the analysis for the primary outcomes.

* primary outcomes

7. Study Endpoints

	Screen-ing	First 24 hours Post partum	1-7 days*	2 weeks	4 weeks	6 weeks	8 weeks	12 weeks	24 weeks END	Up to 1 year pp	Up to 5 years pp
Intake	X										
Postpartum contraception counseling satisfaction survey	X				X						
Device Insert		X			X	X					
Exclusive breastfeeding			X	X	X		X	X	X		
Breastfeeding discontinuation				X	X		X	X	X		
Retrospective Breastfeeding Discontinuation Chart Review Form										X	
Contraceptive use			X		X		X	X	X		X
Diary collection				X	X		X				
Mood (EPDS)				X	X		X				
Sexual function (FSFI)					X		X	X			
Bleeding log review				X	X		X				

7.1. The primary endpoint of this research are to compare continuation of lactation at eight week postpartum between women in the immediate with standard group.

The secondary endpoints of this research are to compare number of days of postpartum bleeding, postpartum sexual function as measured by FSFI score, and postpartum mood as measured by EPDS score, time to resumption of sexual activity, exclusive breastfeeding method, factors associated with discontinuing breastfeeding, timing of breastfeeding discontinuation, patient satisfaction with postpartum contraception counseling and the implant and patient satisfaction with bleeding pattern between the immediate and standard insertion groups.

As in other studies of breastfeeding and hormonal contraception, we will continue to follow women out to 6 months. A survival analysis will be performed to determine longer-term effect of hormonal contraception on breastfeeding.

7.2. The primary study endpoint is also a safety endpoint: breastfeeding continuation through 8 weeks. We have developed a Data Safety and Monitoring Plan related to these endpoints (please see below).

7.3. No exploratory endpoints will be conducted in this research.

8. Research Setting

8.1. Our study will be conducted at multiple clinical sites: the University of New Mexico Hospital, its affiliated clinics and the University of Utah Hospital and its affiliated clinics. These clinical sites are well versed in managing the competing demands of a busy clinical schedule and robust research. This site is part of a Clinical Translational Science Center and the project will be overseen by the University of New Mexico Department of Obstetrics and Gynecology, Family Planning Division with contribution to patient recruitment from the Division of Midwifery and the Department of Family and Community Medicine. The primary investigator of the study is Dr. Jamie Krashin and the faculty mentors are Dr. Eve Espey and Dr. Lawrence Leeman at UNM and Dr. David Turok at the University of Utah. Progress on the project will also be followed by the Fellowship in Family Planning as part of fellowship graduation requirements.

8.2 Patients may be recruited in the following locations/timeframes: 1) antenatal clinics, 2) visits to OB-Triage 2) on admission to L&D for delivery not in active labor or 4) during the first postpartum hours in the Ob-Gyn ward of the UNM and Utah's Hospital. Recruitment may occur remotely.

8.2.The implant insertions will be performed in the UNM Hospital and the University of Utah Hospital for immediate insertion group and in the affiliated clinics for the standard insertion group

Recruitment and research procedure locations:

UNM's Labor and Delivery UNM Westside Clinic UNM Northeast Heights Clinic UNM Southeast Heights Clinic Los Lunas First Choice UNM Women's Health Clinic	UNM Faculty and Midwife Clinic UNM Maternity and Family Planning Clinics UNM Center for Reproductive Health UNM Triage/ OB Special Care Units UNM Family Practice Center / Tucker First Nations Clinic
Utah's Labor and Delivery Utah's associated clinics	

8.4. No community advisory board will participate in this study.
8.5. No research will be conducted outside of UNM HSC and its affiliates.

9. Resources Available

9.1. The PI is a board certified obstetrician-gynecologist with subspecialty training in Family Planning. She has a Master of Science in Clinical Research and was the PI on a 600-participant cohort study that was published in a leading OBGYN peer reviewed journal. She recently published an analysis of immediate postpartum contraceptive implant initiation and breastfeeding continuation. Dr. Krashin spent the previous two years working on the US MEC as a guest researcher. In that role, she presented the data behind CDC's hormonal contraception and breastfeeding recommendations at the Academy of Breastfeeding Medicine's Annual Meeting 2017 and at Grand Rounds for the Medical University of South Carolina in 2018. Also, the Family Planning Research team at the University of New Mexico has successfully conducted a similar RCT of early versus standard insertion of levonorgestrel IUD and impact on breastfeeding. Similar enrollment and data collection policies will be employed for this study.

9.2. All licensed physicians/providers who will be inserting the implant are responsible for medical decision-making, ordering, and evaluation of necessary diagnostics and therapeutics.

9.3. There are ample patients available to participate in this trial as approximately 200 of the 3000 women who deliver at the University of New Mexico have the ENG implant for postpartum contraception inserted before being discharged after delivery. The time that will be devoted to conducting and completing the research is 18 months. The research will be conducted at the UNM Hospital and its affiliated clinics and University of Utah Hospital and its affiliated clinics. The UNM and University of Utah systems have available medical and psychological resources for participants that might need it as a result of an anticipated consequences of the human research. In addition, all persons assisting with the research will be adequately informed about the protocol, the research procedures, and their duties and function through a process of training

10. Prior Approvals

10.1. The national office for the Fellowship in Family Planning approved the research as part for the requirement for completion of the fellowship.

10.2. See attachment.

10.3. No ionizing radiation will be used in this study.

10.4. No biological specimen will collected for this study.

11. Multi-Site Research

11.1. UNM is the lead coordinating site and Dr. Krashin is the lead investigator. This will be a multi-site study in which University of Utah will be an external site for recruitment of participants. All sites have the most current version of the protocol, consent document and HIPAA authorization. All required approvals will be obtained by the UNM IRB and University of Utah's IRB.

