Pre-IVF treatment with a GnRH antagonist in women with endometriosis – A prospective clinical trial

(PREGnant)

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1 Acronyms

Adverse Event	AE	Intent to Treat	ITT
The American College of Obstetricians and Gynecologists	ACOG	In Vitro Fertilization	IVF
Anti-Mullerian Hormone	AMH	Liver Function Tests	LFTs
American Society of Reproductive Medicine	ASRM	Luteinizing Hormone	LH
Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation	AMIGOS	Last Menstrual Period	LMP
Assisted Reproductive Technologies	ART	Medroxyprogesterone acetate	MPA
Twice a day	BID	Norethisterone acetate	NETA
Body Mass Index	BMI	National Institute of Child Health and Human Development	NICHD
Complete Blood Count	CBC	Oral Contraceptive Pill	OCP
Comprehensive Metabolic Panel	CMP	Office for Human Research Protections	OHRP
Case Report Form	CRF	Preimplantation Genetic Testing for Aneuploidies	PGT-A
Data and Specimen Hub	DASH	Protected Heath Information	PHI
Data Coordination Center	DCC	Effects of Physiologic Oxygen Tension on IVF Outcomes Study	PhOx
Data and Safety Monitoring Board	DSMB	Principal Investigator	PI
Estradiol	E2	Pregnancy in Polycystic Ovary Syndrome Study	PPCOS
Electronic Medical Record	EMR	Prolactin	PRL
Food and Drug Administration	FDA	Reproductive Medicine Network	RMN
Frozen Embryo Transfer	FET	Serious Adverse Event	SAE
Follicle Stimulating Hormone	FSH	Society for Assisted Reproductive Technology	SART
Good Clinical Practice	GCP	Selective Estrogen Receptor	SERM
Gonadotropin-Releasing Hormone	GnRH	Study Identification Number	SID
Health Insurance Portability and Accountability Act	HIPAA	Selective Progesterone Receptor Modulator	SPRM
Human Papillomavirus	HPV	Thyroid Stimulating Hormone	TSH
Human Chorionic Gonadotropin	hCG	Unanticipated Problem	UP
Institutional Review Board	IRB	Ultrasound	US

2 Protocol Summary

2.1 Title

Pre-IVF treatment with a GnRH antagonist in women with endometriosis – A prospective clinical trial (PREGnant).

2.2 Study Description

A Phase 3 randomized clinical trial of oral GnRH antagonist pre-treatment for women with endometriosis who are undergoing IVF, with a primary outcome of live birth rate. Participants will include those who agree to be randomized and those who do not want to be randomized. Those who agree to be randomized will be randomly assigned to either the elagolix group or placebo group. Those who do not want to be randomized can choose either the active treatment elagolix and follow the same procedures as those agreeing to be randomized or continue their ongoing or planned IVF and follow standard of care (SOC) (SOC IVF) if they do not want to delay the IVF procedure. Our central hypothesis is that in infertile woman with endometriosis undergoing in vitro fertilization-embryo transfer (IVF-ET), live birth rates will improve in those pretreated with GnRH antagonist (randomized or not randomized) compared to those who were not pretreated with GnRH antagonist (placebo or SOC IVF).

2.3 Objectives

Primary Objective: To compare live birth rates from IVF-ET cycles in women with endometriosis treated with a 60-day course of oral GnRH antagonist (randomized or not randomized) vs not treated with GnRH antagonist (placebo or SOC IVF) prior to ET.

Secondary Objective: To evaluate the efficacy of pre-IVF ORILISSA™ (elagolix) treatment on IVF cycle parameters and on known endometriosis-related obstetrical outcomes.
Tertiary Objective: Biobank serum samples for future microRNA biomarker analysis.

2.4 Endpoints

Primary Endpoint: Live birth per subject, defined as live birth at ≥24 weeks of gestation after treatment with GnRH antagonist (randomized or not randomized) versus no treatment with GnRH antagonist (placebo or SOC IVF) prior to ET.

Secondary Endpoints:

1) IVF cycle parameters including ovarian response as reflected in number of ovarian follicles>14mm, dose of gonadotropin used (units), protocol (GnRH antagonist vs agonist), duration of stimulation (days), estradiol, progesterone levels and endometrial thickness on day of hCG trigger, number of total and mature egg yield, fertilization rate of mature eggs, use of micromanipulation techniques (ICSI, Assisted Hatching), % blastocysts achieved, use of PGT-A, number and quality of embryos transferred, day of ET, cryopreservation of surplus embryos, implantation rate [# of gestation sacs visible by US / # of ET), biochemical pregnancy (positive pregnancy test following ET), clinical

pregnancy (US evidence of intrauterine gestational sac with fetal cardiac activity), multiple pregnancy rate, miscarriage rate (defined as pregnancy loss prior to viability scan and including those confirmed on ultrasound scan up to ≤23+6 weeks of gestation), timing of miscarriage (early <12 week and late between 12-23 weeks), rate of ectopic or pregnancy of unknown location, ongoing pregnancy rate after treatment with GnRH antagonist versus no treatment with GnRH antagonist (placebo or SOC IVF) prior to IVF-ET.

2) Obstetrical outcomes including gestation at delivery, incidence of pregnancy complications including preterm delivery, preeclampsia, incidence of abnormal placentation (placenta previa, accreta, increta, percreta, abruption), bleeding in pregnancy (antepartum or postpartum), birth weight and sex of newborn after treatment with GnRH antagonist versus no treatment with GnRH antagonist (placebo or SOC IVF) prior to IVF-ET.

3) Quality of life in patients before and after treatment with GnRH antagonist versus no treatment with GnRH antagonist (placebo or SOC IVF).

Tertiary End Point:

1) Biomarkers including CA-125 with Micro RNA before and after completion of GnRH antagonist (randomized or not randomized) versus no treatment with GnRH antagonist (placebo or SOC IVF).

2) Serum samples will be collected prior to and following completion of 60 days intervention with GnRH antagonist (randomized or not randomized) and no treatment with GnRH antagonist (placebo or SOC IVF)for future microRNA biomarker analysis.

2.5 Study Population

400 women with endometriosis between the ages of ≥18 and ≤40 years planning on undergoing IVF-ET for infertility management.

2.6 Description of Sites Enrolling Participants

Four clinical sites will be enrolling study participants: Yale University (Yale), University of Colorado (UC), Northwestern University (NU), and Duke. Johns Hopkins University will serve as an ancillary site to Yale University that will be recruiting and serve as the single IRB of record. Additional sites may be added as needed to increase the pace and meet the goal of enrollment timely.

2.7 Description of Study Intervention

Participants will be asked whether they agree to be randomized first. For those who agree to be randomized, they will receive ORILISSA™ (elagolix) 200mg twice a day (BID) ~~and~~ or placebo BID, both for a minimum of 60 days before IVF cycle start. For those who do not want to be randomized and choose elagolix, they will receive elagolix 200 mg BID for a minimum of 60 days before IVF cycle start. For those who do not want to be randomized and do not want to delay the IVF procedure, they will continue their ongoing and planned IVF and follow SOC.

For convenience of IVF cycle scheduling, participants may receive up to an additional 14 days of intervention [ORILISSA™ (elagolix) or placebo] beyond the minimum 60 days of pre-IVF treatment, such that the last dose of study intervention [ORILISSA™ (elagolix) or placebo] is received as close to but no less than 24 hours before start of IVF treatment protocol.

