# Levonorgestrel Intrauterine System For Emergency Contraception: a Randomized Control Trial

**NCT01539720**

December 30, 2014

## The LIFE Study: Levonorgestrel Intrauterine System for Emergency Contraception

Protocol Number: 14-458

**Abbreviation Note**:

IUD = intrauterine device (can be either copper or hormonal (levonorgestrel or LNG);
IUS = intrauterine system (refers to the LNG-IUS or Mirena IUD);
In this protocol, we may refer to the LND-IUS or LNG-IUD (synonyms)

**BACKGROUND & SIGNIFICANCE:**

Among the most frequently used methods of contraception are daily-dosing regimens such as oral contraceptive pills, or coital-dependant methods such as condoms.[1] These methods have high typical use failure rates (> 8%)[2] contributing to the unintended pregnancy rates in the United States that approach 50% each year. Unintended pregnancy has serious economic and social consequences for both individuals and society as a whole.[3,4] Emergency contraception (EC) has been shown to be effective in preventing pregnancy when used within 120 hours of unprotected or under-protected intercourse.[5] Disappointingly, EC has not made a dramatic impact on abortion rates.[6,7] The most common regimen used today is a progestin-only (levonorgestrel) oral regimen which has been shown to reduce pregnancy risk by 60-94%.[8-14] The copper T-380 intrauterine device (IUD) has been shown to have even greater efficacy reducing the risk of pregnancy by 99%.[15-17] This method is not as commonly used, likely because of high up-front cost or associated side-effects. A recent observational feasibility study provided promising results; when offered a choice of the oral levonorgestrel (LNG) regimen or copper T-380 IUD, the ratio of oral LNG to IUD users was 1.5 to 1.[18] This study demonstrated that when cost and access barriers are removed, women are willing to use the intrauterine device for EC. The copper intrauterine device has the added benefit of continued highly effective contraception for up to ten years which has the potential to impact unintended pregnancy rates.

There is a second, more popular intrauterine contraceptive method available in the U.S, the levonorgestrel intrauterine system (LNG-IUS), which has not yet been evaluated as an emergency contraceptive method. The LNG-IUS is more appealing to women as it offers many noncontraceptive benefits with many users reporting lighter and less painful menses. [19-21] There are currently no data available evaluating the LNG-IUS as a method of emergency contraception. However, several of the mechanisms by which the LNG-IUD is thought to work suggest that suggest it may be effective in the post-coital (EC) setting. Potential mechanisms include both pre- and post-fertilization effects. Pre-fertilization effects include disruption of sperm motility and viability, alteration in the speed of ovum transport, and direct damage to the ovum.[22] Immediate endometrial changes initiated by both the LNG and copper-IUD likely inhibit sperm migration in a spermicidal fashion.[23,24] Additionally, the decidualization process initiated by the LNG-IUD may also inhibit sperm survival.[24] Postfertilization mechanisms include slowing of embryo transport, destruction of the embryo during transit, and prevention of implantation.[22] Both IUDs have been shown to produce cytokines and integrins within the endometrial lining that would likely prevent implantation.[25-27] Lastly, an inflammatory response of the endometrial lining most likely contributes to the prevention of implantation in LNG-IUD users.[28]

The proposed research is designed to evaluate the pregnancy rates in women using the LNG-IUS for EC. We expect to show that the LNG-IUS can be used as an effective method of emergency contraception and has higher efficacy rates than oral EC. Confirming effectiveness of the LNG-IUS in this setting will expand access and uptake. *Increasing the use of intrauterine contraception as a method of emergency contraception and providing long-term reversible contraception, has the potential to significantly reduce unintended pregnancy and abortion rates.* In 2009, the Institute of Medicine declared expanding access to long-acting reversible

contraceptive (LARC) methods one of the top priorities of comparative effectiveness research[29], and this study will help reach that goal.

**INNOVATION**:

There are currently no data addressing the use or effectiveness of the LNG-IUS as a method of emergency contraception. This proposal will provide essential information to both patients and clinicians in this field. Specifically, the LIFE study (levonorgestrel IUS For Emergency contraception) will answer the following questions:

1) Is the LNG-IUS an effective method of emergency contraception?
2) Is the LNG-IUS more effective than the oral levonorgestrel regimen?
3) Are women receiving LNG-IUS more likely to be using a LARC method at 6 months?
4) Are women receiving the LNG-IUS as emergency contraception still using and satisfied with their method at 6 months and at 12 months?

Current practices in the United States provide women 4 choices of EC. A modified regimen of combined oral contraceptives (Yuzpe method) has been shown to be the least effective and associated with the most side-effects.[12] There are two additional oral regimens, the levonorgestrel and ulipristal acetate regimens which are effective for a single act of unprotected intercourse. The most commonly-used method is the oral levonorgestrel regimen which is largely available over the counter. Ulipristal acetate is the newest regimen, approved by the FDA in August 2010, requires a physician prescription, and is more expensive than the levonorgestrel option. The most effective, least used and most expensive method of EC is the Cu-T380.[16,17] This method, unlike the previous methods, provides continued highly effective long-term contraception. The levonorgestrel-IUS is the only other intrauterine device available in the U.S. The LNG-IUS is currently used only for standard contraception, not emergency contraception. In this setting it has been shown to be highly effective, convenient, forgettable, cost-effective, and extremely well-liked by users.[30,31] *This research is innovative, because we will be evaluating a new method of emergency contraception and expanding access to include a well-liked, long-term, and extremely effective method of contraception that has the potential to reduce unintended pregnancy and abortion rates.* The American College of Obstetricians and Gynecologists Committee on Gynecologic Practice Opinion, published in 2009 suggested that the high rates of unintended pregnancy may be a direct consequence of low use of long acting reversible contraceptives.[32]

**APPROACH**

General: The purpose of this proposal is to recruit 532 women experiencing an act of under-protected intercourse, defined as a breech or incorrect use of a contraceptive method or no method use at all, who do not desire pregnancy at this time.