The University of Utah will have their side of the study reviewed by the University of Utah IRB and the University of New Mexico will have the UNM IRB reviewing this protocol. The only exchange of patient information is from the University of Utah to the University of New Mexico. All modifications will be communicated to the external sites and approved before the modifications are implemented. All engaged participating sites will safeguard data as required by local information security policies. All local site investigators will conduct the study appropriately. All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

11.2. We will have regularly scheduled contact bi-monthly and potentially monthly as the research progresses to ensure that any adverse events, problems, interim results, data monitoring, and closure of a study are communicated.

11.3. NA.This is not an FDA regulated trial

12.Study Procedures

12.1 NA

12.2 Patients may be recruited in the following locations/timeframes: 1) antenatal clinics, 2) visits to OB-Triage 2) on admission to L&D for delivery not in active labor or 4) during the first postpartum hours in the Ob-Gyn ward of the UNM Hospital and University of Utah Hospital and its associated clinics.

- Patients may be asked for their contraceptive choice in any of these four venues, although ideally in antenatal clinics during prenatal care. When women decide on an implant as a postpartum contraceptive in any of these venues, the PCP (Ob-Gyn, Family Medicine physicians/residents and midwives) may discuss the patient's interest in hearing about the study and may contact the research coordinator by a message in the EMR or by phone or in person to let her know that the patient is interested in hearing about the study.
- Additionally, the research coordinator will review antenatal clinic, OB Triage and inpatient (L&D and postpartum) lists to assess patients' contraceptive plan through review of the EMR. The research coordinator may contact patients who have decided on a postpartum implant to assess her interest in participating in the study.
- If the patient expresses interest, the research coordinator will present the study and ask the patient for her interest in enrolling. If interested, the research coordinator and/or a study co-investigator will explain the study, screen for eligibility and obtain informed consent. Participants can also be consented remotely by phone call or via zoom conference. In the case of remote consent, we will obtain written consent via e-mail or mail due to the current pandemic and research coordinators working from home. We will also allow participants to consent via e-signature via the eConsent feature in the UNM HSC REDCap system if they have that capability. The screen for eligibility will be done by interview and assessment of past medical history with standardized set of questions.

- Women will not be approached for study participation if they are in active labor. Women will be approached and enrolled, if interested, either prior to active labor (e.g., when admitted for induction of labor or scheduled cesarean delivery) or after delivery.
- Once the woman is enrolled in the study a line will be added to the Antenatal Supplemental Visit Form stipulating the patient's participation in the study and the coordinator's phone number: Ex: "Rivera-Montalvo study patient – page at admission ###-####**." This Form is a section of the EMR that is updated at each visit by the clinic provider with important/current antenatal issues; it is standard that the contraceptive plan for each patient is recorded here.

Identification of study patients on L&D

- The PCP on L&D may identify study patients who self-identify as being in the study. They will also be alerted by the "Study Patient" in the antepartum record if the patient has been enrolled antepartum. They will notify the research coordinator who will carry a phone during working hours.
- A reproductive health on-call fellow/attending will be designated 24-7 to ensure randomization and implant insertion within 24 hours for those randomized to the immediate group. After hours (nights and weekends), the research cell will forward to the reproductive health on-call fellow or attending. In addition, the voice message for the research cell will direct callers to contact the reproductive health on-call fellow through Amion, the hospital online paging system. A calendar will specify which co-investigator is on call for study patients.
- The PCP on L&D will call the research coordinator/call physician by phone or by text message that a study patient arrived on L&D for her birth.
- The research coordinator will review the list of admitted patients to L&D twice a day (8 AM and 4 PM) and once daily on Mother Baby Unit and Ob-Special care the (Ob-Gyn wards) to identify enrolled study patients. This modality has been used with other studies in the department of Ob-Gyn and has been successful.

Randomization

- University of Utah coordinators will have access to UNM's REDCap to obtain randomization and enter any data collected for their participants.
- The research coordinator will access REDCap to obtain the randomization assignment for study patients (enrolled antepartum or on L&D not in labor) shortly after admission to L&D for a birth. The reproductive health physician on call will be notified
- For patients enrolled postpartum, the research coordinator will randomize the patient as soon after consent is signed or verbally agreed to and within 22 hours after birth to ensure implant placement for those randomized to the immediate group within 24 hours. For those who verbally agree, we will make an effort to obtain written consent via mail, e-mail, or eConsent in the UNM HSC REDCap system.
- The reproductive health physician on call will be notified to ensure placement of the implant within 24 hours; after hours, the reproductive health physician on call will also have access to the randomization sequence and will notify the research coordinator of the subject's identification number.

Implant insertion

- The implant will be placed in accordance with the Federal Drug Administration (FDA) label instructions and only by providers who have completed the Merck training and are certified to insert the implant by Merck.
- Those allocated to the immediate group will obtain their implant in the hospital, by residents with attending supervision, fellows, attendings or certified nurse-midwives, and by obtaining the implant through the hospital pharmacy or the implants from the Family Medicine grant or LARC Mentoring Program for UNM participants.
- For those randomized to the standard insertion group, the implant will be provided in clinics as per clinic protocol. For UNM participants without insurance or those whose insurance does not cover immediate implant insertion, a limited number of implants (33) will be provided through the Family Medicine grant and additional implants will be available via the LARC Mentoring Program. UNM and University of Utah have established a process to enter all clinical study data via REDCap.

Follow-up procedures:
A research staff will keep a record of contact information for all participants. The staff will schedule visits for standard insertions at 4 weeks postpartum, will contact care provider to let them know the patient is participating in the study and the date of the appointment for the implant insertion. We will schedule standard insertion at 4 weeks postpartum in order to have a 2 week period to reschedule the participant if necessary. UNM appointments can be made at the Center for Reproductive Health Clinic (CRH) for increased convenience and to improve follow up if a participant cannot return to her antepartum clinic.

Research staff will contact participants randomized to the standard insertion group one week before the appointment to remind her of her appointment and will contact the care provider by a message in the EMR to let them know they date of the appointment for the implant insertion. Research staff will coordinate any necessary appointment rescheduling. Research staff will track this information for the purpose of the study CONSORT flow diagram.

Utah's research coordinators will have access to UNM's REDCap and will randomize and enter baseline data. They will also enter the study participants contact information (phone number or email) which is how they will receive the follow up study questionnaires.