2.8 Study Duration

A total of 50 months will be required to complete the study after the first participant is enrolled.

2.9 Participant Duration

Up to six months for participants with maximum of one attempt at ET (either one cycle fresh ET, or one frozen-thawed ET cycle), over specified time period; up to fourteen months participation for pregnant women who will be followed up for pregnancy outcome.

3 Introduction

3.1 Rationale

Infertility is a common complication of endometriosis; while IVF successfully treats endometriosis-associated infertility, pregnancy rates are diminished compared to other etiologies of infertility. Our long- term objectives are to better identify and treat endometriosis related infertility. Our central hypothesis is that in infertile women with endometriosis undergoing in vitro fertilization-embryo transfer (IVF-ET), live birth rates will improve in those pretreated with GnRH antagonist compared to not treated with GnRH antagonist. The use of gonadotropin releasing hormone (GnRH) agonist prior to IVF has been suggested to improve success, however studies have been small and rarely reported live birth rates. Further, use of this approach is limited by the long treatment time required. Recent approval of an oral GnRH antagonist for endometriosis provides a novel option for women with endometriosis who are undergoing IVF. This agent avoids parenteral administration and the prolonged delay in initiation of action as is seen with GnRH agonists. There have been no studies on the efficacy of GnRH antagonists for the treatment of endometriosis-related infertility. This study will be a randomized clinical trial of oral GnRH antagonist pre-treatment for women with endometriosis who are undergoing IVF, with a primary outcome of live birth rate. We have recently demonstrated aberrant microRNAs in the circulation of women with endometriosis, a panel of which we have subsequently validated as a biomarker with high sensitivity and specificity for the detection of active disease. PREGnant trial will create an opportunity to examine, in future studies, if assessment of disease biomarkers will enable identification of those women with endometriosis who will benefit from GnRH antagonist pre-treatment, allowing for a precision medicine approach to endometriosis-related infertility. The study is significant due to the common occurrence of both infertility and endometriosis as well as the lack of precision in both diagnosis and therapy. We will use a novel intervention designed to improve the prognosis of

women with endometriosis undergoing IVF, and will have the potential to pursue an innovative approach to identify affected women who will benefit from this intervention.

3.2 Background

Endometriosis has been estimated to affect up to 10-15% of reproductive aged women (1). Commonly, symptoms present during the reproductive years, being most widespread at 25–35 years of age (2). The association between endometriosis and infertility is well documented, however a definite cause-effect relationship is still controversial. The prevalence of endometriosis increases dramatically to as high as 25-50% in women with infertility and 30–50% of women with endometriosis have infertility (3). The fecundity of normal reproductive age couples without infertility is estimated to be around 15- 20% per month, while the fecundity of women with untreated endometriosis is estimated at 2-10% (4, 5). Women with mild endometriosis have a significantly lower probability of pregnancy over 3 years than women with unexplained infertility (36% vs. 55%, respectively) (6). Studies comparing infertility in the setting of IVF suggest that women with more advanced endometriosis have poor ovarian reserve, low oocyte and embryo quality, and poor implantation (7, 8).

Despite their significantly lower fecundity compared to women without endometriosis, women with mild-moderate endometriosis are still able to conceive in the absence of any medical or surgical intervention. Multiple studies evaluating patients with endometriosis who undergo expectant management report their fecundity at around 2.4–3.0 per 100-person months (9, 10). However, women with more severe disease have far lower pregnancy rates (11). While expectant management may be a reasonable option for patients with mild-moderate disease, it only delays the start of effective fertility treatment in those with severe disease, risking ovarian aging, oocyte aneuploidy and depletion, as well as ovarian destruction by new growth of endometriosis or ablative surgery.

Endometriosis is an estrogen dependent disorder. Common medical therapies used to treat pelvic pain, dyspareunia and dysmenorrhea target ovarian estrogen production. Hormonally active therapies for endometriosis include combined oral contraceptives, progestins, danazol and gonadotropin-releasing hormone agonists or antagonists (GnRH analogs). Although these medications help to treat pain, used outside of IVF, they have shown no benefit in the treatment of endometriosis-associated infertility. A 2010 Cochrane review of 25 trials of ovulation suppressive agents (danazol, progestins, oral contraceptives, GnRHa) in 3043 women with endometriosis-associated infertility who wished to conceive reported odds ratios (OR) for pregnancy following ovulation suppression versus placebo or no treatment of 0.97 (95% confidence interval (CI) 0.68 to 1.34, P = 0.8) for all women randomized and 1.02 (95% CI 0.70 to 1.52, P = 0.82) for subfertile couples (12). Not only was there no benefit from ovulation suppression, but it also delayed the patient from having a live birth while taking the suppressive agents. The exception to this rule is patients undergoing in-vitro fertilization (IVF).

ART using IVF/ET is a well-established and effective technique to manage infertility from a wide variety of causes (13). In vitro fertilization is currently the most effective treatment for endometriosis-associated infertility. The Society of Assisted Reproductive Technology (SART) reported that in 2016, 6084 IVF cycles were performed in patients with endometriosis.

However, present diagnostic testing conducted as part of the infertility evaluation does not include laparoscopy; most cases of endometriosis go undocumented. When laparoscopy was part of the routine fertility evaluation 40-50% of women undergoing IVF had endometriosis; today the number diagnosed with endometriosis is closer to 3% due to lack of routine detection of the condition. Given the amount of endometriosis that is currently classified as unexplained infertility or otherwise misclassified, the comparison of pregnancy rates between women with and without endometriosis is not informative. Therefore, the true effect of endometriosis on IVF outcomes remains highly debated (14, 15). One meta-analysis from 2002 including 22 non-randomized trials reported that the chances of achieving pregnancy with IVF in women with endometriosis was almost half that of those with tubal infertility (odds ratio [OR] = 0.56, 95% confidence intervals [CIs] = 0.44–0.7) (14), and women with severe disease had about half the pregnancy rate of those with mild disease. These data support the notion that when endometriosis is accurately diagnosed, pregnancy rates are reduced, and that there is a dose-response effect in that those with worse disease have a worse prognosis. A more recent study published in 2018 (16) confirmed that women with endometriosis still have a 24% lower likelihood of live birth after IVF than women with unexplained infertility.

Prolonged GnRH agonist treatment prior to IVF improves fertility rates in women with advanced endometriosis (17, 18, 19). Proposed mechanisms are by means of increased retrieved oocytes, higher implantation rates, and reduced preclinical abortions (20, 21). A Cochrane review of 3 RCTs in 165 women with endometriosis concluded that GnRH agonist administration for a period of 3-6 months prior to IVF or ICSI increases the odds of clinical pregnancy (OR 4.28, 95% CI 2.00–9.15) (22). None of those studies were placebo controlled, only one reported live birth rates and none provided sufficient data to investigate important secondary outcomes such as multiple or ectopic pregnancies, miscarriage, fetal abnormalities, or other complications. Taken together, suppressive therapy pre-ART in patients with endometriosis shows promise for improving endometriosis-related infertility when used prior to IVF. However, GnRH agonist treatment is difficult for patients. Administration typically requires intramuscular injection; further, agonists initially stimulate FSH production and increase estradiol, inducing a “flare” effect that can exacerbate disease before achieving suppression. The prolonged treatment (3-6 months) required may be accompanied by severe vasomotor symptoms. In contrast, the recently approved GnRH antagonist, ORILISSA™ (elagolix), is administered orally and rapidly suppresses estradiol levels (with 24 hrs.). The incidence and severity of vasomotor symptoms is far lower than with agonist (23). Thus, a shorter course of therapy should be possible with decreased patient burden.