Participants will be randomized to ulipristal acetate (the most effective oral EC available) or to the study therapy, levonorgestrel intrauterine system (LNG-IUS). The primary outcome of this study is pregnancy occurring despite treatment. We will address the following specific aims:

**Primary Aim**: Our *primary aim* is to evaluate the effectiveness of the LNG-IUS as a method of emergency contraception (EC) by comparing observed pregnancy rates in those receiving oral ulipristal acetate (UPA) and LNG-IUS. The *objective* of this aim is to provide evidence that will expand access to this highly effective

method of long term contraception. We will perform a randomized controlled trial comparing pregnancy rates in women receiving the LNG-IUS to those receiving the oral EC.
*Hypothesis:* The LNG-IUS will be more effective than the oral UPA as a method of EC and through 6 months after enrollment.

The *rational* for this aim is that successful completion of this project will provide important evidence for an alternative method of emergency contraception. It is our *expectation* that the knowledge gained from completion of this project will reduce barriers to intrauterine contraception, thereby increasing the number of women using the method, and subsequently impacting unintended pregnancy and abortion rates.

**Secondary Aim 1:** Our secondary aim is to evaluate long-acting reversible contraceptive (LARC) use at 6 and 12 months following initial treatment. The *objective* of this aim is to demonstrate that offering LARC as EC can increase the number of women using the most effective methods of contraception.
*Hypothesis*: When compared to women who receive the oral UPA, women who receive intrauterine contraception as a form of EC have higher rates of LARC use at 6 and 12 months.

It is our *expectation* that the anticipated difference in LARC use at 6 and 12 months between the two groups will provide supportive evidence for the importance of reducing barriers to intrauterine contraception by offering it as a method of EC.

**Secondary Aim 2**: One secondary aim of this project is to quantify the contraceptive continuation and satisfaction rates of the participants randomized to LNG-IUS. The objective of this aim is to demonstrate that if women have access to the LNG-IUS in this time period, most will continue use for at least 12 months and will have high levels of satisfaction. *Hypothesis*: Greater than 70% of women receiving the LNG-IUS as EC will have continued use and satisfaction.

It is our *expectation* that the information gained from completion of this aim will contribute to the growing body of literature describing continuation and satisfaction rates among different groups of LARC users.

**Research Design and Methodology**:

Research design and general methodological approach: We will perform a randomized control trial comparing oral UPA to LNG-IUS for emergency contraception. We will prospectively enroll 532 women experiencing an act of under-protected intercourse within the previous 5 days (120 hours). Participants with a negative pregnancy test, and who meet all inclusion criteria, will be randomized to either an immediate LNG-IUS insertion or oral UPA EC regimen (30mg ulipristal acetate) in a 3:1 ratio. Participants will be provided with a pregnancy test to perform at home and will be called to report the results of the urine pregnancy test 5-6 weeks after insertion. Participants receiving the LNG-IUS will also be return for a brief visit to check LNG-IUS strings. Participants will be contacted via telephone at 6 and 12months post enrollment to complete a follow-up survey. The primary outcome of this study is observed pregnancy rates at 5 weeks and 6 months after enrollment.

Criteria for selection of subjects: Potential participants for this study will be identified in as follows: 1) Women enrolled in the Contraceptive CHOICE Project (CHOICE) who are not currently using a long acting reversible contraceptive (LARC) method and have experienced an act of under-protected intercourse in the previous 5

days; 2) Women presenting, either in person or via telephone contact, to the Barnes Jewish Hospital Women's Health resident OB/GYN clinic who have experienced an act of under-protected intercourse in the previous 5 days; 3) Women identified from an advertising campaign; and

Enrollment**:** All potential participants receive informed consent and will be directed to make an appointment for consent, randomization, and allocation of method.

Inclusion Criteria:

- Women age 14-45
- Under-protected intercourse within the last five days (120 hours)
- Willingness to accept either IUS intervention or oral EC
- Ability and willingness to follow-up via telephone for results of a urine pregnancy test (UPT)
- Ability and willingness to be contacted by phone for 6 and 12 month follow-up

Exclusion Criteria:

- Positive pregnancy test
- Non-English speaking
- Contraindication to intrauterine contraception or oral UPA
    - Active cervicitis, PID, or recent post-abortal or postpartum infection
    - Undiagnosed abnormal uterine bleeding
    - Known or suspected cervical or endometrial neoplasia
    - Known or suspected breast cancer or other progestin-sensitive cancer
    - Uterine anomalies that preclude IUD insertion
- Inability or unwillingness to comply with follow-up

Randomization: A permuted block randomization scheme will be created using the nQuery software (Statistical Solutions, Saugus, MA) using a computerized random number generator. Block sizes will vary, and will be balanced within each recruitment site. Assignment will be concealed in sealed, opaque envelopes. Participants will be randomly assigned to LNG-IUS or oral UPA with a 3:1 ratio.

