RAPID EC – RCT Assessing Pregnancy with Intrauterine Devices for Emergency Contraception

Protocol Summary

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University of Utah IRB #:	IRB_00073554
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Background and Introduction

In order to reduce our nation's persistently elevated rate of unplanned pregnancy we must seek every opportunity to provide women who desire contraception with the most effective methods. The vast majority of the 3.1 million unintended pregnancies in the U.S. each year result from situations where contraception was used imperfectly or not at all.[1] Unfortunately, the wide availability of oral EC pills has not reduced abortion rates.[2, 3] Providing non-users and users of less effective methods of contraception with highly effective contraception is an efficient strategy to reduce rates of unplanned pregnancy and abortion. Application of this principal has reduced repeat abortions for women who receive immediate post-abortal IUD insertion.[4] Like women seeking abortion, EC users are at high risk of unplanned pregnancy and are making a conscious effort to acutely reduce that risk.

The demand for EC confirms a tremendous unmet public health need for more reliable and more effective contraception. The copper IUD is the most efficacious method of EC (pregnancy rates of 0.1%)[1] and offers continued highly effective contraception for over a decade. While its use is supported by a Cochrane Review,[7] ACOG,[8] and several other professional organizations and authors,[9-15] it is rarely used. While the copper IUD for EC has advantages over oral EC pills, U.S. women selecting IUDs outside of the EC setting have shown a strong preference for the LNG IUD as it minimizes or eliminates menstrual bleeding and discomfort.[2, 3]. The Contraceptive CHOICE project [18] illustrates this. Of the 9,256 women enrolled in this prospective cohort who were provided with their contraceptive method of choice without cost 47% of participants selected the LNG IUD and 9% the copper IUD. We are unaware if offering women the option to receive either IUD method will increase uptake of highly effective methods by EC users.

Offering women presenting for EC the option of the LNG or copper IUD may increase the initiation of highly effective methods of contraception among a population at high risk of unintended pregnancy. Leaders in the field of EC, acknowledging the lack of effect of increasing availability to EC pills on reducing rates of unplanned pregnancy, have called for procedures that streamline the delivery of highly effective methods of contraception when women present for EC.[16]

Our research team working in conjunction with our clinical partners at Planned Parenthood Association of Utah (PPAU) have conducted several studies evaluating use of the IUD in women presenting for EC. The cumulative findings of our research to date show that EC users are willing to have the copper IUD placed[4, 5] and those that obtain it have lower pregnancy rates than those choosing oral LNG for EC.[6] Our recent study assessing the LNG IUD with oral LNG for EC users has shown no pregnancies with 110 women using this approach. In addition, 90% of participants agreed to being randomized to either type of IUD. The potential to further reduce unintended pregnancy in a high risk population by offering the preferred method of IUD supports a randomized controlled trial of the copper and LNG IUDs for EC users.

Study Design:

Non-inferiority randomized controlled trial. If recruitment is not adequate with this design and potential participants report concern about randomization as a reason for non-participation then a patient-preference cohort (PPC) will be offered to interested and qualified individuals.

All women presenting to participating clinics when study participation is offered will be presented with a study information sheet (discussed below) which includes an assessment of interest in the study. If we find that we are not able to meet recruitment goals (e.g. <80 participants enrolled in the first 6 months) and the reason for non-participation is assessed to be lack of willingness to be randomized to the study interventions, then we will add an option for a PPC. Should the PPC be introduced then participants who are interested in the study and eligible for participation but not willing to be randomized will be offered participation through the PPC which has a separate consent form. While 90% of EC users enrolled in a current study where they can choose their IUD type stated they would be be willing to be randomized to either type of IUD, some individuals may be reluctant to agree to random assignment. This potentially impacts result generalizability. In order to evaluate the magnitude and direction of non-participation bias we will offer eligible women presenting for EC who desire an IUD but are not willing to undergo randomization participation in a patient-preference cohort (PPC). Participants in the PPC may choose the IUD they desire. Based on our survey of current participants in an EC Trial offering women the copper IUD or the LNG IUD and oral LNG we expect that the significant majority of potential participants in this trial will agree to randomization. The PPC will allow us to ascertain selection bias due to RCT non-participation. We will evaluate participant demographics and clinical characteristics. This strategy has been successfully used the OPUS trial, an RCT assessing a mid-urethral sling or sham incisions at the time of pelvic organ prolapse repair.[7]