Most infertility patients no longer undergo laparoscopy routinely prior to IVF. When laparoscopic evaluation was part of routine infertility evaluation, endometriosis was diagnosed as a common contributor to infertility. Currently only a small number of women with infertility attributed to endometriosis undergoing IVF are reported to SART. The lack of diagnosis leads to uncertainty; we miss many cases of endometriosis that would benefit from treatment. Many women with undiagnosed endometriosis may benefit from GnRH antagonist therapy. A biomarker will allow a precision medicine approach to IVF identifying all who would most benefit from treatment, preventing needless treatment and reducing cost.

To date there has been no endometriosis biomarker with adequate sensitivity and specificity to prove clinically useful for the diagnosis of endometriosis. Analyzing a combination of biomarkers, rather than a single biomarker, may be the key to the robust prediction of endometriosis (24). Serum cancer antigen CA-125 has been utilized as a circulating marker for the disease, however it does not have sufficient diagnostic sensitivity or specificity (25); increased CA-125 levels mainly reflect advanced stages of endometriosis and are also elevated in other diseases (e.g. fibroids, ovarian cancer, and pelvic inflammatory disorders). A recent meta-analysis of CA-125 studies (using CA-125 ≥ 30 units/ml) found that pooled specificity of the marker was 93%, but pooled sensitivity was just 52%, and it performed especially poorly for detecting early stages of the disease, with only 24% specificity (26). Combining measurements of CA-125 with other inflammatory and non-inflammatory plasma biomarkers (annexin V, VEGF, and sICAM-1), measured during the menstrual phase, yielded a sensitivity of 81- 90% for ultrasound-negative endometriosis, however the specificity of this combination of markers was lower, at 63-81% (27). A systematic review of 141 studies of 122 blood biomarkers, including endometrial antibodies, reported that none of the biomarkers studied to date met the criteria for triage or as replacement diagnostic test (25).

3.3 Risk/Benefit Assessment

3.3.1 Known Potential Risks

Safety of ORILISSA™ (generic name Elagolix) was established in clinical trials that led to FDA approval of this agent. Most common adverse reactions (>5%) in clinical trials included hot flashes and night sweats, headache, nausea, insomnia, amenorrhea, anxiety, arthralgia, depression-related adverse reactions and mood changes. Rare side effects include: abnormal liver functions, appendicitis, suicidal behavior & thoughts as well as anaphylaxis as with virtually any medication.

In addition, the following is the warning and precautions from the drug insert and listed under the Adverse Events:

Bone Loss ORILISSA™ (elagolix) causes a dose-dependent decrease in bone mineral density (BMD). BMD loss is greater with increasing duration of use and may not be completely reversible after stopping treatment. The impact of these BMD decreases on long-term bone health and future fracture risk are unknown.

Women who take ORILISSA may experience a reduction in the amount, intensity or duration of menstrual bleeding, which may reduce the ability to recognize the occurrence of a pregnancy in a timely manner.

Suicidal ideation and behavior, including one completed suicide, occurred in subjects treated with ORILISSA™ (elagolix) in the endometriosis clinical trials. ORILISSA™ (elagolix) subjects had a higher incidence of depression and mood changes compared to placebo, and ORILISSA™ (elagolix) subjects with a history of suicidality or depression had a higher incidence of depression

compared to subjects without such a history.

In clinical trials, dose-dependent elevations of serum alanine aminotransferase (ALT) at least 3 times the upper limit of the reference range occurred with ORILISSA™ (elagolix).

3.3.2 Known Potential Benefits

By improving the live birth rate in women with endometriosis, the study has the potential to change clinical practice and result in more successful family building by improving the prognosis for women with endometriosis undergoing IVF. Collection of biospecimens (serum) will allow establishment of a disease specific reproductive biorepository that will serve as a resource for future studies, help in identifying a broader spectrum of disease specific biomarkers and in improving our understanding of effects of endometriosis on ovarian function.

3.3.3 Assessment of Potential Risks and Benefits

In comparison to the overall potential for benefit, the risks are reasonable.

The most serious risk is a rare potential risk for anaphylaxis in response to the study medication ORILISSA™ (elagolix). Anaphylaxis is a potential risk of virtually any medication and is exceedingly rare. The spectrum of common side effects of the study drug are nuisance side effects and do not pose a safety risk (hot flashes, night sweats, body aches, arthralgias). Notably, add back hormone therapy was not used in the Phase II ORILISSA™ (elagolix) trials and will not be needed by the vast majority of participants.

For those few participants with moderate to severe hot flashes, we allow staged treatment. Based on the FDA Guidance, hot flash severity can be divided into three categories for which only moderate to severe hot flashes may require therapy:

1. Mild hot flash: sensation of heat without sweating
2. Moderate hot flash: sensation of heat with sweating, able to continue activity
3. Severe hot flash: sensation of heat with sweating causing cessation of activity

The first intervention for those with moderate to severe hot flashes is counseling and reassurance. Second line interventions include lifestyle changes and behavioral modifications including:

1. Layered clothing
2. Natural fiber clothing that breathes, light cotton nightclothes, avoid pullovers or turtlenecks
3. Keep a cool pack under the pillow
4. Dual control electric blankets or a bed fan
5. Avoid triggers: caffeine, alcohol, spicy foods
6. Exercise
7. Yoga
8. Relaxation

For those requesting pharmacologic treatments for moderate to severe hot flashes that have proven to be unresponsive to the above interventions, the recommended first line pharmacologic therapy is Brisdelle (paroxetine mesylate 7.5 mg/day); it is the only FDA approved non-hormonal treatment for hot flashes.

Hot Flash Side Effect Protocol: If hot flashes are mild-moderate, first give reassurance and consider lifestyle and behavioral remedies for 2 weeks, recheck with participant. If symptoms persist, consider non-hormonal treatment with Brisdelle.
Over-the-counter (OTC) remedies have limited clinical trial evidence and may potentiate unknown interactions with the study drug. The use of OTC remedies for reported moderate to severe hot flashes will be discouraged and should be avoided.

An emergency unblinding procedure will be available to the investigator and designated persons at each site through the Data Coordination Center (DCC). It is the investigator's responsibility to decide whether it is medically necessary to know the patients' randomization (i.e., unblinding) to ensure the participant's welfare and safety. Breaking of the blind for individual patients in emergency situations could be required in the case of a suspected unexpected serious adverse reaction or in the case of an important adverse event where the knowledge of the treatment arm is required for therapeutic decisions for the management of the subject. The DCC records when and by whom the code is broken. The investigator must record the event of unblinding in the participant's medical record, including the reason for unblinding, but not the treatment allocation if this can be avoided. In the case of accidental unblinding, the investigator must record the event and the same procedures as for emergency unblinding must be followed.

Additional risks include the following warnings and precautions listed from the ORILISSA™ drug insert packaging which are listed under the Adverse Events.

