Management of Etonogestrel Subdermal Implant (Nexplanon) -related bleeding in US Women: a prospective, randomized, placebo-controlled trial

NCT01658995

3/29/2017

Management of Etonogestrel Subdermal Implant (Nexplanon) -related bleeding in US Women: a prospective, randomized, placebo-controlled trial

Principal Investigator:
Petra M. Casey MD, Associate Professor OBGYN, Mayo Clinic Rochester

Co-investigators:
Margaret E. Long, MD*, Mary L. Marnach MD*, Abimbola O. Famuyide MBBS*, Amy Weaver MS**

*Department of OBGYN, Mayo Clinic Rochester

** Division of Biomedical Statistics and Informatics, Mayo Clinic Rochester

Version 2 – 02/10/2012
Version 2.1 – 08/20/2012
Version 2.2 – 05/15/2014
Version 2.3 – 3/29/2017

Proposal outline

1.0 Abstract
2.0 Specific Aims
3.0 Hypotheses
4.0 Background and Significance
5.0 Experimental Design and Methods
- Overview
- Study Population
  - Patient Selection
  - Inclusion Criteria
  - Exclusion Criteria
- Measure of Study Variables
  - Study process
  - Outcome measurements
- Statistical analysis
  - Power calculation
  - Statistical analysis

6.0 Adverse Events
- Serious Adverse Events
- Unanticipated Adverse Device Events
- Anticipated Effects of Implanon placement
- Anticipated Effects of Doxycycline treatment
- Reporting of Adverse Events
- Data and Safety Monitoring Plan

7.0 Ethical Considerations (Human Studies)
8.0 Study expectations and Limitations
9.0 Future Directions
10.0 Budget and Budget Justification
11.0 Consent form
12.0 Bibliography
13. 0 Appendices

1.0 Abstract

Etonogestrel Subdermal Implant (ESI) is an attractive alternative to other long-acting reversible contraception as well as a compliance-independent alternative to estrogen-containing hormonal contraception. Though its safety and efficacy has been established world-wide, only about 1% of women have been reported to use this method [6]. Its use and future expansion is limited by bleeding alterations which result in requests for early removal. Unfortunately, published data regarding bleeding changes and ESI in US women is limited. A multicenter trial of 330 US women reported a 13.0% removal rate for "bleeding pattern changes," within the first 8 months of use [1], consistent with the results of an international trial [2]. We reported on a retrospective cohort of 155 US women and developed an algorithm that improved unacceptable bleeding rates in 66% of patients using Doxycycline (N=9) allowing method continuation [3, 7] Further, ours was the first US study which included women regardless of BMI (mean BMI 28.5) [3]. We further report on an expanded cohort of 337 women with an unacceptable bleeding rate of 28.5%. Where 44% of women who received Doxycycline requested removal, 92% of women who received another intervention or declined intervention requested removal. [29] With the proposed prospective randomized placebo-controlled double blinded trial , we aim to validate the implementation of a simple, affordable, non-hormonal intervention using the most rigorous methodology reported to date.

2.0 Specific Aims

2.1 Specific Aim #1 (primary aim):

- To determine the effect of Doxycycline vs. placebo on the need for additional treatment for unacceptable bleeding at 13 weeks post-randomized treatment.

2.2 Specific Aim #2 (secondary aim):

- To determine if initial treatment with Doxycycline results in higher patient satisfaction with ESI as compared to placebo at 13 weeks post-randomized treatment.

2.3 Specific Aim #3 (secondary aim):

- To determine method continuation and patient satisfaction rate at 26 week post-randomization in patients who choose secondary treatment with Doxycycline for unacceptable bleeding at 13 weeks post-randomized treatment.

In order to evaluate specific aim #1:

- All ESI patients will be offered enrollment in the study at ESI insertion and will begin prospective diaries. They will be contacted at 13 weeks post insertion. If patients report unacceptable bleeding at that time or self-report at any time following an initial 13 week interval, they will be offered randomization to Doxycycline or placebo. Patients will continue a weekly prospective symptom diary for the duration of study.
- Time to recurrence of unacceptable bleeding post-treatment and need for secondary treatment (primary endpoint) will be determined by completion of prospective symptom recording by 13 weeks post-randomized treatment.

- Side-effects and adverse events associated with medical treatment will be documented.

In order to evaluate specific aim #2:

- A patient satisfaction survey will be administered at randomization and 13 weeks post-randomization. The results will be compared between the Doxycycline and placebo study arms.

In order to evaluate specific aim #3:

- Patient satisfaction will be assessed at 13 weeks post-ESI insertion.
- Patients who report unacceptable bleeding after initial randomized treatment and who choose additional treatment will receive secondary treatment with Doxycycline and the method continuation rate and patient satisfaction rate at 26 weeks post randomization will be calculated.
- In patients who leave the study prior to 26 weeks post-randomization, patient satisfaction will be recorded at that time.
- If ESI is removed prior to 26 weeks post-enrollment, the reason, date of removal and alternative contraception will be documented.

3.0 Study Hypotheses

3.1 Study hypotheses for specific aim #1 (primary aim):

- Doxycycline is more effective than placebo in the initial management of ESI-related bleeding.
- **Statistically significant difference between the placebo and Doxycycline groups will be shown in favor of Doxycycline**

3.2 Study hypotheses for specific Aim #2 (secondary aim):

- Patients in the Doxycycline group will report a higher satisfaction rate with ESI scores on a survey as compared to those in the placebo arm at 13 weeks post-randomization.
- **Statistically significant difference in patient satisfaction rates between the placebo and Doxycycline groups will be shown in favor of Doxycycline.**

3.3 Study hypotheses for specific aim #3 (secondary aim):

- In patients who request secondary treatment for unacceptable bleeding, administration of Doxycycline will result in a high method continuation rate and patient satisfaction rate at 39 weeks post ESI insertion.
- The above will be supported by method continuation rate of >75% [3, 8] at 26 weeks post-randomization.