UNM will call UNM participants and Utah will call Utah's participants for the follow up for the contact periods at 2, 4, 8, 12, and 24 weeks postpartum will be made by each site's research team to their respective study participants by phone calls, text messages or email. The text message and the emails will include a link to REDCap to access the follow up questionnaire to be completed by the participant. When/if the patient is contacted through phone call the UNM and Utah research staff will only contact their respective participants for completion of the questionnaires in REDCap.

The questionnaires will contain data about breastfeeding, postpartum depression, and sexual function. A paper diary will be provided to aid the participant in daily recording of data. We will also include a retrospective data collection instrument to account for those we miss at the primary data collection points for breastfeeding information. If the primary questions have been answered either prospectively or retrospectively, then they get the normal prospective survey. If participants do not meet this criteria or if they miss a previous survey, then they will receive a retrospective survey. The diary will be collected at 2, 4, and 8 weeks. If possible, 2-3 good phone numbers will be obtained as well as addresses for each participant. Participants will have a phone number to contact study personnel at their specified site during standard work hours: Monday-Friday 8am- 4:30 pm with any concerns or adverse events. If they call after-hours, a voicemail system will be available, and the participant will be contacted the next working day.

Data collection instruments

Data collection instrument	Manner of collection	Timing	Included data
Enrollment form	Medical chart review In-person, telephone and/or online via UNM's REDCap	After delivery At enrollment	Participant & neonate medical history, delivery details contraceptive history, contraceptive bridge-methods, lactation history, lactation and work expectations
Contraceptive Counseling Survey	In-person, telephone and/or online via UNM's REDCap	At enrollment and 4 weeks postpartum	Satisfaction with contraceptive counseling
Breastfeeding Survey	In-person, telephone and/or online via UNM's REDCap	2, 4, 8, 12, 24 weeks postpartum	Breastfeeding continuation, exclusivity, reasons for discontinuation if applicable, infant weight, resumption of intercourse, and satisfaction with contraception
EPDS	In-person, telephone and/or online via UNM's REDCap	2, 4, 8 weeks postpartum	Postpartum depression scale
FSFI	In-person, telephone and/or online via UNM's REDCap	4, 8, 12 weeks postpartum	Sexual function scale

Bleeding diary	Paper or UNM's REDCap	Reviewed at 2, 4, 8 weeks. Collected at 2, 4, and 8 weeks	Bleeding patterns Side effects
Retrospective Breastfeeding Survey	In-person, telephone and/or online via UNM's REDCap	2, 4, 8, 12, 24 weeks postpartum	Breastfeeding continuation, exclusivity, reasons for discontinuation if applicable, infant weight, resumption of intercourse, and satisfaction with contraception
Retrospective Breastfeeding Discontinuation Chart Review Form	Medical Chart Review	Up to 1 year pp	Breastfeeding continuation if no response from survey. Infant feeding data as clinically described in the infant chart up to 1 year* postpartum may be collected if no response to survey and no data is available in the patient's chart. *Infant age is defined as 0-1 year by the CDC
Retrospective Contraceptive Use Chart Review	Medical Chart Review	Up to years pp* *Nexplanon can be used for up to 5 years after insertion	Nexplanon use at any of the timepoints (2, 4, 8, 12, 24 weeks postpartum). We will review the mother's chart up to 5 years postpartum if contraceptive use data is not obtained from surveys or available from chart review within the first year postpartum.

13.Data Analysis

13.1 We will conduct a primary analysis per protocol and a secondary analysis per intention to treat. The rationale behind this strategy is to analyze both approaches and examine the result for consistency A Repeated measures ANOVA analysis will be used for continuation of breastfeeding. To evaluate secondary outcomes between the two

groups we will use the T-test, Wilcoxon Rank Sum test, Chi-squared test, or Fisher's exact test as appropriate. Secondary outcomes to be evaluated are to compare time of exclusivity of breastfeeding, mix breastfeeding, factors associated with discontinuing breasts feeding, time of breastfeeding discontinuation and patient satisfaction with postpartum contraception counseling and with timing of placing the implant between both groups. If there are significant differences between treatment groups, multivariable linear (for continuous outcomes) and logistic (for dichotomous outcomes) regression will be utilized in addition to control for confounding.

13.2 This study is a non-inferiority trial designed to demonstrate that immediate postpartum insertion of the ENG implant is non-inferior to standard ENG implant insertion with respect to the proportion of women who fail to breastfeed by 8 weeks after delivery. The failure rate for continuation of breastfeeding under the current treatment, standard insertion, is expected to be 30%.

The following sample size determination and plan for data analysis was developed in conjunction the University of New Mexico Clinical and Translational Science Center (CTSC).The non-inferiority margin for both primary outcomes is 15%, meaning that immediate insertion can be regarded as non-inferior (in terms of breastfeeding continuation) to standard insertion if the difference in rate with immediate insertion is no more than 15% worse than with standard insertion. To achieve 80% power with a 1-sided Type 1 error of 5% utilizing the Z test (unpooled) 62 participants are required in each group for a total 124. Accounting for the expected loss of follow up of 20%, the total subjects 149, round to 150. We intend to enroll up to 200 participants due to unanticipated loss to follow up, so this should ensure that we have enough data for data analysis.

14. Provisions to Monitor the Data to Ensure the Safety of Subjects

A Data and Safety Monitoring Plan has been developed and will be led by Dr. Alan Waxman at the University of New Mexico, who is an independent physician. Dr. Waxman will monitor the study at least quarterly.