1. Bone Loss -ORILISSA™ (elagolix) causes a dose-dependent decrease in bone mineral density (BMD). BMD loss is greater with increasing duration of use and may not be completely reversible after stopping treatment. The impact of these BMD decreases on long-term bone health and future fracture risk are unknown. Consider assessment of BMD in patients with a history of a low-trauma fracture or other risk factors for osteoporosis or bone loss, and do not use in women with a known diagnosis of osteoporosis. Limit the duration of use to reduce the extent of bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients.

2. Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy in Women who take ORILISSA may experience a reduction in the amount, intensity or duration of menstrual bleeding, which may reduce the ability to recognize the occurrence of a pregnancy in a timely manner. Perform pregnancy testing if pregnancy is suspected and discontinue ORILISSA™ (elagolix) if pregnancy is confirmed.

3. Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders Suicidal ideation and behavior, including one completed suicide, occurred in subjects treated with ORILISSA™ (elagolix) in the endometriosis clinical trials. ORILISSA™ (elagolix) subjects had a higher incidence of depression and mood changes compared to placebo, and ORILISSA™ (elagolix) subjects with a history of suicidality or depression had a higher incidence of depression compared to subjects without such a history. Promptly evaluate patients with depressive symptoms to determine whether the risks of continued therapy outweigh the benefits. Patients with new or worsening depression, anxiety or other mood changes should be referred to a mental health professional, as appropriate. Advise patients to seek immediate medical attention for suicidal ideation and behavior. Reevaluate the benefits and risks of continuing ORILISSA™ if such events occur.

4. Hepatic Transaminase Elevations In clinical trials, dose-dependent elevations of serum alanine aminotransferase (ALT) at least 3 times the upper limit of the reference range occurred with ORILISSA™ (elagolix). Instruct patients to promptly seek medical attention in case of symptoms or signs that may reflect liver injury, such as jaundice. Promptly evaluate patients with elevations in liver tests to determine whether the benefits of continued therapy outweigh the risks.

5. Reduced Efficacy with Estrogen-Containing Contraceptives Based on the mechanism of action of ORILISSA™ (elagolix), estrogen containing contraceptives are expected to reduce the efficacy of ORILISSA™ (elagolix). The effect of progestin-only contraceptives on the efficacy of ORILISSA is unknown. Advise women to use non-hormonal contraceptives during treatment with ORILISSA and for one week after discontinuing ORILISSA™ (elagolix).”

4 Study Objectives and Endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To compare live birth rates from IVF-ET cycles in women with endometriosis treated with 60-day course of oral GnRH antagonist (randomized or not randomized) versus not treated with GnRH antagonist (placebo or SOC IVF) prior to IVF-ET or ET.	Live birth rate per participant, defined as live birth at ≥24 weeks of gestation.	This is the most clinically meaningful end point.
Secondary		
To evaluate the efficacy of pre-IVF ORILISSA™ (elagolix)treatment on known endometriosis-related obstetrical outcomes. To analyze a number of parameters to determine the effect of GnRH antagonist treatment on IVF cycle parameters. If an improvement in pregnancy rate is detected, we will use these data to evaluate the mechanism of improvement. We will also measure pregnancy related parameters to determine the effect of pre-treatment with GnRH antagonist on pregnancy related complications associated with endometriosis. Finally, quality of life will be assessed.	Abnormal placentation (placenta previa, accreta, increta, percreta), antepartum hemorrhage, pregnancy- induced hypertension, preeclampsia, cesarean delivery, very preterm birth rates. These will include: 1. Estradiol (E2) level on the day of human chorionic gonadotrophin (hCG) administration; 2. Progesterone (P) level on the day of HCG administration; 3. The number of oocytes retrieved; 4. Gonadotropin dosage and duration; 5. Number and percent of mature metaphase II (MII) oocytes; 6. Fertilization rate (Two-pronuclei: 2PN); 7. Blastocyst rate; 8. Incidence of moderate-to-severe ovarian hyperstimulation syndrome (OHSS); 9. Implantation rate; 10. Biochemical pregnancy rate; 11. Clinical pregnancy rate; 12. Miscarriage rate (defined as pregnancy loss prior to viability scan and including those confirmed on ultrasound scan up	To determine if treatment improves important safety parameters leading to healthy pregnancy.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	to ≤23+6 weeks of gestation); 13. Rate of ectopic or pregnancy of unknown location; 14. Multiple pregnancy rate; 15. Birth weight and sex of newborn; 16. Gestational age at birth; 17. Quality of life in patients before and after treatment with GnRH antagonist (randomized or not randomized) versus no treatment with GnRH antagonist (placebo or SOC IVF).	
Tertiary		
To bank serum in our biorepository for future mechanistic studies.	These stored samples will allow secondary analysis of additional endpoints. We anticipate including microRNA biomarkers currently under investigation, CA-125 and alternative biomarkers that may arise subsequent to the initiation of the study. Further, these samples will be available to junior and outside investigators who wish to perform secondary analyses and listed in NIH DASH.	The assessment of disease biomarkers will enable identification of those women with endometriosis who will benefit from GnRH antagonist pre-treatment, allowing for a precision medicine approach to endometriosis-related infertility.

5 Study Design

5.1 Overall Design

We hypothesize that pre-IVF-ET treatment with GnRH will increase live birth rates compared to no treatment with GnRH antagonist (placebo or SOC-IVF). This will be a phase 3, multi-site trial assessing the efficacy of a GnRH antagonist ORILISSA™ (elagolix), administered for a minimum of 60 days prior to IVF start fresh or frozen ET (FET) cycle in women with endometriosis. For convenience of IVF cycle scheduling, participants may receive up to an additional 14 days of intervention ORILISSA™ (elagolix) or placebo) beyond the minimum 60 days of pre-IVF treatment, such that the last dose of study intervention (ORILISSA™ (elagolix) or placebo) is received as close to but no less than 24 hours before start of IVF treatment protocol. Each participant will be allowed a maximum of one attempt at ET (either one fresh IVF-ET attempt, or one frozen thawed ET cycle) over a specified time period.

5.2 Scientific rationale for Study Design

Multiple investigators have described improvement in IVF pregnancy rates in women undergoing pre- treatment with a GnRH agonist, however none have used GnRH antagonists, and none report live birth rate after a placebo controlled randomized trial. GnRH antagonists have clear advantages over agonists. Here we propose a prospective, clinical trial to determine if pre-treatment with a GnRH antagonist will improve live birth rate after IVF. All participants will have diagnosis of endometriosis (either based on prior surgery, pathology or based on ultrasound evidence of ovarian endometrioma/s) and will be recruited from the pool of infertile women already committed to undergo conventional IVF at one of the study sites.

The study team realizes that the arms of the study are not symmetrical but that is necessary to allow for the nature of the IVF care delivery. We believe that the most likely harm from endometriosis is due to its effect on the endometrium, endometrial receptivity and embryo implantation. Hence, treatment must precede the IVF transfer. When a fresh transfer will occur, the treatment must precede the IVF stimulation. When a frozen embryo is to be transferred, the treatment must immediately precede the thaw cycle. The study medication courses as described in the protocol are critical because medical therapy is not curative, rather it suppresses endometriosis only while on therapy. The course of study drug must be in close proximity to each embryo transfer.