4.0 Background and Significance

Unintended pregnancy continues to be a major public health issue in the United States. In 2002, nearly half of the 6.4 million pregnancies in the United States were unintended.

Almost half of unintended pregnancies end in elective abortion. [9] Further, 80% of adolescent pregnancies are unintended.[10] The need for a highly effective, safe, estrogen-free, compliance independent and rapidly reversible contraception can be readily met with ESI. The etonogestrel subdermal implant has been available worldwide since 1998 and received United States Food and Drug Administration approval in 2006. Though studies have confirmed its efficacy, convenience, and cost-effectiveness, bleeding irregularities account for up to 43% of requests for early removal. [4, 11] though **the rate of 28.5% was reported in our population.** [29] Other reasons for removal include weight gain, headaches, mood changes and desire for pregnancy, each accounting for about 10-15% of removal requests.[11] Published data regarding bleeding management in US women is limited. A multicenter trial of 330 US women reported a 13 % removal rate for "bleeding pattern changes," particularly within the first 8 months of use, consistent with international studies. [1, 2]. However, prior trials have excluded women weighing over 130% of ideal body weight [4]. Our retrospective study was the first US study to include women regardless of BMI.[3] Further, an expanded retrospective cohort of 337 women confirmed the efficacy of Doxycycline as 44% of women who received Doxycycline requested removal and 92% of those who received another intervention or declined intervention beyond reassurance requested removal [29]. A recent review of the literature includes interventions for bleeding but admits limited or anecdotal support for these. Further, the first line intervention contains estrogen, which is contraindicated in many ESI users [26. The intervention in this proposed study is hormone-free.

Rationale for using Doxycycline as initial treatment for ESI related bleeding
Doxycycline 100 mg twice daily for 10 days

Matrix metalloproteinases cause endometrial fragility, irregular vessel breakdown, influx of leukocytes, and bleeding. [15, 16] Tetracyclines inhibit matrix metalloproteinase activity independent of their antimicrobial action, with doxycycline being the most potent inhibitor among the tetracyclines [17, 18]. Doxycycline also treats Chlamydia and Ureaplasma infection, which may cause chronic endometritis that presents as abnormal uterine bleeding [19]. A pilot study by Weisberg [21] reported a 50% reduction in ESI-related bleeding duration with doxycycline for 5 days but no long-term improvement and no improvement over placebo in a follow-up study [22]. Doxycycline anti-inflammatory effects are dependent on dose and treatment duration *in vitro* [20] thus supporting a longer therapy course. Clinically there is no precedent for increasing dose beyond 100 mg BID. While there is a clinical precedent for using 10 days of treatment, there is not for 5 days of use. This length of administration was likely used in the Weisberg studies(21,22) for blinding purposes [21,22].In our retrospective cohort (N=9), 10 day course of Doxycycline resulted in bleeding improvement and method continuation in 66% of patients who reported unacceptable bleeding.[3,7] Of 36 untreated patients, 25 (70%) requested early ESI removal.[7]

.

The published experience with Doxycycline in the treatment of unacceptable bleeding associated with ESI is limited to small, retrospective studies. The validation and subsequent clinical implementation of an evidence-based cost-effective treatment is likely to dramatically increase the acceptability and continuation rates of ESI.

5.0 Experimental Design and Methods

5.1 Overview:

This is a double-blinded, randomized, prospective placebo-controlled clinical trial to be conducted within the Mayo Clinic and the Mayo Clinic Health System.

5.2 Study population

The Mayo Clinic and Mayo Clinic Health System offers a network of collaborative practices throughout the Midwest as well as site in Arizona and Florida. During the past year, 7100 female patients were seen for contraceptive related needs at Mayo Clinic Rochester alone. [26] Electronic medical records are easily accessible for data abstraction and patient followup. Further, the patient population is stable. The loss to followup was only 2% in our 27-month retrospective study. [3] In the Obstetrics and Gynecology department of Mayo Clinic Rochester alone, over 350 ESI devices have been inserted since mid-2007. Over 150 ESI devices were placed in the last year by 12 practitioners and additional practitioners will be trained in November 2011. Additional patients can be readily recruited by Implanon providers from the departments of Family Medicine as well as regional Mayo Clinic Health System sites in Minnesota, such as Albert Lea, Owatonna, Faribault, and Austin, with which close collaborative relationships exist and where over 81,000 women between the ages of 18 and 51 were seen as outpatients in 2009. [25].