The ENG implant is an FDA approved drug, which has a well-established record in breast feeding women. Early implant insertion reflects standard practice in many centers, including the University of New Mexico. The data monitored and reviewed will include enrollment and dropout rates, protocol deviations, review of subject symptoms, and preliminary analysis of the primary outcomes (continuation of breastfeeding at 8 weeks). The reports will include enrollment and dropout rates, protocol deviations, review of subject symptoms, and preliminary analysis of the primary outcomes. The trial will be stopped for a cessation of breastfeeding in more than 70% of the early insertion group in the first 8 weeks. Any additional reports to the IRB will occur in response to specific events adverse events. Any serious adverse event defined as an event requiring re-hospitalization will require re-evaluation of the risk determination and continuation of the study. Adverse event reporting will follow

guidelines as proposed by Good Clinical Practice and collected as they occur or are reported by patients. These reports will be compiled for review by the DSMB quarterly; except for serious adverse events which will be reported to the IRB and DSMB within 24 hours of the occurrence. All subjects will have access to clinical care which is not dependent on study participation and will be notified of the availability of that care. All data will be collected for quarterly reporting to the DSMB as well as for final data analysis and reporting. There may be times when we are required by law to share information. However, protected health information (PHI) will not be used in any published reports about this study.

15. Withdrawal of Subjects

15.1 The research team will provide thorough screening to see if the patient will meet inclusion and exclusion criteria. If any circumstances arise such participant experiencing exclusion criteria during study participation or fail to follow study procedures such as having the implant placed or removed before the study ends, the participant will be notified and withdrawn from the study without their consent.

15.2 Participants may have their implant removed at their request at any time. However, removal of the implant automatically terminates participation in the study and no data will be collected further. The data that was already collected from those participants that withdraws or was withdrawn from the study will be use data analysis.

15.3 NA

15.4 Participants may withdraw from study involvement at any point in time and this will not affect their ability to obtain standard clinical care that day. All data points will be collected on the date of the procedure and therefore we anticipate loss to follow up and withdrawal rates will be low. Participants will be given the information on how to withdraw in the study consent.

15.5 The authorization for the use and disclosure of the participant health information for this study shall not expire unless the participant cancels this authorization. The health information will be used or disclosed as long as it is needed for this study. However, the participant may withdraw her authorization at any time providing a notification to the UNM investigators in writing to notifying the study team about the withdrawal. To do this, a letter should be sent to:

Jamie Krashin, MD

Department of Obstetrics and Gynecology

MSC 10 5580, 1 University of New Mexico

Albuquerque, New Mexico 87131-0001

16. Data Management/Confidentiality

16.1. Only IRB-approved study team members will have access to study data and participant materials.

16.2. A study identification number will be assigned to each participant in lieu of using their personal information for identification (e.g., name). All participant data will be de-identified. Participant data will be stored separately from any identifiers to protect patient privacy. We will use de-identified cover sheets for document packets containing PHI.

16.3. This study will not be collecting information considered extremely sensitive or require additional protections such as HIV, genetic test results, mental health information, substance abuse information, and/or criminal records.

16.4. Data will be entered into the data collection software, REDCap, by research staff. Research staff will have completed institutional training prior to initiation of the study. Additionally, only study staff will have access to the REDCap records.

16.5. Study packets will be stored in a secure file cabinet located in the research office. These cabinets will be kept locked at all times. In a separately locked file cabinet, stored in the same room, the study consents will be stored. This second file cabinet is locked with a second, separate key from all other study materials.

16.6. The list that links participant information to the study identification number will be destroyed after data analysis is complete. Data will be stored for five years, and then will be destroyed. Study records of minors will be retained until the minor turns 22 years old, and then will be destroyed.

17. Data and Specimen Banking

NA, no data or specimens will be banked or archived locally for future use.

18. Risks to Subjects

18.1. The ENG implant has been associated with mild side effects including unpredictable bleeding patterns, mood swings, weight gain, acne, depressive mood, vaginitis, breast pain, viral infections, stomach pain, painful periods, nervousness, back pain, headache, dizziness, or nausea and vomiting. In addition, the potential insertion procedure side effects and complications include pain, irritation, swelling, bruising, scaring, infection, nerve injury, implant break and then need for an extensive procedure for removal. Everyone taking part in the study will be followed carefully for any side effects. There are risks of stress, emotional distress, inconvenience and possible loss of privacy and confidentiality associated with participating in a research study. There is also the possible risk of decreased breast milk production. Current but limited data suggest there is no decreased breast milk with progestin-only methods.

The UNM Hospital and its affiliated clinics are staffed by providers trained in postpartum contraception.

The implant has side effects – because of the small amount of hormone, it is unlikely and has not been shown in studies to increase the risk of depression. (29)

Postpartum implant insertion will be inserted according to the standardized procedure approved by the FDA and only by providers certified to insert the implant by Merck.

Regarding data collected for assessment of postpartum mood:
EPDS results will be scored weekly as they are obtained. The research coordinator will forward scores to the on-call study co-investigator as soon as possible/on the day they are obtained. For scores <10 (with a score of 0 for question 10) no immediate action is needed, and the study participant will be reevaluated at the next study interval. For scores < or = to 10 (with a score of 0 for question 10), the co-investigator will 1) call the study participant as soon as possible/on the day they are obtained and offer referral to counseling and/orfor suicidal ideation, to the crisis hotline number (National Suicide Prevention Hotline 1.800.273.8255). For women without suicidal ideation or acute crisis, the study co-investigator will offer an appointment in the OB-GYN perinatal mood disorders clinic, Journeys with a counselor within the next 5 days. Study participants with a non-zero score for question 10 will be contacted by the study co-investigator as soon as possible/on the day they are obtained by telephone and suicide risk will be assessed using the SAHMSA SAFE-T 5-step method (23). For moderate and high-risk study participants, immediate referral to UNM Psychiatric Urgent Care Clinic or Psychiatric Emergency Services will be made in addition to provision of the crisis hotline number above. All study co-investigators are competent to manage patient responses on the Edinburgh.

18.2. NA, no procedures may have risks to the subjects that are currently unforeseeable.

18.3. NA, no procedures may have risks to an embryo or fetus should the subject be or become pregnant. The implant is a contraceptive method.

18.4. NA, there is no risks to others who are not subjects.

18.5. To minimize the probability or magnitude of risks of this study the insertion will be performed as per FDA guidelines. However, side effects cannot be prevented.