5.3 Justification for Dose

Prior studies have demonstrated an effect of GnRH agonists using three months of therapy, and one small non- randomized study suggests improved implantation rates after just two months (28, 29). Importantly, the GnRH antagonist action is rapid (estradiol levels low within 24 hrs.) compared with GnRH agonists. We hypothesize that a shorter two-month course of antagonist should produce similar results to the longer course of GnRH agonist. We will use the FDA approved dose of 200 mg twice daily; this dose produced a more complete response when used in women for treatment of endometriosis related pain.

Figure 1 Flow Chart for participants who agree to be randomized:

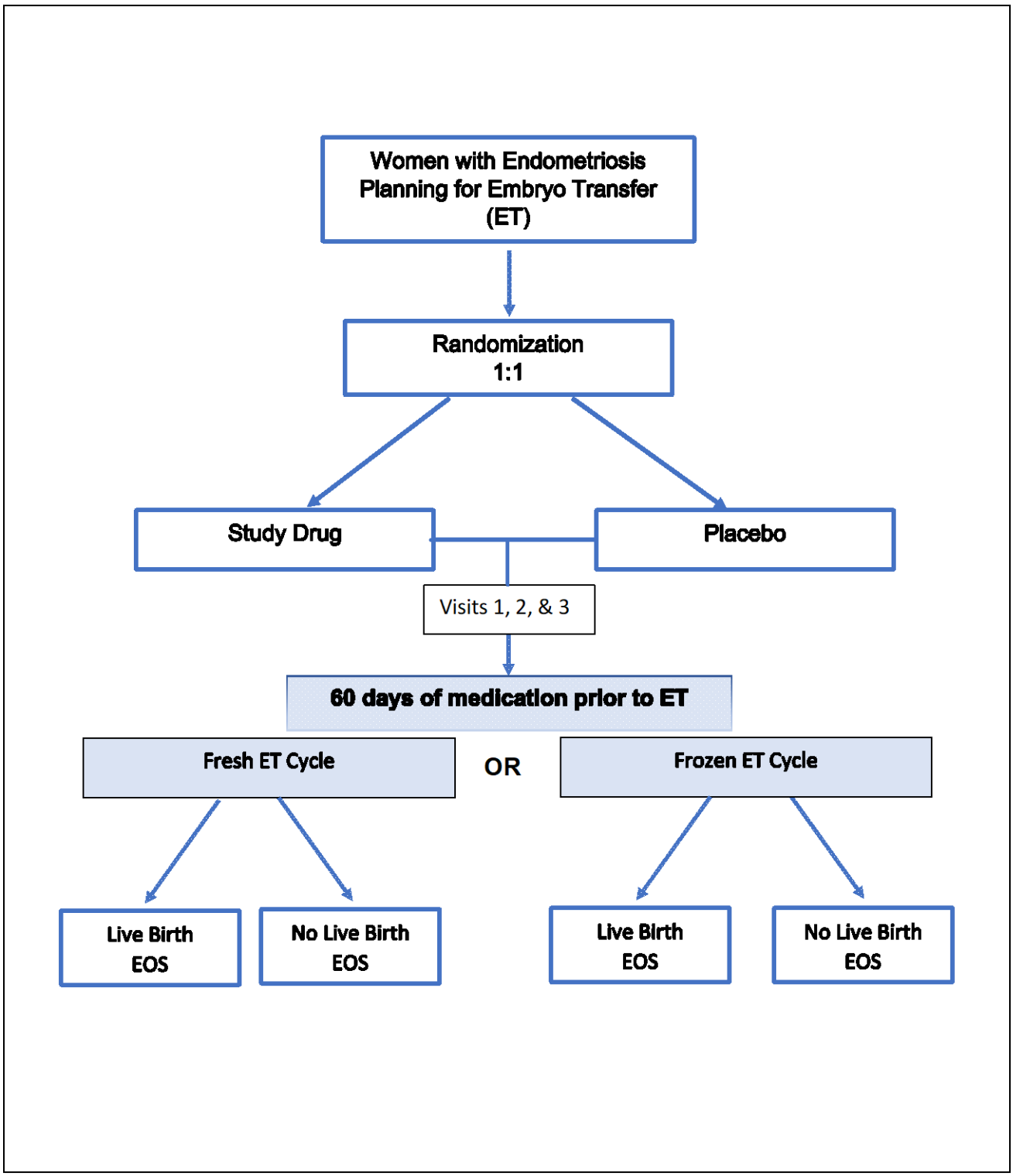
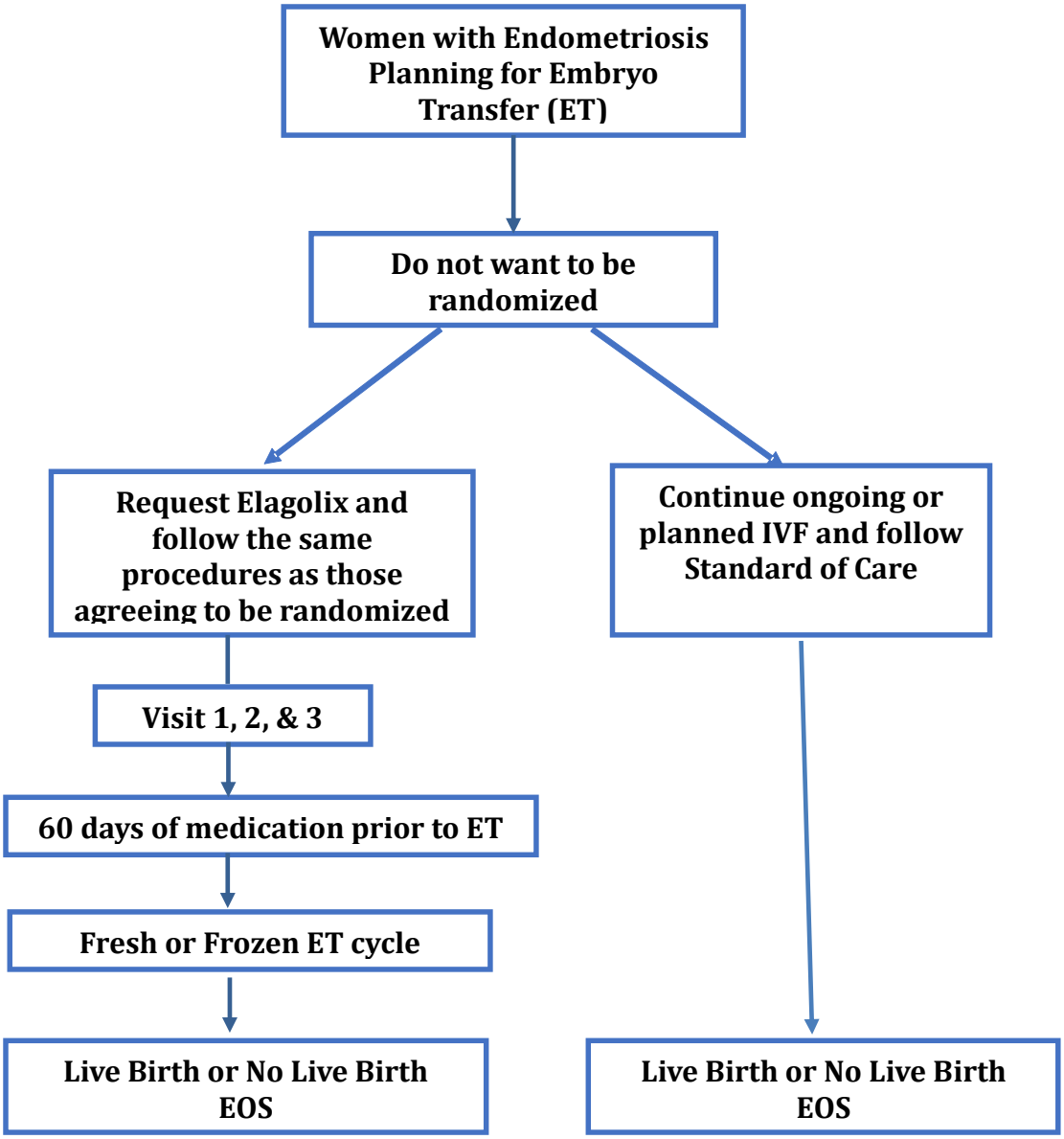


