Merck Investigator Studies Program (MISP) Protocol Template	
Requirements for Submitting a Full Proposal	
Section #1 - MISP Protocol Identification	
Study Title:	**Immediate vs. delayed insertion of Nexplanon after termination of pregnancy over 14-weeks gestation**
Request Date:	• January 20, 2015
Institution Name	Family Planning Associates Medical Group, Inc.
Investigator Contact Information: – Full address – Phone No. – Fax No. – e-mail address	Miriam Cremer, MD, MPH Staff physician, Cleveland Clinic Director of Global Health Research, Obstetrics, Gynecology & Women's Health Institute Phone 412-641-6649 Fax 412-641-1133 miriam.cremer@gmail.com

Section #2- Core Protocol	
2.1 Objectives & Hypotheses	2.1 List the objectives. The primary aim of this study is to determine if Nexplanon placed immediately after termination of a second trimester pregnancy vs. 2-4 weeks post-procedure improves use of Nexplanon at 6 months following the pregnancy termination. Secondary objectives include determining the rates of satisfaction, side effects, and repeat pregnancies in each group. Exploratory objectives: • To examine the type of insurance plan that women seeking a second trimester surgical abortion, who also desire Nexplanon for contraception, are enrolled in. Additionally we seek to determine if insurance status is a covariate of the primary endpoint. • To measure the prevalence of lifetime and recent reproductive coercion (RC) and intimate partner violence (IPV) in women seeking second trimester surgical abortion, who also desire Nexplanon for contraception. 2.1.1 List the clinical hypotheses. • Women who receive Nexplanon immediately post abortion will be significantly more likely to be using the device 6 months after the procedure than those assigned to receive the device 2-4 weeks after the procedure. • Women in the immediate insertion group will report significantly greater satisfaction, the same or fewer side effects, and fewer repeat pregnancies than those in the control group. • Women with private health insurance will be significantly more likely to be using the device 6 months after the procedure than those who have public health insurance or no insurance at all. • Insurance status is a significant covariate in predicting the primary endpoint. • Women with a history of RC/IPV at the time of enrollment will have greater odds of having a prior abortion compared with women who report no history of RC/IPV. • Among women randomized to the delayed insertion group, those with a history of RC/IPV at the time of enrollment will be less likely than those without a history of RC/IPV to return to the clinic 2-4 weeks later for Nexplanon insertion.

2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	Nexplanon, an etonogestrel implant, is a safe, highly-effective and well-tolerated method of long-term birth control. In fact, implants are in the top tier of effective contraception (1). Providing women who have had a second trimester termination with the option of an implant could significantly reduce unplanned and undesired future pregnancies. Immediate rather than delayed implant insertion after a termination of pregnancy may be beneficial for several reasons. The most compelling argument is poor post-operative follow up rates. On a national level the percentage of patients that do not return for this visit is about 35-60% (2). Given the poor follow-up rate, failure to utilize the immediate post procedure period to provide patients with effective long-term contraception is likely to lead to a subsequent undesired pregnancy. Additional benefits of post-procedure insertion include greater patient motivation for contraceptive use as well as avoidance of additional discomfort from a second procedure at a later date (4). A recent study by the primary investigator, Dr. Miriam Cremer, showed that women randomized to immediate insertion were significantly more likely to have an IUD at 6 months compared to delayed (81.7% vs. 28.4%, p=.003). Relative risk was 11.2 (95% CI 5-26) (5). A similar, observational study by Tocce, et al. showed similar results to immediate vs. delayed placement of post-partum etonogestrel implant among adolescents (6). There are no studies to date in a post-abortion population and this information would help guide management.
2.3 Study Design	This is a randomized controlled trial comparing immediate vs. delayed placement of Nexplanon after second trimester abortion procedures. Enrollment will be conducted at Family Planning Associates Medical Group (FPA) in Chicago. This is an independent medical group that is the leading abortion provider in the Chicago area, providing over 1,800 second-trimester abortions per year. Dr. Cremer successfully conducted a similar study at Parkmed and Bellevue Hospital on immediate vs. delayed IUD placement after second trimester abortion (5). Dr. Cowett, the physician in charge of the study at FPA, is a board certified Obstetrician Gynecologist who completed a Family Planning fellowship, an ACOG member, and the former Director of the Fellowship in Family Planning at the University of Illinois at Chicago.