19. Potential Benefits to Subjects

19.1. The completion of this study will show whether women randomized to immediate implant insertion is non-inferior in terms of breastfeeding continuation through 8 weeks postpartum when compared to women randomized standard insertion. The contribution of the proposed research is to determine if inserting the implant in the first 24 hours postpartum interfere with continuation of lactation. This contribution to the literature is significant because current recommendation and previous studies are limited and insufficient.

19.2 There may not be direct benefit to the study participants. However, their participation will help in the treatment of future patients with an understanding of how an implant affects breastfeeding and on the optimal timing of starting the implant to prevent unplanned pregnancies.

19.3 The direct benefits from the contraceptive implant include improved access to the device in either randomization arm: immediate access prior to hospital discharge or help from research staff scheduling clinic appointment for placement. Direct medical benefits from the implant include improved autonomy related to their reproductive health, ability to control when they want to become pregnant again given the high contraceptive effectiveness and ease of use of the implant, longer intervals between pregnancies which is associated with improved maternal and neonatal outcomes, and improvement in menstrual bleeding/reduction in anemia. The implant is a popular contraceptive choice for adolescents, who often prefer a long-acting method that does not require a pelvic examination. These benefits of the contraceptive implant are part of the reason that minors do not need parental consent to have the implant placed clinically.

20. Recruitment Methods

20.1. (Also described under "procedures" in Section 12.) Patients may be recruited in the following locations/timeframes: 1) antenatal clinics, 2) visits to OB-Triage 2) on admission to L&D for delivery not in active labor or 4) during the first postpartum hours in the Ob-Gyn ward of the UNM Hospital and University of Utah Hospital.

- Patients may be asked for their contraceptive choice in any of these four venues, although ideally in antenatal clinics during prenatal care. When women decide on an implant as a postpartum contraceptive in any of these venues, the PCP (Ob-Gyn, Family Medicine physicians/residents and midwives) may discuss the patient's interest in hearing about the study and may contact the research coordinator by a message in the EMR or by phone or in person to let her know that the patient is interested in hearing about the study.
- Additionally, the research coordinator will review antenatal clinic, OB Triage and inpatient (L&D and postpartum) lists to assess patients' contraceptive plan through review of the EMR. The research coordinator may contact patients who have decided on a postpartum implant to assess her interest in participating in the study.
- If the patient expresses interest, the research coordinator will present the study and ask the patient for her interest in enrolling. If interested, the research coordinator and/or a study co-investigator will explain the study, screen the patient for eligibility and obtain informed written or electronically signed consent.
- Women will not be approached for study participation if they are in active labor. Women will be approached and enrolled, if interested, either prior to active labor (e.g., when admitted for induction of labor or scheduled cesarean delivery) or after delivery.
- We will not enroll patients who are under sedation. Most participants will be enrolled and undergo informed consent in the antenatal period; some will be

enrolled when they are admitted to labor and delivery not in active labor; neither of these two groups would be under sedation. For those "up to 22 hours after delivery," we will only enroll women who have not received sedation within a 4-hour period.

- Once the woman is enrolled in the study a line will be added to the Antenatal Supplemental Visit Form stipulating the patient's participation in the study and the coordinator's phone number: Ex: Rivera-Montalvo study patient – page at admission ###-####**. This Form is a section of the EMR that is updated at each visit by the clinic provider with important/current antenatal issues; it is standard that the contraceptive plan for each patient is recorded here.

Identification of study patients on L&D

- The PCP on L&D may identify study patients who self-identify as being in the study. They will also be alerted by the "Study Patient" in the antepartum record if the patient has been enrolled antepartum. They will notify the research coordinator who will carry a phone during working hours.
- A reproductive health on-call fellow/attending will be designated 24-7 to ensure randomization and implant insertion within 24 hours for those randomized to the immediate group. After hours (nights and weekends), the research cell will forward to the reproductive health on-call fellow or attending. In addition, the voice message for the research cell will direct callers to contact the reproductive health on-call fellow through Amion, the hospital online paging system. A calendar will specify which co-investigator is on call for study patients.
- The PCP on L&D will call the research coordinator/call physician by phone or by text message that a study patient arrived on L&D for her birth.

20.2. The research coordinator will review the list of admitted patients to L&D twice a day (8 AM and 4 PM) and once daily on Mother Baby Unit and Ob-Special care the (Ob-Gyn wards) to identify enrolled study patients. This modality has been used with other studies in the department of Ob-Gyn and has been successful.

20.3. Brochures and flyers will be used to recruit participants. See attached documents.

21. Provisions to Protect the Privacy Interests of Subjects

21.1. We will take measures to protect the security of all personal information, but we cannot guarantee confidentiality of all study data. To minimize the privacy risk, the research team will reassure the patient of the following:

Information contained in study records is used by study staff alone. The University of New Mexico and other recruitment sites' Institutional Review Board (IRB) that oversee human subject research and/or other entities may be permitted to access records. Additionally, de-identified data will be shared for reporting to the DSMB, if needed, as well as for final data analysis and reporting. There may be times when we are required by law to share information. However, protected health information (PHI) will not be used in any published reports about this 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 de-identified online REDCap database. Any printed study data (such as signed consent forms) will be secured in a locked cabinet/file-box and only those directly involved in the study will have access to this including the investigators who will process it. Only de-identified data will be saved under a secure file on a computer requiring a log-in password. Data will be stored for five years, and then will be destroyed.

21.2. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law.

21.3. A study participant's privacy interests during recruitment and data collection will be protected through the following measures:

The study will be thoroughly explained to the potential participant using the HRPO-approved consent form. As part of the informed consent process, the recruiting co-investigator or research assistant will provide as much time as needed for the potential participant to consider study participation. If any privacy interests are expressed by the patient, they will be addressed immediately by the research team member and if necessary, the issue will also be considered by the principal investigator.

Participants will be recruited and consented in a private clinic setting. This will also include the recruitment and screening process as well as the data collection procedures.

22. Economic Burden to Subjects

22.1. Participant's third party payer (i.e. insurance company) is responsible for all the costs related to the implant and clinical treatment. This would be the case regardless of study involvement.