Description of drugs and devices:

The U.S. Food and Drug Administration (FDA) approved the LNG-IUS in 2000 as a 5-year method of reversible contraception. The device contains 52 mg of levonorgestrel which is slowly released at a rate of 20 mcg/day into the uterus. The device is safe, effective and easy to use in almost all populations. The standard contraceptive mechanism of action is through cervical mucus thickening and endometrial lining suppression.[33] The device has not yet been evaluated as a method of emergency contraception. However, the WashU study team submitted an IND application to the FDA, and obtained an IND to study the device as a method of EC. A clinician trained in IUD insertions will insert the LNG-IUS.

The FDA first approved oral levonorgestrel with a dedicated indication for emergency contraception in 1998. There are currently two acceptable dosing protocols, single-dose, and two-dose, both of which contain a total of 1.5 mg of levonorgestrel. There are several proposed mechanisms by which this regimen reduces pregnancy: inhibited or delayed ovulation,[34-36] interference with sperm transport and penetration,[37] and

endometrial changes decreasing receptivity. It has been shown to have no effect on an already established pregnancy and is not a form of medical abortion.[38]

The FDA approved Ulipristal acetate in August 2011(ulipristal acetate) is a synthetic progesterone agonist/antagonist. When taken immediately before ovulation is to occur, Ella postpones follicular rupture. The likely primary mechanism of action of ulipristal acetate for emergency contraception is therefore inhibition or delay of ovulation; however, alterations to the endometrium that may affect implantation may also contribute to efficacy.

Ulipristal acetate (UPA) is specifically indicated as an emergency contraceptive for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. UPA is supplied as a tablet for oral administration. The recommended dose is one 30 mg tablet taken orally as soon as possible, within 120 hours (5 days) after unprotected intercourse or a known or suspected contraceptive failure.

Complete descriptions of both LNG-IUS (Mirena) and UPA (Ella) are provided in the Package Inserts. Copies of each package insert are provided in the Appendices.

Evaluation/ Follow-Up:

At enrollment all women will undergo a highly sensitive urine pregnancy test as well as self-collected vaginal swab for sexually transmitted disease (STI) testing for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Randomization and allocation of emergency contraceptive method will occur immediately following consent. A positive test for an STI will not exclude the patient from participation. All positive *N. gonorrhoeae* or *C. trachomatis* tests will be treated with standard CDC-approved treatment. Partner treatment will also be offered. Women randomly assigned to the LNG-IUS group will be asked to return at 5-6 weeks for a string check. All participants will be provided a urine pregnancy test at enrollment and will be called at 5 weeks post enrollment to obtain results. Participants will then be contacted to complete a follow-up surveys at 6 and 12 months following enrollment.

Measures: Urine pregnancy test results will be documented at 5-6 weeks following method allocation. Negative urine pregnancy tests will be validated by a normal menses after enrollment. Participants testing positive at home will be asked to come into the study site for pregnancy test validation and options counseling. We have studied over 9,000 women attempting to avoid unintended pregnancy in the Contraceptive CHOICE Project. Participants were able and willing to report home pregnancy testing results and/or return for a visit for a sensitive pregnancy test. Any woman who suspects pregnancy, is late for her routine menstrual cycle, or who reports a positive home test will be asked to return to our clinic for pregnancy test validation and options counseling (offered option of continuing the pregnancy or pregnancy termination). *We are using the CONSULT urine pregnancy test which is sensitive to a hcg level of 20mIU/mL with a specificity of >99% (Appendix A).*

Women enrolled in an EC study are clearly motivated to avoid an unintended pregnancy. A negative home pregnancy test and regular menses reliably excludes an on-going pregnancy. Self-report of a negative test and menses will not be validated, as they are acceptable measures to reliably exclude pregnancy. Pregnancy

testing in this protocol has been used for the CHOICE project, with two peer-reviewed publications accepted to the New England Journal of Medicine (Winner B. et al. 2012 & Secura G. et al. 2014)

At the follow-up phone surveys, individual level information will be updated with new medical data including any new medical diagnosis, interval pregnancies since enrollment, and interval diagnosis of STIs. We will also assess fertility desires, recent and current contraceptive use, and recurrent emergency contraception utilization.

Primary Outcome: The **primary outcome** of this study is unintended pregnancy following emergency contraception at both 5 weeks and 6 months post-enrollment.

Secondary Outcomes: 1. Long acting reversible contraception (LARC) use at 6 and 12 months following method allocation will be evaluated. 2. Continuation and satisfaction among participants in the LNG-IUS arm.

Potential Confounders: There are a number of variables that make act as potential confounders. These variables will be tested for their association with the primary outcome and treatment assignment. Age is strongly associated with fertility. Other potential confounders include: race/ethnicity, socioeconomic status (measured by income or education level), history of sexually transmitted infection or pelvic inflammatory disease, previous or current contraceptive method. Given random assignment, we expect two arms will be balanced in terms of known and unknown confounding variables. However, if any imbalance is noted, we will control for possible confounders in our multivariable statistical analysis.

Data Management: Study staff located within the Division of Clinical Research will be responsible for data collection, entry, and management. Off-site staff will enroll participants remotely using the RedCap secure website. All telephone follow up surveys will be conducted by study staff of Washington University in St. Louis, School of Medicine. Data from telephone interviews will be entered using a secure web portal and stored on secure Washington University in St Louis Department of Obstetrics and Gynecology servers. All participants will be assigned a study identification number. This study I.D. will be used on all data forms and for all computer entries. Data entry will be completed using a custom software package (Illume ™; DatStat Inc., Seattle, WA). The data manager will be responsible for data processing, validity checks, and communication with the team on data issues.