2.4 Study Flowchart

	Pre-op	Post-op	Immediate*	Delayed*	6 month
Consent/Enrollment	X				
Counseling	X		X	X	
Ultrasound to confirm gestational age	X				
Routine blood work, per clinic protocol (Hct, etc.)	X				
Staff-administered insurance questionnaire	X				
Self-administered RC/IPV questionnaire	X				
Physical Exam	X				
Randomization		X			
Device insertion			X	X	
Implant check-immediately after placement			X	X	
Urine Pregnancy Test				X**	
Directed Physical Exam				X	
Delayed Insertion Questionnaire				X	
Telephone satisfaction Questionnaire					X

* Participants will be randomized to either immediate or delayed insertion.
** A urine pregnancy test will be performed on participants who present for delayed insertion of the device outside of the 2-4 week window. Women who test positive for pregnancy will not be able to receive the device. They will be referred for the appropriate medical care.

2.5 Study Procedures

PARTICIPANTS

Eligibility criteria:

Women will be eligible for the study if they are/have:

1) 18 years of age and older
2) an intrauterine pregnancy ≥14 0/7 weeks and ≤23 6/7 weeks gestation and desire termination of pregnancy
3) desire a Nexplanon for contraception
4) able to give informed consent in English
5) no contraindications to Nexplanon (based on U.S. CDC Medical Eligibility Criteria for Contraception) or D&E

Exclusion Criteria:

Women will be excluded from the study if they are/have

1) unable to give informed consent
2) have any of the following medical conditions: active venous tromboembolism, known or suspected sex-steroid sensitive malignancies,

current hepatic disease with abnormal liver function tests, undiagnosed vaginal bleeding, hypersensitivity to any of the ingredients in Nexplanon
3) non-surgical management of pregnancy
4) prior participation in this study
5) breast cancer or a history of breast cancer

INTERVENTIONS

Eligible women seeking abortion services will undergo standard clinical procedures for preoperative evaluation. These include an ultrasound to estimate gestational age; routine blood work; routine abortion counseling and consenting; and routine contraceptive counseling, with the addition of Nexplanon as an option, since the clinic does not currently offer the device except through the study. Women whose pregnancies are confirmed to be in the second trimester and who express that they would like to use Nexplanon for contraception after the abortion, will be told about the study by clinic staff. Interested women will then be further screened for inclusion and exclusion criteria. If eligible for participation, research staff will then review study procedures and the risks and benefits of participation with the patient. Patients will then review and sign the informed consent with an investigator. Once informed consent is obtained, the subject will be assigned a screening number. Additional screening for exclusion criteria will be completed at the time of examination prior to osmotic dilator insertion. Participants will also sign the manufacturer's Nexplanon device consent, as well as a site-specific Nexplanon consent, prior to randomization.

The following information will be recorded in each participant's research chart:

- Contact and demographic information
- Staff-administered Insurance Questionnaire
- Self-administered RC/IPV Questionnaire
- Pregnancy, reproductive, contraceptive, general health histories
- Height and weight
- Results of general appearance exam and other body systems (if indicated)
- Concomitant medications
- Documentation of contraceptive counseling

All participants will undergo termination of pregnancy by dilation and evacuation (D&E) at Family Planning Associates. Eligible participants will complete enrollment before placement of dilators, which is usually performed one day prior to the D&E, but may be the same day, per clinic protocol. Participants will be randomized after the D&E procedure is complete to either "immediate" or "delayed" Nexplanon placement. Insertion of dilators will be performed by either first-clinician Rose Ali, P.A., or Dr. Allison Cowett. All D&Es, as well as all Nexplanon insertions, will be performed by Dr. Allison

Cowett at FPA. She is trained and approved to place Nexplanon and will place all devices in women enrolled at FPA.

Since randomization occurs after the abortion, both groups will undergo a termination of pregnancy in the exact same manner. Participants in the immediate group will have an etonogestrel rod placed within 15 minutes following the procedure, and while still anesthetized. Participants in the "delayed" placement group will be asked to return to FPA for a post-abortion visit 2-4 weeks following the procedure. Participants in the delayed group will be offered a method of contraception to use in the interim between their procedure and their insertion appointment. At their follow-up visit, an etonogestrel rod will be placed in their arm using standard procedure.

Women randomized to "delayed" insertion will receive one reminder phone call, email, or text message (method of their choosing) about their appointment from the research staff. Attempts will not be made to contact them after a missed appointment.

In the event that participants miss their appointment for Nexplanon placement and still desire the device, they are eligible for placement up to 6 months after their abortion procedure. Under this circumstance, it is the subject's responsibility to coordinate an appointment with the research office.

All participants will receive a phone call from a research assistant at 6 months to complete a Satisfaction Questionnaire.

Delayed Insertion Visit
The following procedures will be conducted at the delayed insertion visit.