New Mexico Medicaid reimburses for immediate postpartum implant placement (prior to hospital discharge) and will cover all costs related to the implant and clinical treatment. Private insurers do not cover the costs. We will be enrolling participants that are Medicaid, uninsured, underinsured and private insurers, until the supply of 33 implants run out. We do anticipate receiving additional no-cost implants; if this occurs, we will continue enrollment of private insured and un or under-insured women. Please see the table below.

Research Procedures	**Number of Samples/Procedures**	**Responsible Party**	
		Study	**3rd Party Payer or Participant**
Immediate implant insertion	75	☐	☒
_____	_____	☐	☐
_____	_____	☐	☐

_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
Standard of Care Procedures	**Number of Samples/Procedures**	**Responsible Party**	
		Study	**3rd Party Payer or Participant**
Implant insertion at 4-6 weeks	75	☐	☒
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐

22.2. No other costs to participants are anticipated

22.3. The participants and/or the third party will be charged for the implant device in case the participant cannot afford the implant or the implant is not covered by the third party (insurance) for the immediate insertion, there will be 33 of implants out of charge paid by a private grant. Additional implants are available via the LARC Mentoring Program, However, this is subject to availability and once the product is out of stock no more implants will be available from the grant or the LARC Mentoring Program.

22.4. Participants will not be billed for the cost of tests and procedures directly associated with this study. However, reimbursement for all related costs of care will be sought from the patient's insurer, managed care plan, or other benefits program. If they do not have insurance, they may be responsible for these costs. Patients will also be responsible for any associated co-payments or deductibles required by their insurance.

23. Compensation

In return for the participant's time and the inconvenience of participating in this study, the participant will be paid a total of $40 to participate in this research study. This incentive will be divided in two gift cards of $20. The first gift card will be given at the time of enrollment. The second gift card of $20 will be given after completing the 8 week follow up. In the event that timeline of compensation is changed, the research team will send a letter to the affected participants to notify them of the change. Participants that have surpassed the new date of compensation will be paid immediately and those who have not will be paid at the time of completion of the surveys at that time.

24. Compensation for Research-Related Injury

In the event that the patient has an injury or illness that is caused by participation in this study, patients will be verbally reminded of the following during the consent

process: reimbursement for all related costs of care will be sought from the patient's insurer, managed care plan, or other benefits program. If they do not have insurance, they may be responsible for these costs. Patients will also be responsible for any associated co-payments or deductibles required by their insurance.

25. Consent Process

25.1.1. The inclusion and exclusion criteria for study participation will be reviewed by a member of the research team to confirm eligibility. Prior to consent, the study will be described verbally to women, and potential subjects will receive a copy of the consent form to read. If patients are comfortable enrolling in the study at that point, they may do so. All potential participants will be reassured that declining study participation will have no effect on the care that they receive. If patients choose not to participate, they will not be approached again unless they broach the subject. Women who elect to participate will be informed about the standard risks, benefits and alternatives of the procedure per standard of care. Co-investigators or trained research staff will follow HRPO regulations for written documentation of consent or verbal consent. For women ages 13-17, we will obtain parental consent which could also occur verbally by phone and collected via mail or e-mail. Electronic consent will be noted on the updated consent form. Due to the pandemic, research coordinators are mainly working from home and going through the consent with participants by phone for the safety of everyone. Privacy is still maintained as the coordinator ensures they have a place they can talk privately by phone.

25.1.2. The consent discussion will take approximately 5-10 minutes after the consent has been read by the potential participant. Research staff will review the consent with the potential participant and provide ample opportunity for the subject to ask questions in a private setting.

25.1.3 Steps that will be taken to minimize the possibility of coercion or undue influence include providing ample opportunity for the subject to ask questions they may have about research, providing time for the possible participants to think about participating in the study and providing privacy for subjects.

25.1.4 Research staff will confirm the participant's interest and allow more opportunity for questions before the consent form is finally signed or electronically signed by the patient.

25.1.5 Steps that will be taken to ensure understanding include providing ample time for the potential participant to read the consent. The recruiting co-investigator or trained research assistant will speak directly to potential subjects about the aims of the study and participant involvement in this study. Potential subjects will be asked if they understand the study and its importance, and side effects will also be emphasized as well as the voluntary nature of participation.

25.1.6 Spanish-speaking patients will be recruited using a UNMH certified Spanish interpreter service or a fluent Spanish-speaking research team member. Spanish-speaking patients will be provided with a hard or emailed copy of the Spanish consent form.

25.1.7 After counseling, potential candidates will be asked to teach back as a proof of understanding. .

Subjects not fluent in English

25.1.8 This study will enroll English and Spanish speaking patients only.

25.1.9 Spanish-speaking patients will be recruited using a UNMH certified Spanish interpreter service or a fluent Spanish-speaking research team member. Spanish-speaking patients will be provided with a hard copy of the Spanish consent form.

25.1.10 Study materials will be translated into Spanish after the English versions are approved. Consent forms will be available in English and in Spanish.

Cognitively Impaired Adults/Adults Unable to Consent/Use of a Legally Authorized Representative

25.1.11- 25.1.20 We will not enroll cognitively impaired women.

Subjects who are not yet adults (infants, children, teenagers)

25.1.21 Minor females from ages 13-17 will be included in the study.

25.1.22 As per the "*SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)"* all people under the age of 18 are minors.

25.1.24 Consent will obtained by biologic or adoptive parents or an individual legally authorized to consent on behalf of the child.

25.1.25 All children enrolled in the study must be capable to provide assent.

25.1.26 Assent will be obtained from all of the children in order to enroll them in the study along with parental consent.

25.1.27 The process for obtaining assent will follow the same process for obtaining consent. The study will be explained to the child in simple language. A copy of the consent/ assent form will be given, questions regarding the study will be answer and in the case the participant will need time to think more about participating in the study time will be given.

Waiver or Alteration of Consent Process (consent will not be obtained, required element of consent will not be included, or one or more required elements of consent will be altered)

A partial waiver of consent for screening/recruitment will be obtained.