5.2.1 Patient selection

After appropriate IRB approval, ESI users aged 18-51 years old who meet the inclusion and exclusion criteria, and sign a written consent will be **enrolled in the study at the time of ESI insertion.** Every effort will be made to insert ESI on the same day as consent unless medically contraindicated. They will complete a prospective symptom diary from date of ESI insertion. All patients will be contacted by study personnel 13 weeks after enrollment and queried as to the presence of unacceptable bleeding. Bleeding concerns will be objectively assessed using a modification of the Pictorial Blood Loss Assessment Chart (PBLAC) [27}. Patient–initiated contact in with bleeding concerns at any time after 13 weeks post ESI insertion will result in enrollment and randomization at the time of contact. **The basis for randomized treatment will be whether or not the bleeding is "unacceptable" to the patient. This is inherently subjective, but constitutes the basis for most removal requests.** Patients who report unacceptable bleeding at 13 weeks post-ESI insertion, and those who call with bleeding concerns after 13 weeks post ESI insertion, will be randomized into two groups (Doxycycline or placebo). Patients who do not report unacceptable bleeding will continue to complete diaries and may be eligible for randomized treatment if unacceptable bleeding develops. Patients will receive diaries sufficient for completion of the study with instructions to contact study personnel if more diaries are needed or if diaries are lost. Patients and investigators will be blinded to the group assignment as well as the study coordinator who will be responsible dispensing of appropriate study medication by the pharmacy.

Patients who continue to have unacceptable bleeding after 4 weeks post-randomized treatment and wish to have secondary treatment will be treated with Doxycycline. Secondary treatment will not be blinded. Rates of unacceptable bleeding and patient satisfaction scores at 26 weeks post-randomized treatment in remaining study participants will be calculated.

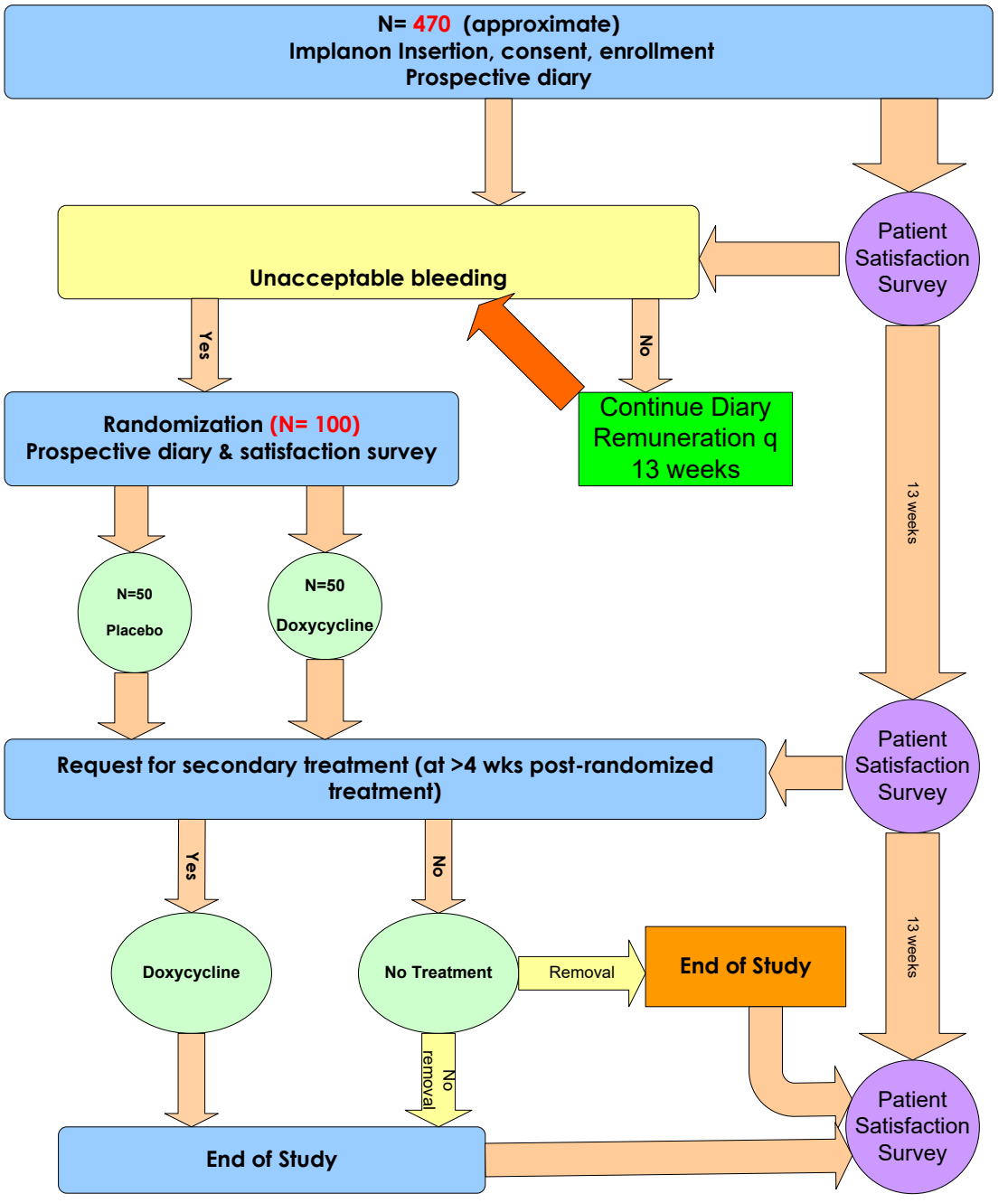
5.2.2 Inclusion Criteria

- Premenopausal women, aged 18-51 years
- Expressed desire for compliance-independent contraception
- No current pregnancy or anticipated desire for childbearing within 3 years of study enrollment and ESI insertion
- Agreement to participate in all study related procedures and evaluations as documented by a signed informed consent (see appendix)

5.2.3 Exclusion criteria

- Current or prior use of ESI
- Current long-term use of Doxycycline for other indications
- Known structural uterine abnormalities such as polyp, submucosal leiomyoma
- Prior permanent sterilization or endometrial ablation
- Pregnancy or desire for childbearing within 3 years
- Contraindications to or intolerance of etonogestrel
- Allergy to or intolerance of Doxycycline
- Inability or unwillingness to complete study related procedures and evaluations, and document this agreement by signing the informed consent