Figure 2 Flow Chart for participants who do not want to be randomized:



6 Study Population

6.1 Inclusion Criteria

1. Women who plan to undergo IVF for treatment of infertility.
2. Age ≥18 and ≤40 years at time of egg retrieval or signing informed consent.
3. Documentation of diagnosis of endometriosis by surgical visualization of endometriosis (laparoscopy or laparotomy) or diagnosis by pathology within the last 10 years before the initial trial entry visit or by aspiration of chocolate colored fluid on ultrasound guided aspiration of persistent ovarian cyst or radiological (MRI or ultrasound) documentation of persistent hyperechogenic cyst of any size, characteristic of endometriosis. If entry is based on the presence of an endometrioma, transvaginal ultrasound evaluation must document the same unambiguous endometrioma on two separate occasions in more than one menstrual cycle.
4. Body mass index (BMI) of 18-40 kg/m^2 (both inclusive) at screening.
5. AMH ≥ 0.5ng/ml, within 12 months of a fresh IVF cycle start. For frozen embryo transfers (FET) , AMH level eligibility criteria may not be met as long as the patient has at least one good quality blastocyst stored for the FET.
6. No known uterine cavity abnormalities at time of screening. Uterine cavity assessment by sonohysterogram or hysteroscopy within 12 months of embryo transfer indicating absence of focal intracavitary pathology and hence establishing adequate cavity at the time of embryo transfer. Ultrasound or MRI features suggestive of adenomyosis will be acceptable for inclusion. Type 3 fibroids are allowed up to 4cm size.
7. Presence of at least one ovary with no clinically significant abnormalities other than endometrioma. For eligible women with evidence of a hemorrhagic ovarian cyst, a repeat US will be needed in a subsequent menstrual cycle to ensure persistent cyst for patient to be deemed eligible.
8. Negative urine or cervical swab for gonorrhea and chlamydia within 12 months of screening.
9. Willing and able to comply with trial procedures, including reporting of obstetrical outcomes after delivery.
10. If applicable, the study participant will inform their partner of trial participation.

6.2 Exclusion Criteria

1. Use of depot GnRH agonists within 6 months of study start. Use of subcutaneous antagonists or nasal agonist within 2 months of study start unless part of regular IVF or previous IUI cycle.*
2. Use of depot medroxyprogesterone acetate (MPA) (injectable) or birth control implants (e.g., Implanon® or Nexplanon®) within 6 months of study start.*
3. Continuous use of oral progestins (MPA, NETA) within 1 month of study start. *

4. Use of aromatase inhibitors, danazol or hormonal contraceptives (Including combined oral contraceptive pill, progestin-only pill, transdermal patch or contraceptive ring, or double barrier contraception) within 1 month of study start.*
5. Pregnancy greater than 8 weeks in length within the last 6 months.
6. Number of previous IVF/ICSI attempts ≥3 unsuccessful (negative pregnancy test).
7. Presence of hydrosalpinx measuring >2cm on ultrasound, untreated endometrial polyps or intrauterine adhesions.
8. Abnormal cytology on a cervical screening based on the American College of Obstetricians and Gynecologists (ACOG) guidelines and patient age. (CIN1 or HPV allowed to participate in the study, CIN2 excluded unless treated and cleared, CIN3 excluded).
9. History of malignancy within 5 years of the start of screening, except for treated basal cell carcinoma and squamous cell carcinoma of the skin.
10. Any thoughts of suicide in the last 12 months per self-report, or documented in the electronic medical record (EMR).
11. Hypersensitivity to the study drugs.
12. Planned surgical treatment of endometriosis or planned surgery in the abdominal-pelvic area within the duration of the trial.
13. Untreated abnormal prolactin or TSH
14. Any conditions that preclude pregnancy.
15. Patients with a known history of a low-trauma fracture or other risk factors for osteoporosis or bone loss.
16. Patients with cirrhosis or abnormal LFTs per self report or documented in the electronic medical record (EMR).

* Exclusion criteria number 1,2, and 3 are not required to be met by individuals in the standard of care arm of the study. The study team will collect the information regarding whether the subject has used these drugs in the aforementioned time frame using the concomitant medication log and the individual will be allowed to participate in the study under the standard of care arm only.

6.3 Prohibited Medications

Although hot flashes and other vasomotor symptoms may occur with treatment of GnRH antagonist, these symptoms can be managed primarily with trial of Brisdelle.

Specifically, hormonal contraceptives, other estrogens or progestins, and drugs that mimic or alter sex steroid hormone action are not permitted (OCPs, depo MPA, levonorgestrel IUD, aromatase inhibitor, SERM, SPRM, androgens such as danazol). Non-conventional IVF therapies outside of those following standard protocols at each site will not be performed (for example patients pursuing natural cycle IVF will not be eligible).

Use of organic anion transporting polypeptide 1B1 inhibitors (OATP1B1) are not permitted in PREGnant.

6.4 Drug Wash Out

1. GnRH agonist within 6 months: with the exception of SOC patients
   leuprolide acetate brand names: Lupron -depot injectable,
   goserelin acetate brand Zoladex®, triptorelin brand Trelstar LA triptorelin (Pro) ® injectables

2. GnRH antagonist or nasal agonists within 2 months: unless part of regular IVF or previous IUI cycle with the exception of SOC patients
   elagolix brand Orilissa®
   ganirelix brand Antagon® SQ
   cetrorelix brand Cetrotide® SQ
   SQ or nasal lupron

3. Depot medroxyprogesterone acetate (MPA) injectable within 6 months

4. Continuous use of oral progestins within 1 month with the exception of SOC patients
   norethindrone acetate (NETA) brand Agestin®
   medroxyprogesterone acetate (MPA) brand Provera

5. Progestin only contraceptives within 1 month, norethindrone brands Camila®, Micronor®, Heather®, Jolivette®, & Nora-BE®

6. Aromatase inhibitors within 1 month
   letrozole brand Femara®
   anastrozole brand Arimidex®

7. Combined oral contraceptives pills (contains estrogen & progestin) within 1 month (below are a few examples from a large number of existing regimens)
   desogestrel & ethinyl estradiol brand Apri®
   levonorgestrel & ethinyl estradiol brand Aviane®, Alesse®, Orsythia®
   norethindrone acetate & ethinyl estradiol brand Orto-Novum®
   drospirenone & ethinyl estradiol brand Yasmin® or Yaz®
   norgestrel & ethinyl estradiol brand Lo Ovral

8. Transdermal patch norelgestromin-ethinyl-estradiol (contains estrogen & progestin) within 1-month brand Ortho-Evra® or Zulane®

9. Contraceptive ring (contains estrogen & progestin) brand NuvaRing® within 1 month

10. Birth Control Implants within 6 months
    etonogestrel brand Implanon® or Nexplanon® implant

11. IUD: levonorgestrel brand's Mirena®, Skyla, Kylenna, Liletta within 1 month.

6.5 Study Termination Criteria

Participant termination- Participants will be withdrawn from the study:

1. After failed ET cycle under trial assigned treatment.
2. Any serious adverse drug reaction will be considered as reason for termination of assigned intervention; participant will be followed up for cycle outcome, and if pregnant, for the duration of the pregnancy, and will contribute research data towards intent to treat analyses.