26.Documentation of Consent

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26.1 Consent will be obtained in-person or electronically during the current pandemic. The patient will be provided with a physical or electronic copy of the consent form and will read and discuss the study with trained research staff. Before signing the consent form, staff will confirm the patient's interests in participating as well as answer any remaining questions. After signing or e-signing the consent form, the patient will receive a copy for their own personal records.

26.2 This study will not be collecting tissue samples.

26.3 NA

27.Study Test Results/Incidental Findings

27.1 Results will not be shared with participants.

27.2 Incidental Findings: Based upon the nature of the research, and the intervention that will be performed, we anticipate that the research may not result in incidental findings. However, if an incidental finding that threatened the life of a participant is found this will be disclosed with the participant. All other clinical care provided, including the technique to place the implant and reporting of any incidental findings will be handled according to routine clinical care.

28. Sharing Study Progress or Results with Subjects

28.1. We will not directly share study results with participants; however, all participants will be told, during the informed consent process, that results for this study will be uploaded to ClinicalTrial.gov, which is publicly accessible.

28.2 We will not directly share study summary with participants; however, all participants will be told, during the informed consent process, that results for this study will be uploaded to ClinicalTrial.gov, which is publicly accessible.

29.Inclusion of Vulnerable Populations

29.1 This study will include postpartum females ages 13 years and older. This study seeks to include adolescent population since postpartum contraception is important to this population as well as adult women. This research study focuses on women seeking voluntary postpartum contraception options. This study is inclusive to all adolescent girls and women 13 years and older of varying ethnic backgrounds. It may happen that a participant is a student or an employee. However, this study is not intended solely in these populations. Research staff will approach these girls and women to assess their 1) interest and 2) meet eligibility criteria as determined by staff and their provider. Once the possible participant show interest, the research staff will go forward with the enrollment to reduce coercion, research staff will conduct a thorough consent process and reiterate that their participating is completely voluntary.

1. This study will not include women who are incarcerated, or children that are wards of the state or any other organization similar.

2. This study will not include women with cognitive impairments and/or are unable to understand the consent process.

3. No neonates will be involved in this research.

30. Community-Based Participatory Research

NA

31. Research Involving American Indian/Native Populations

31.1 This research study focuses on females seeking postpartum contraception options. This study is inclusive to all girls and women 13 years and older of varying ethnic backgrounds so long as they are English or Spanish speaking. This study does not focus solely on women of American Indian heritage.

32. Transnational Research

NA

33. Drugs or Devices

33.1 This research involve using ENG implants devise in all participants. The implants for immediate insertion will be stored at the UNM Hospital pharmacy. The implants for standard insertion will be stored at the affiliated clinics. The implants given by the Family Medicine grant are stored in the Family Medicine faculty Room in Labor and Delivery area. Implants provided by the LARC Mentoring Program will be stored on Mother Baby Unit.

33.2 No investigational drug will be used in this study.

33.3 No drugs will be involved in this study.

33.4 See device check list.

34. Principal Investigator's Assurance

By submitting this study in the Click IRB system, the principal investigator of this study confirms that:

☒ The information supplied in this form and attachments are complete and correct.

☒ The PI has read the Investigator's Manual and will conduct this research in accordance with these requirements.

☒ Data will be collected, maintained and archived or destroyed per HSC Data Security Best Practices, including:

1. **Best Practice for data collection** is for it to be directly entered onto a data collection form that is in a secured access folder on an HS drive behind a firewall, or in a secure UNM Data Security approved system such as RedCap.
2. **Data collection of <u>de-identified data</u>**, if done in a clinical setting or other setting that does not allow direct entry into a secured system, may be done temporarily using a personal or university owned electronic storage device or hard copy document. **The important security safeguard is that no identifiers be include if the data is entered or stored using an untrusted device or storage.**
3. **Permanent (during data analysis, after study closure**) storage must reside on HSC central IT managed storage. Processing of data (aggregation, etc.) are to be carried out in such a way as to avoid creating/retaining files on untrusted storage devices/computers. Trusted devices are HSC managed and provide one or more of following safeguards: access logs, encryption keys, backups, business continuity and disaster recovery capabilities.
4. **Alternate storage media** must be approve by HSC IT Security as meeting or exceeding HSC central IT provided security safeguards.

Checklist Section

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

I. Waivers or Alterations of Consent, Assent, and HIPAA Authorization

A. Partial Waiver of Consent for Screening/Recruitment

Complete this checklist if you are requesting a partial waiver of consent so that you can review private information to identify potential subjects and/or determine eligibility prior to approaching potential subjects for consent or parental permission.

1. Describe the data source that you need to review (e.g., medical records):

   UNM Medical records through PowerChart and postpartum floor schedule

2. Describe the purpose for the review (e.g., screening):

   Screening and recruitment to determine eligibility prior to approaching potential subjects for consent.

3. Describe who will conducting the reviews (e.g., investigators, research staff):

   UNM research staff will be conducting review for recruitment purposes.

4. Do all persons who will be conducting the reviews already have permitted access to the data source?

   ☒ Yes

   ☐ No. Explain:

5. Verify that each of the following are true or provide an alternate justification for the underlined regulatory criteria:

   a) The activity involves no more than minimal risk to the subjects because the records review itself is non-invasive and the results of the records review will not be used for any purposes other than those described above.

      ☒ True

      ☐ Other justification:

   b) The waiver or alteration will not adversely affect the rights and welfare of the subjects because eligible subjects will be approached for consent to participate in the research and are free to decline. Further, the information accessed during the records review will not be disclosed to anyone without a legitimate purpose (e.g., verification of eligibility).

      ☒ True

☐ Other justification:

c) The research could not practicably be carried out without the waiver or alteration because there is no other reasonably efficient and effective way to identify who to approach for possible participation in the research.