**Statistical Approach & Data Analysis**:

Preliminary Analysis: Descriptive analyses will include comparison of the baseline characteristics of participants in the two treatment arms. Continuous variables will be summarized using means, medians, and standard deviations. Categorical variables will be presented as frequencies. Continuous variables that are normally distributed will be analyzed with Students T-test, and for those that are not normally distributed nonparametric tests will be used. Chi-square and Fisher's exact will be used to analyze ordinal variables.

Primary Aim: Observed pregnancies in the LNG-IUS group will be compared to those in the oral group. Because our primary outcome, pregnancy rate (yes/no) is a dichotomous variable, logistic regression will be used.

Secondary Aim1: One secondary aim is to evaluate long-acting reversible contraception (LARC) use at 6 and 12months. We hypothesize that women randomized to the LNG-IUS group will be more likely to be using a LARC method. This categorical variable (yes/no use) will be presented as frequency of LARC use in the two groups. Chi-square and logistic regression will be used for analysis.

Secondary Aim2: Continuation and satisfaction in LNG-IUS arm will be evaluated. Both continuation and satisfaction will be assessed as dichotomous variables. Continuation and satisfaction (satisfied/ not satisfied) will be presented as frequencies and analyzed with Chi-square and logistic regression.

**Power Analysis and Sample Size**

Power analysis and Sample size calculation was performed with Epi-Info v 6.0.

**Sample Size:** With an alpha (α) = 0.05, power of 90%, and assuming unintended pregnancy rates (total 5 weeks through 6 months) of 11% for the oral UPA regimen and 2% for the LNG-IUS, and a 3:1 ratio of LNG-IUS allocation to UPA, we calculate our sample size to be 532 participants (399 LNG-IUS and 133 UPA). This accounts for approximately 20% loss to follow-up rate by 6 months. We chose a 3:1 ratio of LNG-IUS to UPA to allow for a more precise estimate of immediate failure rates of the LNG-IUS group.

**Data Analysis/Statistical Methods:**
*Preliminary Analysis*: Descriptive analyses will include comparison of the baseline characteristics of participants in the two treatment arms. Continuous variables will be summarized using means, medians, and standard deviations. Categorical variables will be presented as frequencies. Continuous variables that are normally distributed will be analyzed with Students t-test, and nonparametric tests will be used for those that are not normally distributed. Chi-square and Fisher's exact tests will be used to analyze categorical variables.

*Primary Aim*: Observed pregnancies at 5-6 weeks and at 6 months in the LNG-IUD group will be compared to those in the oral UPA group. The analysis population is enrolled women who complete 5-6-week and 6 month follow-up. "Modified" intent to treat analysis will be used. Pregnancies will be presented as frequencies and chi-square tests will be used for analysis. We expect the two groups to be balanced on important confounding variables such as menstrual cycle day at the time of unprotected intercourse. However, if there are significant imbalances, stratified or multivariable analysis will be performed. Pregnancies at 5-6 weeks and 6 months will be compared by intervention arm with Kaplan-Meier estimates, using dating from last menstrual period time. Logistic regression will be used to control for confounding (if necessary) using the dichotomous outcome of pregnancy (yes/no) at each time point.

*Secondary Aim1*: Descriptive analyses will be used to compare demographic characteristics of participants who screen eligible, but decline to participate and those who enroll in the study. Reasons for declining participation will also be collected and qualitatively evaluated for recurrent themes.

*Secondary Aim2*: Long-acting reversible contraceptive (LARC) use (either an IUD or contraceptive implant) at 6 and 12 months will be compared between the two randomization groups and presented as frequencies. Women who become pregnant will be censored at that point, as well as those who stop the method because they desire pregnancy. Use of LARC and satisfaction in the LNG-IUD arm will be assessed as an ordinal variable and models with ordered logistic regression analysis.. We will compare women lost-to-follow up with the baseline sample to assess whether they vary on demographic factors or method type. If we detect non-random loss-to-follow-up, we will consider the impact on the interpretation of our results.

**Right to Withdraw or Removal from Study:** Participants are free to withdraw from this study at any time. The subject must inform the Investigator immediately if they intend to withdraw. To terminate the subject's participation in this study, they must contact PI listed on the informed consent form. They will be asked complete a brief end-of-study telephone interview. Their decision to participate in this study or to withdraw from this study will not influence the availability of their future medical care and will involve no penalty or loss of benefits to which they are otherwise entitled.

Study Principal Investigators, the FDA, or NEIRB (central IRB) can remove the subject from this study without their consent for any reason, including, but not limited to:

a. Investigator judgment that any condition or circumstance may jeopardize their welfare or the integrity of the study.
b. Participant fails to follow the instructions of the investigator(s).
c. Side effects or complications experienced by the participant.
d. If the study is stopped by the sponsor, Data Safety and Monitoring Board (DSMB), investigators, FDA, or NEIRB prior to completion.

**RISK MANAGEMENT:** All other known risks will be disclosed to the subject via the informed consent process. Risks of either method of EC are outlined in the package insert and this protocol. There is also a risk of unintended pregnancy. Patients with a positive pregnancy test will be provided with options counseling.

**ADVERSE REACTIONS:** There are few side effects of UPA and LNG-IUS. These are listed in the protocol and informed consent form. Most side effects resolve spontaneously. Anticipated events means reactions to treatment previously observed that may require medical intervention but are not serious in nature.

All adverse events that occur will be recorded in the Source Documents. Adverse events should be captured in the medical history.

Adverse Events occurring will be captured and followed until the condition resolves, stabilizes, or is otherwise explained, or the subject is lost to follow-up. Subjects will be instructed that they may contact one of the Principal Investigator at any time throughout the course of the study.