Purpose and Objectives

In this prospective observational study, all women presenting for Emergency Contraception (EC) at Planned Parenthood Association of Utah (PPAU) clinics will be counseled using a standardized script; those interested in an IUD, who meet study qualifications and agree to participate, will be randomized to either the hormonal IUD (LNG 52mg IUD commonly known as Mirena® or Lilleta®) or the copper IUD (Paragard®). Participants will be followed for one year. If enrollment goals are not achieved due to a lack of willingness among potential participants to be randomized then we will initiate a PPC (patient preference cohort). In that case, participants who are interested in the study and eligible for participation but not willing to be randomized will be offered participation in a PPC.

This study has three specific objectives.

Objective 1: Determine the efficacy of the levonorgestrel IUD and copper T380 IUD for emergency contraception as assessed by urine pregnancy tests 1 month after EC use.

Hypothesis: The LNG IUD is non-inferior to the copper T380 IUD for EC based on a 1% non-inferiority limit.

Objective 2: Compare the one-year unintended pregnancy rates from women initiating the levonorgestrel IUD vs. copper T380 IUD for EC.

Hypothesis: At one-year the LNG IUD users will have lower pregnancy rates compared to copper IUD users.

Objective 3: Assess the one-year continuation, satisfaction, pain, and bleeding patterns of a LNG20 IUD to a copper T380 IUC as a method of EC and the mechanisms of continuation.

Hypothesis: The LNG IUD will have superior rates of continuation and non-inferior satisfaction (what about pain and bleeding patterns) compared to the copper IUD as a method of EC and the mechanisms of continuation.

Study Population

Age of Participants: Women ages 18-35

Sample Size:

At Utah:	706
All Centers:	Up to 850

Inclusion Criteria:

Eligible participants must be:

1. Between 18-35 years old
2. In need of EC (had unprotected intercourse within 120 hours – 5 days)
3. Desire to prevent pregnancy for 1 year
4. Fluent in English and/or Spanish
5. Have a regular menstrual cycle (21-35 days)
6. Know their last menstrual period (+/-3 days)
7. Be willing to comply with the study requirements
8. Participants current preferred phone number must be functioning at the time of study entry and will be tested prior to enrollment

Exclusion Criteria:

1. Current pregnancy

2. Breastfeeding

3. Intrauterine infection within the past 3 months

4. Sterilization

5. Already have an IUD or contraceptive implant (Nexplanon) in place

6. Vaginal bleeding of unknown etiology

7. Known Gonorrhea or Chlamydia infection in the last 30 days (unless successfully treated at least 7 days prior to study entry)

8. Allergy to copper or Wilson's disease

9. Known abnormalities of the uterus that distort the uterine cavity

10. Use of oral emergency contraception within 5 days prior to enrollment

Design

Prospective Biomedical Intervention or Experiment
Randomized Trial

Both medications being studied in this trial are FDA approved and have undergone Phase 3 testing and extensive post-market surveillance. This study evaluates both of these medications for off label use as emergency contraceptives.

If enrollment goals are not being met (for example, <80 enrolled in the first 6 months or less than 10 participants per site at any time in the study when staff are available to enroll participants) and lack of willingness to be randomized is a stated barrier to participation, then we will introduce a PPC whereby participants who are interested in the study and eligible for participation but not willing to be randomized will be offered participation in a patient-preference cohort (PPC).

Study Procedures

Recruitment/Participant Identification Process:

Women who present for emergency contraception at Planned Parenthood clinics will be provided with an information sheet describing the two IUD options offered in this study. This will be provided to them by a member of the PPAU clinical staff. The information sheet also asks if they are interested in participating in a study where they would be randomized to one of the two IUDs offered in this study. They are also asked for age, ethnicity, site, and reason for declining participation. They are asked to mark Yes or No before giving the information sheet back to the clinical staff member. No identifiable information is collected on these participant

information sheets and unless a woman agrees to screening for the study, she is not listed in a screening log.

Those women who mark yes are then approached either by the study coordinator or other IRB approved research staff for further screening and information on the study.

Note: Women who are under age 18 will be included in those who present for emergency contraception at Planned Parenthood clinics and complete the study information sheet. After a member of the research team reviews the initial eligibility criteria, these under age 18 women would be considered screen failures and would not be offered participation in the study.