- Review of contact information/emergency contact information
- Review of concomitant medications and contraception since D&E procedure
- Review of adverse events since D&E
- Confirmed continued eligibility to receive Nexplanon
- Review of sexual intercourse history since D&E procedure
- Staff-administered Delayed Insertion Questionnaire
- Collection of vital signs (blood pressure, pulse)
- Directed physical exam
- Insertion of Nexplanon device using standard procedure

Additional procedures to be performed if visit is conducted outside of 2-4 week window

- Urine pregnancy test
- Review of sexual intercourse since LMP

Phone Call (6 month) Procedures
Participants will be contacted by research staff 6 months (+/- 2 weeks) after

	their abortion procedure. A Satisfaction Questionnaire will be completed during the phone call. Participants will be asked to palpate their implant while on the phone to confirm current use of Nexplanon. Phone calls completed out of window will be documented as a protocol deviation. Those who complete this follow-up will have their addresses re-confirmed and a $25 gift card will be mailed to them. **Comparison Groups and Outcomes** Participants who are randomized to have Nexplanon placed immediately post procedure will be compared to participants who were randomized to have Nexplanon placed 2-4 weeks post procedure. The primary outcome will be participants using Nexplanon at 6 months following the procedure. Secondary outcomes will be repeat pregnancy rates, side effects, and contraceptive method satisfaction as assessed by the Satisfaction Questionnaire. Data will also be collected on women who return to have their Nexplanon placed beyond the 2-4 week post-procedure period. Within- and between-group analyses will also be performed to see if insurance status or history of RC/IPV are predictors of the primary or secondary outcomes.
2.6 Study Duration	24 months
2.7 Statistical Analysis and Sample Size Justification	The data will be analyzed by a contract statistician, Dr. Todd A. Alonzo at the University of Southern California. **STATISTICAL METHODS:** The primary outcome to be analyzed is the percentage of women using Nexplanon at the end of 6 months. This analysis will be done with a chi-square test. Secondary outcomes to be analyzed include the proportion of participants using other high or middle tier contraception, pregnancy rates, side effects and satisfaction with the procedure. **SAMPLE SIZE:** We aim to recruit 120 women seeking termination over 2 years who agree to participate in this study and desire to have Nexplanon as their postpartum contraceptive method. The sample size was calculated based on a power of 0.80 to demonstrate a 20% difference in usage rates of Nexplanon between groups, assuming 40% of women overall are not using Nexplanon six months after their procedure. **RANDOMIZATION/SEQUENCE GENERATION/IMPLEMENTATION** Prior to randomization allocation of treatment will be unknown by the investigators or the patient. Consent will be obtained prior to the scheduled procedure. However, randomization will occur immediately after the procedure in the operating room, while the patient is still sedated. Sequentially numbered, opaque, sealed envelopes will be placed in the FPA office. An unopened envelope will be placed in the participant's chart before

	the procedure. If the subject changes her mind about participation, the envelope will be returned unopened to the FPA office. Participants will be randomized using a computer-generated table of random numbers. A permutated block design will be used, with a block size of 10. However, since two subjects were recruited at another site that was closed for the study before the completion of follow-up, the first block will be a block of 8. **Blinding**: After randomization, neither the participants nor the physicians will be blinded to the treatment. **Withdrawals, Losses and Deviations:** Every attempt will be made to minimize withdrawal from the study. In the event that a woman does withdraw from the study, the investigators will try to determine the reason for the withdrawal and include this information in the analysis. Participants will be contacted 6 months following the procedure and asked to complete a Satisfaction Questionnaire. Participants will be asked to palpate their device while on the phone. If the device is palpable she will be considered as using Nexplanon at 6 months. In the rare case that the participant cannot palpate the device she will be brought in to FPA for clinician evaluation (unscheduled visit). Research staff will make at least three attempts to contact participants by phone at 6 months. If these attempts are unsuccessful a certified letter and U.S. mail letter will be sent to the participant's last known address. If the certified letter is returned to the research office unopened, staff will contact the participant's emergency contact provided at enrollment. This patient population is at high-risk for loss to follow-up. At enrollment participants will give their contact information as well as names and phone numbers of two people who do not live with them who may be able to contact them in case they cannot be reached. To ensure that we reach the 120 sample size we will enroll 150 women since there will be a proportion of women who cannot be reached at the end of the study. All participants will be compensated $75 for participation at screening/enrollment. Participants in the delayed group will receive $15 at their follow-up visit for Nexplanon placement. Finally, all participants will be compensated with a $25 gift card, delivered by mail, after completing the Satisfaction Questionnaire at 6 months. Patients who deviate from the protocol will be analyzed according to their allocation group at the time of enrollment (intention-to-treat). **Data Collection/Outcome Measurement** All patients undergoing termination of pregnancy will have a complete history, physical exam and routine labs prior to the procedure. This