The Investigator will review each event and assess its relationship to method of EC (not related, unlikely, possible, probable, and highly probable). The following definitions will be used for rating relationship to the treatments or investigational device:

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

Each adverse event reported will be graded on a 3-point severity scale. The following definitions for rating severity will be used:

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

**A Serious Adverse Event** is any adverse device experience that results in any of the following outcomes: death, a life-threatening adverse device experience, in-patient hospitalization or prolongation of hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may or may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse device experience when, based upon appropriate medical judgment, they may jeopardize the subject or subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition

If any of the above adverse events are serious as defined by the FDA Code of Federal Regulations (CFR), Title 21, special procedures will be followed. All serious adverse events will be reported within 24 hours of acknowledgment to the Medical Monitor whether or not the serious events are deemed treatment-related. All serious event reporting will adhere to 21 CFR part 812 and the IRB will be notified accordingly.

Adverse events, whether serious or non-serious, will be followed until the condition is resolved, stabilized, or otherwise explained, or the subject is lost to follow-up. Adverse events will be captured up to one week after a subject completes the study and where appropriate, medical tests and examinations will be performed to document the resolution of event(s).

Outcomes may be classified as resolved, improved, unchanged, worse, fatal, or unknown (lost to follow-up). Following the resolution of any study-associated adverse events there will be no further adverse event reports for that subject.

**PROTOCOL DEVIATIONS:** No deviations from this protocol will be permitted, except in a medical emergency, without the approval of the Coordinating Center/Sponsor. Any amendment to this study will be discussed by the Investigators and the Coordinating Center. If agreement is reached concerning the need for modification, this will be made in a formal amendment to the protocol. All requests for protocol deviations must be approved by the IRB. If a deviation occurs, the Investigator must inform the Sponsor and IRB in writing within 10 days.

**DATA COLLECTION AND MONITORING:** The coordinating center (WashU/sponsor) will train all investigative sites. The sponsor will also monitor the site at various intervals and upon request expects to receive intermediate results by fax following each visit to evaluate treatment progress in accordance with the sponsor's monitoring procedures and guidelines. Case Report Forms and Investigator Binders will be reviewed for current data. The sponsor will collect data at the end of the follow-up period. The sponsor will list the study on clinicaltrials.gov as required by FDA regulations.

**CONFIDENTIALITY AND DISCLOSURE OF MEDICAL INFORMATION:** As part of this study the Investigator and the team at each research facility will keep records of subject participation in the study. These study records will include personal information that the subjects provide including age, sex, etc., the results of the study, information about response to treatments, and other medical information relating to participation in the study. Under federal law the study records cannot be used or disclosed by the research Investigator for research purposes unless subjects sign the informed consent authorization.
The sponsor and its consultants will analyze and evaluate study results and information and may report them to the U.S. Food and Drug Administration (the FDA) or other regulatory agencies in the United States. Study records will be assigned a code number by the study team and the subject will ordinarily not be identified by name in the study records that are sent to the Sponsor and its consultants. However, The Sponsor and its consultants will have the right to see the complete study records.

The research facility will review and use the study records for purposes of this study. De-identified data sets will also be shared with potential investors and others related to the business of the Sponsor. However, no identifiers will be shared with these third parties. They will keep the subject identity confidential and, except for the disclosures described above, will not disclose the study records to other parties unless disclosure is required by law. Once the research facility discloses information in the study records or medical records to the Sponsor or its consultants, the information will no longer be protected by federal law. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. However, the Sponsor and its consultants will only use the information for purposes of the study and will not disclose the study records to parties other than the FDA and similar government agencies, unless disclosure is required by law. If reports or articles are written about the study, subjects will not be identified by name or other identifier.

**CLINICAL RESEARCH CONDUCT:** The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) GCP guidelines, applicable regulations and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki. The investigators ensure that the study is conducted in accordance with the provisions as stated in the FDA regulations and complies with the applicable local or regional regulatory requirements.

**INFORMED CONSENT**: All participants will be introduced to the study and will be screened for eligibility based on above stated inclusion/exclusion criteria. If interested and eligible, potential participants will be given an informed consent form to read and review. Research personnel will then explain the study to the potential participant, outline key risks, benefits, and alternatives (including not participating), and then have participants signed the informed consent form (ICF). A copy of the ICF will be given to the participant, and a copy will be kept in the participants research file.

**REPORTING FOR THE STUDY:** A study summary report will be generated. It will include a description of the clinical conduct of the study and results, and the statistical analysis described in the data analysis section of this protocol. We anticipate that the results of this investigation will be submitted for publication in peer-reviewed journals.

**RESPONSIBILITY OF THE INVESTIGATOR:** The Investigator is responsible for ensuring that the clinical study is performed in accordance with the Declaration of Helsinki (revised version of Edinburgh, Scotland, 2000 including notes of clarification, Washington, 2002 and Tokyo, 2004) and FDA Good Clinical Practice Regulations (21 CFR parts 50, 56, and 812). Investigators will supply information to the sponsor such that the sponsor can comply with the Financial Disclosure Rules (21 CFR Part 54).

**INSTITUTIONAL REVIEW BOARD**: This protocol, informed consent forms, and any amendments to the protocol will be reviewed by the appropriate Institutional Review Board prior to initiation. The study will not be initiated without the approval from the Institutional Review Board.