6.6 Strategies for Recruitment and Retention

6.6.1 Recruitment

This will be a multicenter study with four enrolling sites and one ancillary site, with additional sites to be added as needed to increase the pace of enrollment. Each of the four main sites is expected to recruit an average of 100 participants each for a total of 400 women.

Our main four sites (Yale, UC, NU, Duke) and one ancillary site (JHU) along with potential ancillary sites of consideration on an as-needed basis (Brigham and Women's and Colorado Center for Reproductive Medicine) performed a total of over 8,500 fresh IVF cycles and frozen embryo transfers as reported to SART in 2016. That number has increased to approximately 12,000 in 2018. Several of our centers and their key personnel are known for their special expertise in endometriosis (Taylor, Young, Bulun, Surrey and Hornstein) and see a larger than average number of women with endometriosis. For example, the incidence of endometriosis reported to SART at Yale in 2016 was 6%, twice the SART average; Duke reports a >10% incidence of endometriosis. Additionally, according to 2016 SART data, approximately 80% of endometriosis patient undergoing IVF are in the <35 or 35-37 age categories, our target population.

Participants will be recruited from the existing population of patients already committed to undergo IVF at any of the four main and ancillary clinical sites designated for patient recruitment. We will initially allow for equal recruitment; however, enrollment will be competitive and larger sites may accrue more rapidly. Advertisements may be used per local and central Institutional Review Board regulations. Informed consent will be obtained in a manner consistent with Good Clinical Practices (GCP) and a screening number will be assigned to each participant who has provided informed consent. Sample size calculations are based on the average volume of endometriosis patients seen at the participating IVF clinical sites. We will be able to screen over 720 endometriosis patients per year for a total of 2880 patients over four years. Assuming that 70% of the patients meet eligibility criteria, sites will generate a potential participant pool of 2,016 trial candidates. Target enrollment for a sample size of 400 participants will require that 19.8% of the eligible candidates initiate the trial. Given that women seeking infertility treatment are already engaged with providers at the IVF sites we are confident in the multi-site collaborative efforts of providers and the array of recruitment options through EMR review and public advertising to achieve our target sample size of N = 400

participants over four years. This total N is attainable as reflected by the proportion of participants in the RMN PhOx trial in which there were only three participating sites (30).

The GnRH antagonist will be administered during the routine pre-IVF evaluation period as following decision to proceed with IVF, patients routinely undergo requisite testing including evaluation of the uterine cavity by sonohysterogram or hysteroscopy as well as extensive laboratory testing of patient and partner (if applicable) and semen analysis of partner (if applicable). A 60-day pre-IVF course of GnRH antagonist is unlikely to significantly delay onset of IVF cycle start.

We will take additional measures to assure that we meet or exceed the necessary numbers:

- Direct provider referral.
- We will use case identification through the EMR and direct physician referral to enhance recruitment for the trial. Using the appropriate diagnostic codes, we shall identify patients within our healthcare systems with an infertility diagnosis who appear to meet the criteria for the trial and assess their interest in participation. This method has been effective for other recruitment.
- Website advertising: departmental websites will be submitted to the IRB for approval to be used to advertise the study and attract patients.
- Social media: We will post study details as well as post on clinical practices' Facebook homepage.
- Public service announcements and radio interviews. All public advertising will be sIRB approved with local IRB acknowledgement.
- Campus wide advertising: We will avail ourselves of all institutional resources available to apprise the providers and potential patient populace of the clinical trial.

6.6.2 Retention

Eligible women will be already committed to proceeding with IVF for infertility management. Based on our clinical experience, recommendations for strategies aimed at improving IVF outcomes (such as smoking cessation, correction of endometrial defects, weight loss and suppression of endometriosis) are welcomed by patients and any delay in IVF treatment initiation resulting from implementation of optimizing strategies by 2-3 months is deemed acceptable by the vast majority of our patients. Thus, based on our clinical experience, we anticipate an overwhelming majority of eligible patients will agree to participation in a clinical trial that aims to optimize IVF cycle outcome.

7 Study Intervention

7.1 Study Intervention(s) Administration

7.1.1 Study Intervention Description

For those who agree to be randomized (Figure 1) or those who do not want to be randomized and choose elagolix (Figure 2, left side), the intervention will consist of a minimum of 60-day pre-IVF treatment with an oral GnRH antagonist ORILISSA™ (elagolix, AbbVie) 200mg twice daily or an identical placebo regimen prior to ET cycle (fresh or FET). Participants may additionally receive up to 14 more days of intervention [ORILISSA™ (elagolix) or placebo] beyond the minimum 60 days of pre-IVF treatment to allow for IVF cycle start planning such that the last dose of study intervention [ORILISSA™ (elagolix) or placebo] is received as close to but no less than 24 hours before start of IVF treatment protocol. Each participant will be allowed a maximum of one attempt at ET (either one fresh IVF-ET attempt, or one FET attempt) over a specified time period. Participants who undergo a fresh ET cycles (see Figure 1, left arm) will receive one treatment course (elagolix or placebo) over the duration of the study (60-day treatment prior to ET cycle). Participants whose IVF treatment plan involves elective freezing of embryos (per standard clinical care) will receive one treatment course (see Figure 1, right arm) over the duration of the study (a 60-day treatment course prior to the frozen ET attempt.
For those who do not want to be randomized and do not want to delay the IVF procedure, the participants will continue their ongoing or planned IVF and follow the standard of care (Figure 2).

7.1.2 Dosing and Administration

For participants who would like to be randomized to elagolix/placebo the medication will be taken orally, 200mg twice daily (BID). For participants who choose not to be randomized and select the elagolix option, the medication will be open label elagolix, taken orally, 200mg twice daily (BID). Participants will be counseled to take the medication at the same time each day. Participants will be instructed to take a missed dose on the same day as soon as they remember and then to resume regular dosing. Participants will be told to take no more than 2 tablets each day. Study medication will be dispensed at 30-day intervals. Pill counts will be conducted and recorded at both the 30- and 60-day visit. Participants can begin taking elagolix/placebo at any time if they have been practicing contraception for the month/menstrual cycle prior to starting study drug. If a participant has not been practicing contraception for the month/menstrual cycle prior to starting study drug, then she should begin taking Elagolix/placebo within the first 7 days of her menstrual cycle starting.