Should the PPC be initiated, then potential participants interested in the study but who decline randomization will be offered participation in the PPC.

Informed Consent:

Description of location(s) where consent will be obtained:

Consent will be obtained in a private examination room at the clinic where the patient is receiving care.

Description of the consent process(es), including the timing of consent:

Due to the nature of this study, it may not be possible for patients to return at a later time to enroll in the study. Participants will have all questions answered prior to enrollment. The research staff are experienced in interviewing and working with this population. They will be certain to take the time needed to ensure that the patient understands the study and is consenting willingly. If the woman continues to have questions, she will be offered the opportunity to discuss the study in further detail with the PI or other medical providers with extensive experience with the clinical care of IUDs and emergency contraception.

Procedures:

Women who meet inclusion/exclusion criteria will be offered participation in the randomization arm of the study. For those who agree, they will be randomized to either the copper IUD or the LNG IUD and the study procedures below will apply. All participants in the RCT will be informed to use a backup method of contraception (e.g. condoms) or sexual abstinence for the next 7 days to protect against unplanned pregnancy as women assigned to the LNG IUD will need this early protection. Providing this information to only women in the LNG IUD group could inform them of which device they received in the first month. This is a component of the treatment blinding. In the PPC only women selecting the LNG IDU will be informed to use a backup method as the copper IUD protects against future pregnancy risk immediately.

Should enrollment not meet expectations as previously described, then for those patients who meet all inclusion/exclusion criteria and wish to participate in the study, but do not agree to random assignment, we will offer them participation in a PPC. Participants in the PPC may

choose the IUD they desire. Once the participant decides which IUD they prefer, the study procedures below will apply.

Enrollment (Initial Clinic Visit)

- Consent process
- Urine pregnancy test (Completed at the Planned Parenthood Clinic Lab)
- Assignment to either randomized arm or PPC arm
- IUD Insertion
- Data collection
- Diary instructions
- Gonorrhea/Chlamydia testing, if recommended per PPAU STI screening protocols

1 Month Follow-Up

- The 1 month follow-up appointment will be made on the day of enrollment. Urine pregnancy test and confirmation of IUD position will be conducted at the clinic. An IUD string check may also be performed.
    - Participants will be asked to complete a home pregnancy test on the day before their 1 month clinic visit that will be given to them at their enrollment visit. They will be asked to take a picture of the pregnancy test results and text the results picture to a dedicated Planned Parenthood clinic cell phone (number will be provided at the time of enrollment). This at-home testing will be confirmed at the in-clinic appointment as a proof-of-concept to establish this as a norm for future studies with the goal of reducing participant burden.
- The following information will also be obtained either at the 1 month follow-up appointment or by phone, text, or email link to an online data collection instrument for those participants not able to return to clinic for the 1 month follow-up.
    - Bleeding history
    - Sexual activity
    - Data collection including evaluation of satisfaction of method chosen, current use of contraception and review for potential adverse events
- If urine pregnancy test is positive, the following will occur:
    - Ultrasound and/or serum quantitative hCG pregnancy test as necessary to date the pregnancy (this will be completed at the Planned Parenthood Clinic Lab)
    - Removal of IUD
    - Follow-up throughout remainder of pregnancy
    - Pregnancy options counseling and appropriate referral for pregnancy care based on desire to continue or terminate the pregnancy.

3, 6, and 9 months after enrollment

- Telephone, text, email links to online survey or completion with a research assistant by telephone, text, or email (based on participant preference)
- Review for potential adverse events

- Review of bleeding experience, questionnaire review including: unplanned pregnancy, abortion, sexual activity, IUD complications, contraception related side effects, participant clinic visits, use of condoms, employment status, income, school attendance and satisfaction with contraception method

12 months after enrollment (return visit)

- Urine pregnancy test (Completed at the Planned Parenthood Clinic Lab).
- IUD string check.
- Review for potential adverse events.
- Review of bleeding experience, questionnaire review including unplanned pregnancy, abortion, sexual activity, IUD complications, contraception related side effects, participant clinic visits, use of condoms, employment status, income, school attendance, and satisfaction with contraception method.
- If participant cannot come to the clinic for their for 12-month visit, they will be contacted by a research assistant for review of follow-up information (bullet point #4 above) which can be completed via telephone, text, or email links to an online survey (based on participant preference). The study team will also provide participants with a urine pregnancy test they can take at home (if unable to come into the clinic for this final visit) and ask that participants send the results of the home-urine pregnancy test to the study team via email, phone or text.