**TERMINATION OF STUDY**: The Coordinating Center/Sponsor, Investigators, FDA, and NEIRB reserve the right to discontinue this study for administrative reasons at any time. Coordinating Center/Sponsor, Investigators, FDA, and NEIRB reserve the right to discontinue the study for safety reasons at any time.

**STUDY RECORDS**: All records and documents pertaining to the study will be maintained in appropriate permanent files as per the ICH guidelines for Essential Documents for the Conduct of a Clinical Trial and 21 CFR 11, and will be available for inspection by the Sponsor, Sponsor designee, or the Food and Drug Administration at any time.

**CONFIDENTIALITY**: After the informed consent has been signed, each subject will be entered on a screening/enrollment log, which will be kept with the study records. Once a subject is consented, a unique subject identification number will be assigned. No two subjects will have the same subject identification number. This subject identification number will identify the subject throughout the study and will be used for all source documents, and Data Collection Forms. The subject identification number will be held confidential so

far as permitted by law. Investigative site staff, the Sponsor or its designee, and, under certain circumstances, the FDA and Institutional Review Board (IRB) will be able to inspect and have access to the subject identification number and the confidential data that it links to. Any publication or presentation of data will not contain any identifiable subject information.

**DATA SECURITY**: To ensure the privacy and confidentiality of data for this protocol, the data will be stored on a restricted access location on a WashU server. Access to the project directory containing the data will be limited to the investigators and research staff. Information about data security awareness is promoted through user training and education, supplemented by policies and procedures. Password protection will be used for all transactions that allow viewing, editing, and analysis of data, or that provide access to data fields derived from the original source documents.

**References Cited:**


1. Mosher WD, Jones J. Use of contraception in the United States: 1982-2008. *Vital Health Stat. 23.* Aug 2010(29):1-44.
2. Hatcher RA TJ, Nelson A, Cates W, Stewart F, Kowal D. *Contraceptive Technology.* 19 ed: Ardent Media; 2007.
3. Sonfield A, Kost K, Gold RB, Finer LB. The public costs of births resulting from unintended pregnancies: national and state-level estimates. *Perspectives on sexual and reproductive health.* Jun 2011;43(2):94-102.
4. Monea E, Thomas A. Unintended pregnancy and taxpayer spending. *Perspectives on sexual and reproductive health.* Jun 2011;43(2):88-93.
5. Cheng L, Gulmezoglu AM, Piaggio G, Ezcurra E, Van Look PF. Interventions for emergency contraception. *Cochrane Database Syst Rev.* 2008(2):CD001324.
6. Raymond EG, Trussell J, Polis CB. Population effect of increased access to emergency contraceptive pills: a systematic review. *Obstet Gynecol.* Jan 2007;109(1):181-188.
7. Glasier A, Fairhurst K, Wyke S, et al. Advanced provision of emergency contraception does not reduce abortion rates. *Contraception.* May 2004;69(5):361-366.
8. Ngai SW, Fan S, Li S, et al. A randomized trial to compare 24 h versus 12 h double dose regimen of levonorgestrel for emergency contraception. *Hum Reprod.* Jan 2005;20(1):307-311.
9. Arowojolu AO, Okewole IA, Adekunle AO. Comparative evaluation of the effectiveness and safety of two regimens of levonorgestrel for emergency contraception in Nigerians. *Contraception.* Oct 2002;66(4):269-273.
10. von Hertzen H, Piaggio G, Ding J, et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. *Lancet.* Dec 7 2002;360(9348):1803-1810.
11. Ho PC, Kwan MS. A prospective randomized comparison of levonorgestrel with the Yuzpe regimen in post-coital contraception. *Hum Reprod.* Mar 1993;8(3):389-392.
12. Randomised controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. Task Force on Postovulatory Methods of Fertility Regulation. *Lancet.* Aug 8 1998;352(9126):428-433.
13. Hamoda H, Ashok PW, Stalder C, Flett GM, Kennedy E, Templeton A. A randomized trial of mifepristone (10 mg) and levonorgestrel for emergency contraception. *Obstet Gynecol.* Dec 2004;104(6):1307-1313.
14. ACOG Practice Bulletin No. 112: Emergency contraception. *Obstet Gynecol.* May 2010;115(5):1100-1109.
15. Trussell J, Leveque JA, Koenig JD, et al. The economic value of contraception: a comparison of 15 methods. *Am. J. Public Health.* Apr 1995;85(4):494-503.
16. Zhou L, Xiao B. Emergency contraception with Multiload Cu-375 SL IUD: a multicenter clinical trial. *Contraception.* Aug 2001;64(2):107-112.
17. Fasoli M, Parazzini F, Cecchetti G, La Vecchia C. Post-coital contraception: an overview of published studies. *Contraception.* Apr 1989;39(4):459-468.