☒ True

☐ Other justification:

d) Whenever appropriate, potentially eligible subjects will be presented with information about the research and asked to consider participation. *(Regulatory criteria: Whenever appropriate, the subjects will be provided with additional pertinent information after participation.)*

☒ True

☐ Other justification:

Partial Waiver of HIPAA Authorization for Screening/Recruitment

Complete the following additional questions/attestations if the records you will review to identify potential subjects and/or determine eligibility include Protected Health Information (PHI).

6. Will you be recording any PHI when conducting the records review to identify potential subjects and/or determine eligibility?

   ☒ Yes. Describe: *We will only record the reason the patient was not eligible and their name in order to avoid reviewing a patient's information more than once.*

   ☐ No

7. If you answered "Yes" to question 6 above, please describe when you will destroy identifiers (must be the earliest opportunity consistent with the conduct of the research) or provide justification for why they must be retained:

   We will destroy identifiers once the study is complete and closed with the IRB.

8. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

   ☒ True

   ☐ False

II. Vulnerable Populations

A. Children

Complete this checklist if the subject population will include children.

i. Select the category of research that you believe this research falls within and provide justification for any associated criteria. If there are different assessments for different groups of children or arms (e.g., placebo versus drug), include a memo to provide an assessment for each group.

☒ Research not involving greater than minimal risk. *(Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.)*

☐ Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

Provide justification for each of the following criteria:

a. The risk is justified by the anticipated benefit to the subjects:

b. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches:

☐ Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

Provide justification for each of the following criteria:

- The risk represents a minor increase over minimal risk:

- The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations:

- The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition

III. Medical Devices

Complete this checklist if the research evaluates the safety or effectiveness of a medical device. If more than one medical device is being evaluated, provide the requested information for each.

A. Device Name: *Nexplanon*

B. Manufacturer: *Merck & Co., Inc.*

C. Does the research involve a Significant Risk Device under an IDE?

☐ Yes. Include documentation of the FDA approval of the IDE with your submission. *Acceptable methods of documentation include: (1) FDA letter noting IDE number and approval status; (2) Industry sponsor letter noting IDE number and FDA approval status; or (3) FDA-approved industry sponsor protocol with IDE number noted*

☒ No

D. Is the research IDE-exempt?

☐ Yes. Include a FDA letter with your submission noting the determination that the research is IDE-exempt or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is IDE-exempt*.

☒ No

E. Does the research involve a Non-Significant Risk (NSR) Device?

☐ Yes. Include a FDA letter with your submission noting the determination that the research is NSR or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is NSR**.

☒ No

* This FDA guidance includes a description for when a device study is exempt from the IDE requirements:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf

**This FDA guidance includes information on how to differentiate between Significant Risk and Non-Significant Risk device studies:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

1. Data Transfer/Sharing (Checklist)

Complete this checklist if the research involves transferring/sharing of data with an external entity (institution, company, etc.).

A. Will data be transferred/shared with an external entity (institution, company, etc.)?

☒ Yes

☐ No. **The remainder of this section does not apply.**

B. Indicate if the data is incoming and/or outgoing: incoming

C. Provide the name of the entity that data will be transferred/shared with: University of Utah

D. Provide the contact name, email and phone number with whom data is being transferred/shared with: Marie Gibson, Marie.Gibson@hsc.utah.edu

E. Who is responsible for transmission of the data? *Utah's approved study team members*

F. Who is responsible for receiving the data? UNM's approved study team members

G. Describe how the data will be transferred/shared. Please note data cannot be transferred/shared without assistance from UNM HSC IT. **Requesting HSC Central IT Transfer is detailed on the Sponsored Projects website:** Through UNM's REDCap, *Utah's study team members will be set up as a UNM affiliate to gain access to UNM's REDCap database to enter the Utah's study participant's email or phone number, the REDCap electronic survey will then be sent directly to the study participant for them to complete the electronic survey and the data will automatically load into UNM's REDCap database. An approved Utah study team member that is a UNM affiliate with a login to UNM's REDCap could also enter the survey data in the case of the data being collected in person or over the phone.*

H. For data being transferred/shared with outside locations or entities, describe the following: NA

- Where is data storage and how will it be maintained in a secure manner (i.e. encryption, password protection, use of Qualtrics or REDCap, etc)?
- What is method in which data will be collected and stored (i.e. electronic, hard copy, etc)?
- How long will the data be stored?
- Who will have access to data?

I. Please list all specific data elements, variables, etc. to be sent out and/or received. Indicate if the data contains identifiers and health information. Please note that identifiers that MUST be removed to make health information de-identified are as follows: Names, All geographic subdivision smaller than a State, All elements of year (except year), Telephone, Fax numbers, E-mail addresses, Social Security, Medical record number, Health plan beneficiary, Account numbers, Certificate/license numbers, Vehicle identifiers and serial numbers, Device identifiers and serial numbers, Web URLs, IP address numbers, Biometric identifiers, full face photographic images, and Any other unique identifying number, characteristic or code.) *Names, emails, phone numbers, appointment dates/times. All data collected through UNM's RedCap database.*

J. If the research requires the access, use, or disclosure of any of the 18 individually identifiable protected health information (PHI) identifiers that can be used to identify,

contact, or locate a person (e.g., name, medical record number, etc.), are the subjects going to consent to or authorize the disclosure of their individually identifiable health information? *Participants will consent to disclose their individual identifiable information.*

a. ***Or*** is HIPAA authorization altered or waived?

K. What is the classification of the data (de-identified, limited data set, protected health information, other). Protected health information
L. Does the request to transfer/share data include clinical data that belongs to the UNM Health Systems? The data is incoming, it does not belong to UNM Health Systems.
M. Does the data to be transferred/shared include information about patients seen at external health system or at a third party medical provider? The data is incoming, from Utah, an external health system.
N. Is the external entity a "covered entity"? Yes, University of Utah
O. Is the data that is going to be transferred/shared owned or partially owned by another party or have any type of restrictions including regulatory restrictions (i.e. HIPAA, FERPA, etc.)?
P. Is the data publically available? If yes, please provide details: *No*
Q. Does the data include information about substance abuse treatment, sexually transmitted diseases, genetic testing results, HIV/AIDS testing results, and/or mental health? Yes

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