Patient Process Chart



5.3 Measurements of Study Variables

5.3.1 Study Process

a. Enrollment

Subjects who meet the eligibility criteria will be required to sign an informed consent form and HIPAA authorization prior to enrollment. Subjects will receive identification numbers at this time and will be considered enrolled into the study. Patient demographic characteristics, prior contraceptive method, postpartum and breastfeeding status will be recorded. All subjects will undergo a history and physical examination including pelvic examination, height and weight if this was not done within an age-appropriate interval. A baseline BMI will be calculated. A Pap test using ThinPrep® will be obtained if none has been taken in the preceding 12 months. A retrospective symptom diary to date of ESI insertion and prospective symptom diaries for the duration of the study will be provided to the patient with instructions to contact study personnel if materials are lost or more are needed.

b. Randomization

Patients enrolled in the study at the time of ESI insertion who either report unacceptable bleeding when contacted by study personnel at 13 weeks post-ESI insertion or self-report unacceptable bleeding after 13 weeks post ESI insertion will be offered randomization to placebo or Doxycycline. Randomization will be done with stratification based on: age (< 30 years, ≥ 30 years), postpartum status and body mass index (BMI< 30, BMI ≥ 30). The randomization will be performed using a dynamic allocation approach based on the Pocock-Simon method to ensure a balance in the treatment groups across the stratification levels. The randomization assignment for each patient will be obtained upon entering the patient's stratification levels into a web-based application created and supported by the Division of Biomedical Statistics and Informatics. Investigators and patients will be blinded to group assignment. For this reason, all pills will be made to look identical. **Enrollment of new patients will continue until approximately 100 patients are randomized (50 in each group).** Additional patients will need to be enrolled given the lower than expected reported unacceptable bleeding rates.

c. Placebo group

If a patient reports bleeding concerns as described in section 5.2.1 and is randomized to the placebo group, she will be given a pill bottle containing placebo made to look identical to treatment to be taken twice daily for 10 days. Patient and investigators will be blinded as to group assignment.

d. Doxycycline group

If patient has bleeding concerns determined in section 5.2.1 and is randomized to the Doxycycline group, she will be given a pill bottle containing Doxycycline 100 mg to be taken twice daily for 10 days. Patient and investigators will be blinded as to group assignment. Patients who experience unacceptable bleeding but are not bleeding at the time of study personnel contact will be instructed to call back if unacceptable bleeding recurs for randomization to treatment or placebo.

e. Treatment compliance process

Pill counts at the end of each treatment course will be performed to assess patient compliance with treatment. A pill diary given to patients at the time of randomization will provide temporal correlation between treatment initiation and bleeding symptoms.

f. Symptom recording

Upon enrollment and ESI insertion, patients will begin a weekly prospective symptom diary in order to self-assess bleeding and additional symptoms for a **total of 39 weeks from study enrollment**. A modification of the PBLAC where 1= no bleeding, 2=spotting requiring 1-2 panti-liners per 24 hours only, 3= bleeding requiring 1-3 tampons/pads in 24 hours, 4=bleeding requiring 4-6 tampons/pads per 24 hours, and 5=bleeding requiring >6 tampons/pads per 24 hours will be utilized for bleeding recording.[27] Bleeding diaries will be collected every 13 weeks and completion will be required for continued enrollment in the study and receipt of remuneration after every 13 week interval. Patients will also record any other associated symptoms such as headache, mood changes, acne and intolerance to treatment detailed in sections 6.2.2 and 6.2.3. Prospective symptom diary can be captured on a paper formate or via Mayo Clinic website RED Cap.

A bleeding episode is defined by the WHO as any set of one or more bleeding days (either consecutive or separated by only one bleeding-free day) bounded at each end by two or more bleeding-free days**. The bleeding pattern will be analyzed within each 13-week reference period** and categorized into 6 groups [4, 13, 14]:

- Amenorrhea (no bleeding during the reference period),
- Infrequent bleeding (fewer than 3 bleeding episodes),
- Normal bleeding frequency (3-5 bleeding episodes).
- Frequent bleeding (more than 5 bleeding episodes),
- Prolonged bleeding (1 or more bleeding episodes lasting 14 days or more)

Subgroup analysis may provide additional insight into the efficacy of treatment for various bleeding patterns.

g. Patient satisfaction surveys

Patients will be asked to fill out short satisfaction surveys at randomization measuring satisfaction prior to any treatment, and at 13 and 26 weeks post randomization (see appendix). If patient has their ESI removed prior to 26 weeks post randomization, she will be given a final satisfaction survey at removal. Patient satisfaction surveys will be recorded on a paper formate or via Mayo Clinic website RED Cap.