18. Turok DK, Gurtcheff SE, Handley E, Simonsen SE, Sok C, Murphy P. A pilot study of the Copper T380A IUD and oral levonorgestrel for emergency contraception. *Contraception.* Dec 2010;82(6):520-525.
19. Beatty MN, Blumenthal PD. The levonorgestrel-releasing intrauterine system: Safety, efficacy, and patient acceptability. *Ther Clin Risk Manag.* Jun 2009;5(3):561-574.
20. Hubacher D, Grimes DA. Noncontraceptive health benefits of intrauterine devices: a systematic review. *Obstetrical & gynecological survey.* Feb 2002;57(2):120-128.
21. Hendlish SK, Horowicz-Mehler NC, Brixner DI, et al. Contraceptive and noncontraceptive benefits of the LNG-IUS in a vertically integrated HMO. *Contraception.* Jul 2008;78(1):36-41.
22. Stanford JB, Mikolajczyk RT. Mechanisms of action of intrauterine devices: update and estimation of postfertilization effects. *Am. J. Obstet. Gynecol.* Dec 2002;187(6):1699-1708.
23. Sivin I. IUDs are contraceptives, not abortifacients: a comment on research and belief. *Stud. Fam. Plann.* Nov-Dec 1989;20(6 Pt 1):355-359.
24. Mishell DR, Jr. Intrauterine devices: mechanisms of action, safety, and efficacy. *Contraception.* Sep 1998;58(3 Suppl):45S-53S; quiz 70S.
25. Ammala M, Nyman T, Strengell L, Rutanen EM. Effect of intrauterine contraceptive devices on cytokine messenger ribonucleic acid expression in the human endometrium. *Fertil. Steril.* Apr 1995;63(4):773-778.
26. Archer DF, DeSoto KR, Baker JM. Interleukin-6 and tumor necrosis factor-alpha concentrations in the intrauterine cavity of postmenopausal women using an intrauterine delivery system releasing progesterone. A possible mechanism of action of the intrauterine device. *Contraception.* Mar 1999;59(3):175-179.
27. Savaris R, Zettler CG, Ferrari AN. Expression of alpha4beta1 and alphavbeta3 integrins in the endometrium of women using the T200 copper intrauterine device. *Fertil. Steril.* Dec 2000;74(6):1102-1107.
28. Nilsson CG, Luukkainen T, Arko H. Endometrial morphology of women using a d-norgestrel-releasing intrauterine device. *Fertil. Steril.* Apr 1978;29(4):397-401.
29. Institute of Medicine (US). Initial national priorities for comparitive effectiveness research. Wshington DNAP.
30. Peipert JF, Zhao Q, Allsworth JE, et al. Continuation and satisfaction of reversible contraception. *Obstet. Gynecol.* May 2011;117(5):1105-1113.
31. Trussell J. Update on the cost-effectiveness of contraceptives in the United States. *Contraception.* Oct 2010;82(4):391.
32. ACOG Committee Opinion no. 450: Increasing use of contraceptive implants and intrauterine devices to reduce unintended pregnancy. *Obstet. Gynecol.* Dec 2009;114(6):1434-1438.
33. Luukkainen T, Toivonen J. Levonorgestrel-releasing IUD as a method of contraception with therapeutic properties. *Contraception.* Nov 1995;52(5):269-276.
34. Durand M, del Carmen Cravioto M, Raymond EG, et al. On the mechanisms of action of short-term levonorgestrel administration in emergency contraception. *Contraception.* Oct 2001;64(4):227-234.
35. Hapangama D, Glasier AF, Baird DT. The effects of peri-ovulatory administration of levonorgestrel on the menstrual cycle. *Contraception.* Mar 2001;63(3):123-129.
36. Marions L, Hultenby K, Lindell I, Sun X, Stabi B, Gemzell Danielsson K. Emergency contraception with mifepristone and levonorgestrel: mechanism of action. *Obstet Gynecol.* Jul 2002;100(1):65-71.
37. Kesseru E, Camacho-Ortega P, Laudahn G, Schopflin G. In vitro action of progestogens on sperm migration in human cervical mucus. *Fertility and sterility.* Jan 1975;26(1):57-61.
38. Conard LA, Gold MA. Emergency contraceptive pills: a review of the recent literature. *Current opinion in obstetrics & gynecology.* Oct 2004;16(5):389-395.

**Study Devices and Medications**

**Package Inserts:**

**LNG-IUS**
**http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM245685.pdf**

**Ulipristal Acetate**
**http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022474s000lbl.pdf**

**Risks and Benefits**

The interventions compared in this trial are oral UPA versus LNG-IUS. No serious or life-threatening adverse events are expected. Nonetheless, the following measures will be taken to monitor and investigate adverse events. Immediate EC failures should be uncommon. If more than one pregnancy occurs in the LNG-IUS arm, an urgent DSMB meeting will be convened to discuss the preliminary outcomes. These immediate failures must be put into context of the number of long-term (6 and 12-month) failures to determine if the trial will continue.

According to the Prescribing Information, the most common adverse reactions (≥ 5%) to UPA are headache (18%), abdominal pain (12%), nausea (12%), dysmenorrhea (9%), fatigue (6%), and dizziness (5%). The most common adverse reactions to the LNG-IUS reported in clinical trials (> 10% users) are uterine/vaginal bleeding alterations (51.9%), amenorrhea (23.9%), intermenstrual bleeding and spotting (23.4%), abdominal /pelvic pain (12.8%) and ovarian cysts (12%). With any IUD insertion, there are risks of infection (<1%) and uterine perforation (approximately 0.1%).

Pregnancy

UPA is 93-94% effective in preventing pregnancy
LNG-IUS: We hypothesize the LNG-IUS will be as effective as the Copper IUD for EC

If participant reports a positive pregnancy test, we will: 1) invite the participant in for pregnancy testing and transvaginal ultrasound to confirm location and dating of pregnancy. If the LNG-IUS is in place and intrauterine pregnancy is confirmed, we will recommend and complete removal of IUD.

Pregnancy with IUD

Increased risk of spontaneous abortion
Increased risk of infection in the uterus
Early delivery of fetus if pregnancy continued and IUD left in place

The impact of increased EC access (some forms are now available over-the-counter) on population outcomes and concluded that although use of has EC increased, there has been no demonstrable reduction in unintended pregnancy. By contrast, increased uptake of IUDs in an at-risk population has been shown to dramatically reduce unintended pregnancy and abortion rates. The continued highly effective pregnancy prevention the IUD provides beyond the post-coital period offers a unique opportunity to effect change in the stagnant unintended pregnancy and abortion rates in this country.