**Note: We have provided specifics about the questionnaires/surveys that will be asked of participants under each of the study procedure sections. It is our understanding that we are not required to submit full versions of the surveys to the IRB, as long as we have provided thorough descriptions of what will be asked of participants.

PI Conflict of Interest Management Plan

The PI has met all requirements of the COI Management Plan, as follows:

I will provide annual reports of my compliance with this management plan to the Conflict of Interest Office for review.
I will disclose my financial conflict(s) of interest to the editors of all publications (journals, books, etc.) when submitting manuscripts or other reports of the results of this research.
I will disclose my financial conflict(s) of interest in all public presentations of this research.
The University of Utah will disclose my financial conflict(s) of interest on a publicly available web site. The publicly available disclosures will include my name, the name of the business entity(ies), the nature of the financial interest(s) and the dollar ranges or value of the financial interest(s) as available.
I will disclose my financial conflict(s) of interest in writing to all members of the research team. Members of the research team will be informed that if they have any concerns about my conflict(s) of interest, they can discuss those with the Individual Conflict of Interest Committee.
I will disclose my financial conflict(s) of interest in writing to all subordinates working on this project. Subordinates will be informed that if they have any concerns about my financial

conflict(s) of interest, they can discuss those with the department chair or the Individual Conflict of Interest Committee.

My evaluation of University subordinates will not be based, in whole or in part, on their participation (or refusal to participate) in non-University activities involving any business entity in which I have significant financial interest(s) as defined by the University Individual Financial Conflict of Interest Policy. The participation of subordinates in non-University activities involving such business entities will not be expected or required.

I will disclose my financial conflict(s) of interest in writing to all students working on this project. Students will be informed that if they have any concerns about my financial conflict(s) of interest, they can discuss those with their department chair, the chair of their graduate committee or the Individual Conflict of Interest Committee.

My evaluation of University students will not be based, in whole or in part, on their participation (or refusal to participate) in non-University activities involving any business entity in which I have significant financial interest(s) as defined by the University's Individual Financial Conflict of Interest Policy. The participation of students in non-University activities involving such business entities will not be expected or required.

Publication of student, subordinate, or other investigator's work on the project will not be delayed beyond the standard University agreement for review of intellectual property issues.

I will promptly disclose any and all new intellectual property arising from this research to the University of Utah Technology & Venture Commercialization.

I will identify a non-conflicted peer subject to the approval of the Individual Conflict of Interest Committee to review the research and results prior to publication.

I will disclose my financial conflict(s) of interest to all potential research participants in the informed consent documents.

A member of the research team who does not have any conflicts of interest related to this research or an appropriate third party will inform potential research participants of my financial conflict(s) of interest during the informed consent process.

I will recuse myself from participation in the process of obtaining informed consent from all potential research participants for this study. Informed consent for all potential research participants will be obtained by a member of the research team who does not have any conflicts of interest related to this research or by an appropriate third party approved by the Individual Conflict of Interest Committee.

Procedures performed for research purposes only:

Randomization, for those participating in that arm of the study, is distinct from the us clinical care that is provided at participating clinics. In addition, the use of a LNG IUD alone for EC is unique to the study and is not currently offered at the clinics.