Patients will rate their satisfaction with a) ESI and b) bleeding with ESI on a 5-point Likert scale ranging from very satisfied to very dissatisfied. If patient has ESI removed prior to 26 weeks post-study enrollment, she will be given a final satisfaction survey at removal.

h. Treatment issues

At enrollment, patients will be provided with a contact number allowing them to reach study personnel at all times with concerns. Instructions will be provided for instances of drug intolerance/allergy, heavy bleeding or other ESI related issues and clinical appointments for evaluation scheduled as needed.

i. Secondary Treatment

If a patient reports unacceptable bleeding at >4 weeks post randomization to treatment or placebo, study participation will be recorded as **need for additional treatment, and will represent the primary endpoint**. If she wishes to have secondary treatment, she will be treated with Doxycycline. Treatment will be limited to two interventions per 13 week

interval to allow for assessment of efficacy of each course of Doxycycline. Rates of unacceptable bleeding in all patients remaining in the study at 26 weeks post–randomization will be calculated and participation in the study will end. If patients request ESI removal at any time during the study after randomly assigned treatment, study participation will be recorded as a **removal.** Method satisfaction will be assessed at removal and study participation will end. Patients will be provided with alternative contraception of choice at their expense. **Need for additional treatment at >4 weeks post–randomized treatment will represent the primary endpoint.** Satisfaction with ESI at randomization, and 13 and 26 weeks post randomization, and method continuation at 26 weeks post -randomization represent the secondary endpoints.

j. Post-treatment Followup

All patients will be contacted by study personnel at 26 weeks (± 2 weeks) post - randomization for final satisfaction survey and weight. Study completion BMI will be calculated. All diaries will be collected for analysis and patients will receive remuneration. When all patients complete the study, the data will be unblinded for analysis.

k. Special Considerations

If patients receive randomized treatment toward the end of the 39 week study interval (rather than at about 13 weeks post ESI insertion), post-treatment data for at least 13 weeks will be collected for a maximum study length of 52 weeks post-ESI insertion.

l. Additional testing

Additional laboratory testing or imaging for heavy or unusual bleeding will be individualized as clinically indicated.

5.3.2 Outcome measurements

A. Primary treatment efficacy and safety end point (primary endpoint addressing specific aim #1)

- The efficacy of Doxycycline on ESI-related bleeding will be compared to placebo based on rates of **unacceptable bleeding** and weekly prospective symptom diary at 13 weeks post-randomization.

B. Primary treatment efficacy and safety endpoints (secondary endpoints addressing specific aim #1)

- Method continuation rate at 13 weeks post-randomization will be compared for women in the Doxycycline vs. placebo group.
- Bleeding patterns will be quantified based on the PBLAC and WHO classification of clinically important bleeding patterns over each 13 week reference period.[13,14, 29].
- Incidence of additional symptoms including acne, headache, mood changes in the treatment groups will be compared to placebo at randomization and 13 weeks post-randomization based on the weekly prospective symptom diary
- Interval to recurrence of unacceptable bleeding post- randomized treatment (i.e., need for additional treatment) will be determined
- Rate of adverse events associated with medical treatment will be documented by prospective symptom diary and BMI calculation. These include headache, mood changes, acne and change in BMI.

C. Patient satisfaction with primary treatment endpoint (primary endpoint addressing specific aim #2)

- Patient satisfaction with ESI at randomization for a baseline pre-treatment satisfaction and at 13 weeks post-randomized treatment following primary treatment with Doxycycline vs. placebo will be compared

D. Patient satisfaction with secondary treatment endpoint (primary endpoint addressing specific aim #2)

- Patient satisfaction with ESI at 26 weeks post–randomized treatment for patients with continued unacceptable bleeding following primary treatment who receive secondary treatment with Doxycycline will be calculated.

E. Secondary treatment efficacy and safety endpoint (primary endpoint addressing specific aim #3)

- Method continuation rate at 26 weeks post -randomized treatment for patients with continued unacceptable bleeding after primary treatment who undergo secondary treatment with Doxycycline will be calculated

F. Secondary treatment efficacy and safety endpoint (secondary endpoints addressing specific aim #3)

- Rate of ESI removal for bleeding between 13 and 26 weeks post randomization.
- Rate of ESI removal for reasons other than bleeding with enumeration of reasons for removal between 13 and 26 weeks post -randomization.
- Alternative contraception chosen if ESI removed will be documented.

5.4 Statistical Analysis:

Baseline demographic and clinical characteristics will be documented as detailed in section 5.3.1a patient enrollment.

5.4.1 Power statements

Based on prior Mayo data, we anticipate about 30% of patients will develop unacceptable bleeding following ESI insertion.[3,29] These patients will be approached for participation in this study. The study plans to randomize a total of 100 patients with unacceptable bleeding to either placebo (N=50) or Doxycycline (N=50). The following calculations were based on a two-sided chi-square test with a type I error rate of 0.05.

Aim1: Of the patients with bleeding concerns, based on our prior experience we anticipate that 44% of the patients randomized to Doxycycline will request additional treatment, and about 80% in the placebo arm. We are purposely overestimating the placebo effect over that noted in our cohort (92% removal requests) to allow for variation in the study group. Given the sample size of 50 per treatment arm, the study will have >90% power to detect the anticipated difference in the need for additional treatment.

Aim 2: Across the two arms, we anticipate that 66 of the 100 patients will request additional treatment and will receive additional treatment with Doxycycline. Within this subset we plan to estimate the method continuation rate following additional treatment. Based on a sample size of 66, the ½ width for a 95% CI around an estimate of 75% is ±10%.

Aim 4: Among the anticipated 66 patients who will request additional treatment for continued unacceptable bleeding at 26 weeks post-ESI insertion, we plan to quantify the patient satisfaction rate. If we assume 75% will be "very satisfied" or "satisfied", then the ½ width for a 95% CI around this estimate will be ±10%.