	information will be filled out on a data extraction form following enrollment. Subjects who are enrolled in the study to delayed placement will have an extra visit to place the device. All subjects will be contacted by phone at 6 months to fill out a questionnaire and a satisfaction survey.
2.8 Specific Drug Supply Requirements	We are requesting 150 Nexplanon devices to use for the study. All devices will be accounted for and any unused devices will be shipped back to Merck at the end of the study.
2.9 Adverse Experience Reporting	<u>Adverse Event (AE)</u> An adverse event (AE) is any untoward or undesirable event experienced by a participant regardless of whether the event is expected or related to the participant's involvement in the research. Possible adverse events unique to this study include complications from Nexplanon insertion. <u>Serious Adverse Event (SAE)</u> A serious adverse event (SAE) is any untoward medical occurrence or effect involving • Death • A life-threatening condition (participant at immediate risk of death) • Persistent or significant disability/incapacity • In-patient hospitalization or prolongation of existing hospitalization • A congenital anomaly or birth defect • An important medical event that may jeopardize the participant or may require intervention to prevent one of the outcomes listed above. <u>Unanticipated Problems</u> In addition to adverse events as described above, there are events that occur during studies that represent unanticipated problems but are not considered adverse events. In other words, harm to a participant need not occur in order for an event to be an unanticipated problem e.g., laptop with data is stolen. <u>Procedures</u> The Site Investigator, Dr. Cowett, will report AEs, SAEs, and unanticipated problems to the Principal Investigator, Dr. Cremer, to be reviewed and evaluated throughout the study. Dr. Cremer will decide how to report these according to the guidelines below. All SAEs will be followed until satisfactory resolution or until the PI deems

	the event to be chronic or the patient to be stable. Treatment of study-related adverse events will be provided by the study site by qualified health providers and/or referred to the appropriate clinical institution for management. Treatments administered are to be recorded on the participant's data collection form as a complication and will be reported as necessary to the site's IRB (NEIRB). Reporting Procedures Dr. Cowett will report AEs, SAEs, and unanticipated problems to the New England Independent Review Board. Any relevant information that becomes available after the SAE report form has been sent (outcome, precise description of medical history, results of the investigation, copy of the hospitalization report) should be forwarded as soon as possible to Dr. Cremer. The anonymity of the participants shall be respected when forwarding this information.
2.10 Itemized Study Budget	See attached excel spread sheet
2.11 References	**References:** **1.** Steiner, MJ, Dalebout S, Condon S, Dominik R, Trussell J, Understanding Risk: A Randomized Controlled Trial of Communicating Contraception Effectiveness: Obstet Gynecol 2003; 102: 709-17. 2. Westfall JM, Sophodes A, Burggraf H and Ellis S, Manual Vacuum Aspiration for First-Trimester Abortion *Arch Fam Med.* 1998;7:559-562. 3. Personal communication, October 2005,.Dr. Rachel Masch, Director of Family Planning Services Bellevue Hospital, NY, NY 4. Grimes DA, Lopez LM, Schultz KF, Stanwood N, Immediate postabortal insertion of intrauterine devices (Review), The Cochrane Library, Issue 3, 2006: Oxford Updated Software 5. Cremer,M, Bullard KA, Mosley RM, Weiselberg C, Molaei M, Lerner, V Alonzo T Immediate vs delayed post-abortal copper T380A IUD insertion in cases over 12 weeks of gestation, Contraception 2011; 83: 522-7 6. Tocce, KM, Sheeer, JL, Teal SB, Rapid repeat pregnancy in adolescents: do immediate postpartum contraceptive implants make a difference, Am J Obs Gyn, In press
2.12 Publication Plan	The following should be considered for the publication plan:

	• What are your publication plans? We plan to submit this study for publication in the Green Journal or in Contraception. • How many manuscripts do you anticipate? 1-2 • Include projected target date for manuscript submission and name of the journal. Submission by October 31, 2015, to the Green Journal or Contraception. • Do you anticipate abstracts? Yes How many? 2-3 • What scientific meetings would you consider presenting the study results? The Society of Family Planning's "North American Forum on Family Planning"; Medical Students for Choice's "Conference on Family Planning", ACOG's "Annual Clinical and Scientific Meeting"
2.13 Curriculum Vitae	Investigator should provide curriculum vitae in English and a listing of references to Merck/MSD.
2.13 Protocol Submission for Investigator-Initiated Studies	U.S. protocols should be submitted by US investigators directly or through the Global Research Specialist at www.merckiisp.com Non U.S. protocols should be submitted to the MSD office by the investigators.