Statistical Methods, Data Analysis and Interpretation

Sample Size and Randomization: There are two arms to the study. The main study is a randomized controlled trial with non-inferiority design and participants will be assigned 1:1 to either the copper T380 IUD or the LNG20 IUD for EC. The non-inferiority margin is 2.5% and we assume a pregnancy rate of 0.1% for copper IUD EC users and a 1% EC pregnancy rate for LNG IUD users. This estimate, based on our current COLIEC study (IRB# 50483) is conservative, falling within the 95% confidence interval (CI) of 0%-5.2% of the pregnancy rate of LNG20 IUD plus oral LNG for EC users. **To achieve 80% power to detect a two-sided 95% CI around the EC pregnancy incidence, a percent difference that does not cross the 2.5% noninferiorty margin, will require 335 participants per study arm (total of 670). We will recruit an additional 5%, 36 participants, (total of 706) to accommodate for potential early loss to follow up.** Five percent is a conservative estimate based on our prior successful IUD EC studies. Even with obtaining multiple points of contact information and testing them prior to enrollment this can be a difficult population to maintain contact with. In our prior EC studies at 1 month we lost contact with 12 of 218 (5.5%) IUD users in our copper T IUD vs. oral LNG study and 8 of 176 (4.5%) in the COLIEC study. The use of the 2.5% noninferiority margin is within confidence intervals of previous literature for pregnancies among oral LNG users, which is one of the clinical standards of care (1.7%; 95% CI 0.8%-2.6%) (76) and the continued protection against future unintended pregnancy explored in aim 2 makes this clinically acceptable. In addition, women who currently present for EC and decline a copper IUD are left with a choice of oral EC, which also falls within this confidence interval. While approaching the higher limit of the oral LNG per cycle pregnancy rate from the aforementioned study, it is well below per cycle pregnancy events in some subpopulations using oral LNG, which can result in pregnancy events of 5.8% for women with higher BMIs (>30BMI) and 7.3% in women who have additional unprotected sexual intercourse(28). The LNG20 IUD is not affected by BMI and offers protection against pregnancy following future intercourse.

The maximum number of participants in the entire study is 706.

If recruitment is not adequate with this design and potential participants report concern about randomization as a reason for non-participation then a patient-preference cohort (PPC) will be offered to interested and qualified individuals.

All women presenting to participating clinics when study participation is offered will be presented with a study information sheet, which includes an assessment of interest in the study. If we find that we are not able to meet recruitment goals (e.g. <80 participants enrolled in the first 6 months) and the reason for non-participation is assessed to be lack of willingness to be randomized to the study interventions, then we will add an option for a PPC. Should the PPC be introduced then participants who are interested in the study and eligible for participation but not willing to be randomized will be offered participation through the PPC. While 90% of EC users enrolled in a current study where they can choose their IUD type stated they would be willing to be randomized to either type of IUD, some individuals may be reluctant to agree to random assignment. This potentially impacts result generalizability. In order to evaluate the magnitude and direction of non-participation bias we will offer eligible women presenting for EC who desire an IUD but are not willing to undergo randomization participation in a patient-preference cohort (PPC). Participants in the PPC may choose the

IUD they desire. The PPC will allow us to ascertain selection bias due to RCT non-participation.

Outcomes

Primary Outcome: Emergency contraception failures in both arms as assessed by positive urine pregnancy tests (HCG >25 IU) 4 weeks after having the IUD inserted.

Secondary Outcomes:

one-year unintended pregnancy rates

Assess the one-year continuation, satisfaction, pain, and bleeding patterns of a LNG20 IUD to a copper T380 IUC as a method of EC

- Pregnancy rates in the first year after presenting for EC
- Timing of IUD insertion relative to time in the menstrual cycle (pre-ovulatory, ovulatory, post-ovulatory)
- Unplanned pregnancy rates in the first year after presenting for EC
- Effect of IUD choice on vaginal bleeding assessed monthly by Pictorial Blood Assessment Chart
- Infections
- IUD continuation, expulsions, and removals through the first year after presenting for EC
- Satisfaction with EC method and contraception chosen
- Sexual satisfaction at baseline and through the first year after presenting for EC
- Frequency of unprotected intercourse since presenting for EC
- Use of contraception in the year following presentation for EC
- New diagnosis of any STI
- IUD related complications
- Abortion
- Contraception related side effects
- Use of a barrier method for prevention of sexually transmitted infections

Data Analyses:

The primary objective will be tested by non-inferiority design to test the hypothesis that the LNG IUD is no worse than the copper IUD with a noninferiority margin of 2.5%. Using Blackwelder's approach for equivalence testing,[8] comparing those who become pregnant during the menstrual cycle in which their study IUD was inserted. Noninferiority will be established if the lower bound of a two-sided 95% CI does not cross the noninferiority bound. Analysis will be by intention to treat.

For objective #2, comparison of one-year unintended pregnancy rates from women initiating the levonorgestrel IUD vs. copper T380 IUD for EC, will be assessed by Kaplan-Meier estimates. This same approach will be utilized to construct estimates of the proportion of patients who continue with their selected IUD for 1 year (continuation

proportion). Continuous variables will be assessed by t-tests and discrete variables by Chi-square testing as appropriate.

All data will be analyzed using Stata statistical software (College Station, Texas). Standard quality control methods will be employed including use of an independent data safety monitor.