5.4.2 Proposed Statistical Analysis:
Patients will be analyzed according to their randomized treatment arm. All calculated p-values will be two-sided and p-values less than 0.05 will be considered statistically significant. Analyses will be performed using SAS software package (version 9.2). Comparisons of categorical endpoints (e.g. need for additional treatment, bleeding pattern based on the WHO classification, presence of adverse event(s), satisfaction survey questions) between the two arms will be evaluated using the chi-square test. Additional comparisons of these endpoints, adjusted for potential confounders, will be assessed by fitting separate logistic regression models. Time-to-event methodology (e.g. Kaplan-Meier method and Cox proportional hazards regression models) will be utilized for binary versions of these endpoints if patient follow-up becomes an issue and patients don't comply with the planned follow-up before completing the study.
Poisson regression models will be used to compare the diary responses between the treatment arms. In the Poisson model, the endpoint will be the number of bleeding and spotting days per patient (and likewise the number of days with additional symptoms), offset by the total days of diary follow-up per patient. Ninety-five percent confidence intervals (95% CI) will be constructed around the estimates for method continuation and satisfaction.

6.0 Adverse events

An adverse event is any untoward medical occurrence in a study subject which does not necessarily have a causal relationship with the medicinal product. This includes any unfavorable and unintended sign (including an abnormal, clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. It also includes any pre-existing condition that increases in intensity or severity or any new events after the patient has given informed consent.

6.1 Serious Adverse Events:
A serious adverse event is any untoward medical occurrence that results in one of the following:

- Death
- Life threatening illness or injury
- Permanent impairment of a body function or structure
- Inpatient hospitalization or prolongation of existing hospitalization;
- Medical or surgical intervention to prevent permanent impairment
- Fetal distress, fetal death, congenital abnormality, or birth defect

6.2 Unanticipated Adverse Device Effects:
Any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

6.2.1 Anticipated Adverse Effects of ESI insertion

- Pain at insertion site
- Infection at insertion site
- Non-insertion
- Deep insertion (non-palpable implant)
- Pregnancy at time of insertion

The above is minimized by strict adherence to the ESI insertion technique in the ESI prescribing information [4] including exclusion of pregnancy.

6.2.3 Anticipated Adverse Drug Reactions of Doxycycline

Serious side-effects include

- pseudotumor cerebri (rare)
- seizure
- swelling of face, lips, tongue, or throat
- headache
- wheezing
- chest tightness
- fever

Other side effects include

- abdominal pain
- Nausea or vomiting.
- Diarrhea
- loss of appetite.
- vaginal yeast infection
- skin itching and sensitivity to the sun
- cough

6.3 Reporting of Adverse Events:
All adverse events will be recorded on the case report forms. Serious adverse events forms must be completed and faxed to ESI clinical affairs within 3 days of knowledge of

the event. Unanticipated adverse device effect and/or unanticipated adverse drug reaction forms must be completed and faxed to ESI Clinical Affairs within 24 hours of knowledge of the event.

6.4 Data and Safety Monitoring Plan

The ESI device was FDA approved in 2006 with no major morbidity or mortality reported to date. Further, its efficacy in preventing pregnancy is > 99%. [4] In over 300 procedures performed at Mayo, no complications of insertion or removal have been noted. All practitioners involved in ESI insertion and removal have successfully completed the FDA mandated training. Further, the principal investigator and Co-Investigators, Drs. Margaret Long, Abimbola Famuyide and Mary Marnach will monitor the safety of the subjects and are available on call 24 hours, 7 days a week. A review of the complications data will be performed after the enrollment of 50 patients; any unexpected complication or major complication will prompt the PI to notify the IRB.

7.0 Ethical Considerations (Human Studies):

Informed consent will be obtained in the Mayo standard written form. Since the interventions are a component of routine clinical practice, we do not anticipate any ethical issues or risks beyond what is currently deemed as acceptable for standard practice. All insertion and removal procedures will be performed by practitioners who have completed the FDA mandated training program. The risks of medical therapy are detailed in sections 6.2.2 and 6.2.3.

7.1 Study Duration

Patients will be offered enrollment in the study upon ESI insertion. They will begin completing weekly prospective symptom diaries at that time. If they report unacceptable bleeding at the time of study personnel contact at 13 weeks post ESI insertion or self-report unacceptable bleeding at > 13 weeks post ESI insertion, they will be offered randomization to Doxycycline or placebo. They will continue prospective weekly symptom diaries for 26 weeks post randomization or until they discontinue study participation. A patient who self-reports unacceptable bleeding late in the study interval will be followed for at least 13 weeks after randomized treatment in order to have a meaningful study conclusion. The maximum study length for such a patient would be 52 weeks from ESI insertion. Based on current numbers of ESI insertions per year, **we anticipated that all 100 subjects with unacceptable bleeding will randomized within 30 months. However, the rate of reported unacceptable bleeding was lower than expected and therefore we propose an additional enrollment of 120 patients (total 470 patients) to achieve 100 randomized patients.**

8.0 Study Expectations and Limitations:

This study is a double blinded placebo-controlled randomized prospective trial of Doxycycline for the management of ESI-related unacceptable bleeding. The study will include US women regardless of BMI. Randomization will be done using a dynamic

allocation process with stratification by age, BMI and postpartum status. This will avoid confounding effects of these variables on our outcomes.

8.1 Limitation of a single center study

We appreciate that the conduction of the study in one center may limit the external validity of results and may be associated with some referral selection bias

Limitation of objectivity in the assessment of ESI-related bleeding

In the assessment of bleeding and other ESI-related symptoms, we will ask patients to keep weekly prospective diaries of bleeding and use a well established system of bleeding pattern classification based on the WHO classification of clinical relevant bleeding patterns. We understand that unacceptable bleeding is inherently subjective but we believe that our method of weekly diary entries and analysis using the above mentioned classification will provide the maximal degree of objectivity and meaningful interpretation. Weekly recording will minimize recall bias while being practical and reasonable for patients. This represents the most rigorous methodology reported to date.