Use of the LNG-IUD as an EC method has tremendous public health implications. The device is extremely well liked by users indicating women will continue using it beyond the immediate risk behavior. The numerous non-contraceptive benefits of the LNG-IUD and improved bleeding profile have led to increase uptake when compared to the copper IUD.

Increasing the number of women using IUDs in the post-coital period has the potential to decrease long-term unintended pregnancy and abortion rates in a way that oral regimens have not been able to. Despite improved access to emergency contraception with over the counter availability, rates of unintended pregnancy in the US have not.

## Study Communications Plan

1. Washington University School of Medicine LIFE study staff will have regularly scheduled weekly meetings.
    a. Monthly calls will be scheduled with off-site locations
    b. Create agenda
        i. PI needs to approve agenda
        ii. Email agenda to all members of the LIFE research team the day before the call
    c. Take minutes during call
        i. PI needs to approve the minutes
        ii. Email minutes to all members of the LIFE research team

2. There will be regularly scheduled calls with all study sites. In the early stages of the study the calls and communications may be more frequent.

**3.** Any adverse events should be reported to the PI immediately.

**Retention Plan**

As in past contraceptive studies, we will provide incentives to assist with transport and childcare. We plan to closely monitor follow-up rates as well. When participants enroll, we will collect contact information to include the participant's address; home, cell and work phone numbers; email address; and contact information for two alternate contacts as well.

Participants are called and 5-weeks post enrollment, six-months post enrollment and 12-months post enrollment for short follow up surveys. They are provided a gift card with each completed survey. Participants are able to schedule calls or complete them at the time of contact. At each survey they are reminded that we will be calling them back in a specific time frame.

Participants are contacted at their preferred contact method which is usually a cell phone. If, after 2 attempted calls they are not reached or do not call back, a call is made to alternate contact numbers for the participant; email contact is then attempted, if the participant has still not responded alternate contacts are called.

**<u>Study Flow, Clinic Visits, and Duration of Surveys</u>**

**Initial contact**

Call to screen (5-10 minutes)

- Participant is introduced to the study
- Participant is screened
  If eligible participant is scheduled to enroll as soon as possible

**Enrollment**

Clinic visit (30-45 minutes approximately)

- Participant is directed to an enrollment room and given a copy of the *Informed Consent* to read
- Research assistant logs into RedCap, allowing the participant to read the consent paperwork
- Research assistant goes over the consent document allowing the participant to ask questions
- Consents are signed and dated
- Participant is directed to the clinic restroom with instructions given to provide a urine sample for the *Urine Pregnancy Test* (UPT); and the *self-administered swabs* for chlamydia and gonorrhea testing
- Return to enrollment room and wait for UPT test results to determine eligibility for enrollment
- If participant is not currently pregnant the contact information form, baseline enrollment questionnaire, and clinical enrollment forms are completed
- Randomization to method of Emergency Contraception (EC) is determined
- Participant is directed to clinic waiting room
- Research assistant confers with clinician
- If randomized to oral EC,
    - Participant is given the pills and a cup of water and research assistant observes the participant taking the pill
    - A prescription for refillable oral contraceptive pills is offered
    - Tax forms are filled out and gift card is offered
    - Participant is given UPT to take home
    - Participant is reminded that she will be called for first follow-up in 4-5 weeks
- If randomized to LNG-IUS,
    - Participant is directed to a clinic exam room
    - Clinician performs pelvic exam to determine if there is evidence of cervicitis
    - If no cervicitis is present the LNG-IUS will be inserted by a properly-trained clinicians
    - Tax forms are filled out and a gift card is offered
    - Participant is given UPT to take home
    - Participant is reminded that she will be called for first follow-up in 4-5 weeks

**5-week follow-up**

Phone call (less than 10 minutes)

- Participant is called and asked if she has time to complete 5-week follow-up or would like to schedule an additional call for a more convenient time
- If scheduling a call,
    - Schedule a call for an appropriate time
- Completing 5-week follow-up,
    - Verify participant's date of birth (DOB)
    - Verify contact information
    - Administer 5-week follow-up in RedCap
    - Ask participant if she has any questions
    - Fill out tax office paperwork
    - Mail gift card
    - Remind participant we will call her for another follow-up in about 5 months

**6-month follow-up**

Phone call (less than 10 minutes)

- Participant is called and asked if she has time to complete 6-month follow-up or would like to schedule an additional call for a more convenient time
- If scheduling a call,
    - Schedule a call for an appropriate time
- Completing 6-month follow-up,
    - Verify participant's date of birth (DOB)
    - Verify contact information
    - Administer 6-month follow-up in RedCap
    - Ask participant if she has any questions
    - Fill out tax office paperwork
    - Mail gift card
    - Remind participant we will call her for another follow-up in about 6 months

12-month follow-up

Phone call (less than 10 minutes)

- Participant is called and asked if she has time to complete12-month follow-up or would like to schedule an additional call for a more convenient time
- If scheduling a call,
    - Schedule a call for an appropriate time
- Completing 12-month follow-up,
    - Verify participant's date of birth (DOB)
    - Verify contact information
    - Administer 12-month follow-up in RedCap
    - Ask participant if she has any questions
    - Fill out tax office paperwork
    - Mail gift card
    - Thank participant for participating in the LIFE study