8.2 Limitation relating to recall bias

We expect some recall bias and late entries to the symptom diary.

8.3 Limitation of discontinuation of study participation

Patients may discontinue study participation and/or request ESI removal at any time. Additional patients may need to be enrolled in order to maintain adequate statistical power. However, we believe that lack on invasive procedures associated with the study and remuneration upon completion of each 13 week cycle of prospective diary and at study completion will provide a powerful incentive for women to enroll and to complete the study.

8.4 Impact of Expected results

<u>The expectation of the study is that we will satisfy our hypotheses and find that</u>

- **The failure of treatment, assessed as the requiring additional treatment, in the Doxycycline group will be statistically significantly lower than in the placebo group (primary endpoint)**
- The rate of removal for bleeding at 13 and 26 weeks post-randomized treatment will be lower in the Doxycycline group as compared to the placebo group though it may not be statistically significantly lower given the expected removal rate [3] and study sample size.
- **The rate of patient satisfaction at 13 and 26 weeks post–randomized treatment will be statistically significantly higher in the Doxycycline as compared to the placebo group**
- The incidence of associated symptoms, adverse events and treatment associated events will be low and consistent with prior studies
- No ESI-related contraceptive failures will be reported regardless of patient BMI.

9.0 Future Directions

Following the completion of this trial and analysis of results, we plan to explore issues which we are not able to address with the proposed study. These will include implementation of ESI-related bleeding treatment guidelines and impact on method continuation, long term (up to 3 year) followup and treatment of ESI-related bleeding, counseling best practices relating to ESI-related bleeding as well as cost analysis of various medical treatments.

10.0 Budget (attached separately)

10.1 Budget Justification:

10.1.1 Remuneration

Patients will receive $25 after each interval of 13 weeks for completion of prospective symptom diary (and pill diary if applicable) and satisfaction survey. Patients who discontinue study participation prior to completion of each 13 week set of diaries/ satisfaction survey, those who do not turn in all diaries/satisfaction survey or turn in incomplete diaries/satisfaction survey will not receive this remuneration. Patients who complete the study will receive $50.00 upon receipt of final set of diaries, satisfaction survey and study coordinator clinic visit.

Dr. Casey Principal Investigator

- Proposal and associated material preparation
- IRB approval process
- patient consent, patient satisfaction surveys, bleeding diary preparation
- study marketing within Mayo and to MHS sites
- training and oversight of study personnel, troubleshooting
- clinical appointments for concerns
- progress report preparation
- data analysis
- manuscript preparation/submission/revision

Dr. Long Co-Investigator

- study marketing within Mayo and to MHS sites
- training and oversight of study personnel, troubleshooting
- clinical appointments for concerns

Study coordinator

- Patient Consent & Enrollment
- (available on-call for routine GYN clinic, scheduled for women responding to advertising)
- Available for phone contact by subjects throughout the study (triage of subject concerns)
- Phone contacts at 13 weeks for all subjects (450+)
- Clinic visits for “unacceptable bleeding” and randomization (150+)
- Phone contact at 26 weeks for all subjects
- Clinic visit at 39 weeks for all subjects

- Potential additional post-39 week phone contact for limited # subjects with late randomization

- Baseline - Consent form copying & scanning
- Baseline – data collection / case report form completion
- Subject education re: diary completion, study plan, subject responsibilities
- Collection of subject diaries at 13 – 26 – 39 weeks
- Assessing treatment compliance for randomized and secondary treatment
- Satisfaction surveys at 13 – 26 – 39 weeks
- Documentation of study participation, randomization, and follow-up in medical record
- Data entry into electronic database (clinical data, diary data, satisfaction survey data)
- Maintain subject binders / folders (150+ complex and 300+ simple)
- Organize and develop system for follow-up visits and phone calls
- Scheduling of follow-up visits (prefer to have support of the PAC office)
- Remuneration for all subjects

- Consent form development
- Initial IRB submission
- Annual IRB progress reports
- Data collection / case report form development
- Randomization and Electronic database development
- Maintain regulatory binders

Family Medicine / Primary Care and Mayo Clinic Health System Enrollment

- Develop a plan for consenting
- Develop a plan for data collection at baseline
- Develop a system for follow-up
- Develop a plan for diary collection
- Develop a plan for randomization
- Develop a plan for dispensing study treatment medication
- Study Training for MCHS personnel

11.0 Patient Consent Form (attached separately)

12.0 References

[1]Funk S, Miller MM, Mishell DR Jr. et al. Safety and efficacy of Implanon, a single-rod implantable contraceptive containing etonogestrel. Contraception 2005; 71:319-26.
[2]Mansour D, Korver T, Marintcheva-Petrova M et al. The effects of Implanon on menstrual bleeding patterns. Eur J Contracept Report Health Care 2008; 13 (Supp 1):13-28.

[3] Casey PM, Long ME, Marnach ML et al. Bleeding related to etonogestrel subdermal implant in a US population Contraception 2011 May;83(5):426-30. Epub 2010 Nov 6.,
[4] Implanon prescribing information http://www.implanon-usa.com/HCP/Global/Prescribing.asp?C=17145404716401967593&ComponentID=144728&SourcePageID=174232 accessed. March 17,2011
[5] Archer DF, Philput CB, Levine AS, Cullins V, Stovall TG, Bacon J, et al. Effects of ethinyl estradiol and ibuprofen compared to placebo on endometrial bleeding, cervical mucus and the postcoital test in levonorgestrel subcutaneous implant users. Contraception. 2008 Aug:78(2):106-12.
[6] Chandra A, Martinez GM, Mosher WD, et al. Fertility, family planning, and reproductive health of U.S. women: Data from the 2002 National Survey of Family Growth. National Center for Health Statistics. Vital Health Stat 23(25). 2005. Available at http://www.cdc.gov/nchs/data/series/sr_23/sr23_025.pdf. Accessed April 10, 2007
[7] Long ME, Marnach ML, Casey PM. Management of Bleeding Associated With Etonogestrel Subdermal Implant (Implanon) in a US Population[a] (2011 unpublished data)
[8] Lakha F, Glasier AF.Continuation rates of Implanon in the UK: data from an observational study in a clinical setting. Contraception. 2006 Oct;74(4):287-9.
[9] Finer LB, Henshaw SK. Disparities in rates of unintended pregnancy in the United States, 1994 and 2001. Perspect Sex Reprod Health. 2006;38:90-6.
[10] Guttmacher Inst Facts on induced abortion in the US. http://www.guttmacher.org/pubs/fb_induced_abortion.pdf Accessed March 17, 2011.
[11] Agrawal A, Robinson C. An assessment of the first 3 years' use of Implanon in Luton. J Fam Plann Reprod Health Care. 2005 Oct;31(4):310-2.
[12] Fraser IS, McCarron G. Randomized trial of 2 hormonal and 2 prostaglandin-inhibiting agents in women with a complaint of menorrhagia. Australian & New Zealand Journal of Obstetrics & Gynaecology 1991;31:66-70.
[13] Belsey EM, Machin D, d'Arcangues C. The analysis of vaginal bleeding patterns induced by fertility regulating methods. Contraception 1986;34:253-60.
[14]. Belsey EM, Pinol APY, Task Force on Long-Acting Systemic Agents for Fertility Regulation. Menstrual Bleeding Patterns in the untreated Women. Contraception 1997; 55:57-65.
[15].Vincent AJ, Salamonsen LA. The role of matrix metalloproteinases and leukocytes in abnormal uterine bleeding associated with progestin-only contraceptives. Hum Reprod. 2000 Aug:15 Suppl 3:135-43.
[16].Fraser IS, Hickey M, Song JY. A comparison of mechanisms underlying disturbances of bleeding caused by spontaneous dysfunctional uterine bleeding or hormonal contraception. Hum Reprod. 1996 Oct:11 Suppl 2:165-78.
[17]. Smith GN Jr, Mickler EA, Hasty KA, Brandt KD. Specificity of inhibition of matrix metalloproteinase activity by doxycycline: relationship to structure of the enzymes Arthritis Rheum. 1999 Jun:42(6):1140-6.
[18]. Vernillo AT, Ramamurthy NS, Golub LM, Rifkin BR. The non-antimicrobial properties of tetracycline for the treatment of periodontal disease. Curr Opin Periodontol. 1994:111-8.
[19]. Cicinelli E, De Ziegler D, Nicoletti R, Colafiglio G, Saliani N, Resta L, et al. Chronic endometritis: correlation among hysteroscopic, histologic, and bacteriologic

findings in a prospective trial with 2190 consecutive office hysteroscopies. Fertil Steril. 2008 Mar:89(3):677-84.
[20].Li R, Luo X, Archer DF, Chegini N. Doxycycline alters the expression of matrix metalloproteases in the endometrial cells exposed to ovarian steroids and pro-inflammatory cytokine. J Reprod Immunol. 2007 Apr:73(2):118-29.
[21].Weisberg E, Hickey M, Palmer D, O'Connor V, Salamonsen LA, Findlay JK, et al. A randomized controlled trial of treatment options for troublesome uterine bleeding in Implanon users. Hum Reprod. 2009 Aug:24(8):1852-61.
[22].Weisberg E, Hickey M, Palmer D, O'Connor V, Salamonsen LA, Findlay JK, et al. A pilot study to assess the effect of three short-term treatments on frequent and/or prolonged bleeding compared to placebo in women using Implanon. Hum Reprod. 2006 Jan:21(1):295-302.

[23].Diaz S, Croxatto HB, Pavez M, Belhadj H, Stern J, Sivin I. Clinical assessment of treatments for prolonged bleeding in users of Norplant implants. Contraception. 1990 Jul:42(1):97-109.
[24 Abdel-Aleem H, d'Arcangues C, Vogelsong KK, Gülmezoglu AM Treatment of vaginal bleeding irregularities induced by progestin only contraceptives. (Review) Cochrane Database Syst Rev. 2007 Oct 17;(4):CD003449.
[25] Daniel Roline, senior analyst, Mayo Health System, personal communication November 3, 2010
[26] Travis Paul, operations manager, OBGYN Department, Mayo Clinic Rochester, personal communication November 15, 2010
[27] Reid PC, Coker A, Coltart R. Assessment of menstrual blood loss using a pictorial chart: a validation study.Br J Obstet Gynaecol 2000; 107:320-2.

[28] Mansour D, Bahamondes L, Critchley H, Darney P, Fraser I. The management of unacceptable bleeding patterns in etonogestrel-releasing contraceptive implant users Contraception 83 (2011) 202–210

[29] Long ME, Casey PM, Marnach ML, DrozdowiczL. Management of Implanon related bleeding with non-hormonal interventions. Poster accepted to COGI, Paris, November 2011 (Unpublished data).