7.2 Preparation/Handling/Storage/Accountability

7.2.1 Acquisition

ORILISSA™ (elagolix) and placebo will be obtained from AbbVie Pharmaceuticals.

7.2.2 Formulation, Appearance, Packaging and Labeling

ORILISSA™ (elagolix)will be provided as 200 mg tablets. The placebo will look identical to the ORILISSA™ (elagolix). Both the ORILISSA™ (elagolix)and placebo will be provided in similar packages. The package will state the study name but will not reveal allocation assignment. The ORILISSA™ (elagolix) and placebo will be provided in bottles. Study participants will be assigned enough medication at each medication dosing visit containing a 37 days' worth of medication/placebo which will allow for a window of 7 days for the 30-day visit.

7.2.3 Product Accountability and Storage

The ORILISSA™ (elagolix) and placebo will be blinded and shipped by AbbVie to investigators' sites (in batches). Sites will maintain accountability for all study product at their sites. The DCC will coordinate the randomization and distribution of the study product.

All investigational study product will be stored between 15°C -25°C (59°F-77°F) in a locked cabinet or box per labeling requirements.

7.3 Measures to Minimize Bias: Randomization and Blinding

For those who agree to be randomized, eligible women will be randomized in a 1:1 fashion to one of two treatments:

1. ORILISSA™ (elagolix) 200 mg BID daily for 60 days prior to undergoing IVF.
2. Placebo BID daily for 60 days prior to undergoing IVF.

A computer-generated randomization list will be created by the PREGnant Data Coordinating Center (DCC) and randomization will be performed prior to the first dose of ORILISSA™ [ORILISSA™ (elagolix)]. Randomization will have random sizes (2, 4, or 6) of blocks and be stratified by site, (e. g. whole blocks are assigned to sites) and by age group (<35 versus ≥ 35 years). are assigned to sites. The randomization list will not be available to any person involved in the conduct and evaluation of the trial until the trial is complete and database is declared clean and is released by the DCC. Likewise, treatment allocation information will not be accessible to investigators (except for serious safety concerns), trial staff at the site or central laboratory personnel during the trial. The treatment (antagonist vs placebo) applied during the fresh cycle frozen-thawed embryos resulting from the initial fresh egg retrieval cycle. Most women using ORILISSA™ (elagolix) menstruate in the first 2 months with only a 50% amenorrhea rate after 1 year in the Phase III clinical trial, enabling blinding to remain intact.

7.4 Study Intervention Compliance

Study medication will be dispensed every 30 days and compliance with the medication regimen will be determined by counting the remaining tablets. Tablet counts will be recorded on the study's clinical research forms. Frequent contact with participants will be maintained by telephone, secure email and text messaging to determine if they are having any barriers with taking the study medication. Participants who have less than 80% medication compliance will be put on an enhanced communication protocol with more frequent contact, and further attempts to identify and remove barriers to adherence.

8 Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

8.1 Discontinuation of Study Intervention

If a participant develops a serious adverse reaction, the medication will be discontinued until clarity is obtained whether this reaction is or is not due to the study drug. If the participant chooses to discontinue the study medication for perceived intolerable side-effects the participant will be withdrawn from the study. Arrangements for returning study drug to the research team will be made and recorded in the CRF. The participant will continue to be followed as they will be included in intent to treat analysis.

8.2 Participant Discontinuation/Withdrawal from the Study

If a participant wishes to withdraw from the study, they will be asked to do an End of Study visit and to give the site permission to use their IVF cycle and pregnancy data. They will then be included in the intent to treat analysis.

8.3 Lost to Follow-up

Because SART requires careful follow-up, study investigators will always have access to early pregnancy data. Attrition is a rare event prior to determination of live birth in SART. Participants who are lost to follow-up will be included in the intent to treat analysis.

9 Study Assessments and Procedures

9.1 Efficacy Assessments

The efficacy assessment for the primary outcome will be live birth rate per participant compared between the two study groups, those who are treated with GnRH antagonist (randomized or not randomized) and those who are not treated with GnRH antagonist (placebo or SOC IVF). For the secondary outcome, live birth rate per embryo transfer cycle will be compared between the two study groups.

9.2 Safety and Other Assessments

Adverse events will be monitored and assessed between the two study groups.

9.3 Study Procedures

Except for those who will go to SOC IVF, -participants will receive a minimum of 60 days of treatment with GnRH antagonist or placebo. Participants may receive up to an additional 14 days of intervention (ORILISSA™ (elagolix) or placebo) beyond the minimum 60 days of pre-IVF treatment, such that the last dose of study intervention (ORILISSA™ (elagolix) or placebo) is received as close to but no less than 24 hours before start of IVF treatment protocol. Planned visits and interventions are outlined in Table 1. IVF cycle stimulation, fertilization, embryo culture, and embryo transfers will all be performed per local clinical standard of care protocols.

Participants in either arm (elagolix or placebo) will be given an equal opportunity to conceive by allowing the same number of embryo transfers. Each IVF stimulation with fresh embryo transfer or frozen embryo transfer cycle will be preceded by a 60-day course of study drug. Participants undergoing IVF stimulation followed by an immediate fresh embryo transfer will receive one course of study drug. Participants undergoing IVF stimulation followed by complete embryo freezing and delayed embryo transfer will undergo one course of study drug treatment prior to FET.

For those who will go to SOC IVF, no pre-treatment is needed. They will continue their ongoing or planned IVF, and follow the procedures per standards of clinical care as applicable at each participating site (Section 9.3.8).

9.3.1 Screening Visit

Screening Visit

Participants will be prescreened for eligibility by a member of the research staff via the physicians EMR clinic schedules. Once in clinic during a regularly scheduled visit, eligibility will be confirmed by their physician and/or research staff. Once the Inclusion/Exclusion criteria have been met, study participation will be offered. The study protocol is adaptable to perform both the baseline Screening Visit and Visit 1 on the same day if all criteria are met. Should the participant express interest in combining these two visits to facilitate study initiation, clinical and research staff will take all measures to accommodate the request and plan the baseline Screening and Visit 1 accordingly. Comprehensive Metabolic Panel (CMP) labs must be

documented in the EMR within the 60 days of Visit 1 for allowable window for randomization to occur. If a CMP report is not available, the participant will return for Visit 1 after the CMP drawn and reported in the medical record. STD panel to be completed within 12 months of screening visit including HIV ½, Hepatitis B, Hepatitis C and Syphilis.

1. If history of self-harm is documented and the patient does not have a completed suicide assessment in their EMR, contact the clinic physician prior to consent to complete evaluation.

2. Obtain informed, signed consent.

3. Urine pregnancy test performed.

4. Complete medical and reproductive history.

5. Perform transvaginal ultrasound measuring uterine and ovarian characteristics including antral follicle count, measurement of any ovarian cyst/endometrioma (3 dimensions), documentation of number, size, and location of uterine fibroids (3 dimensions).

6. Collect blood for CMP Safety Laboratory tests as well as STD test and obtain results with physician review if <u>not</u> in participant's clinical record:

    a. Draw safety screening labs not extracted from medical record.
    b. Once initial eligibility established, CMP Safety Labs that were documented within the last 60 days.
    c. Urine or cervical swab for gonorrhea and chlamydia if not documented within 12 months enrollment.
    d. Draw HIV, Hepatitis B, Hepatitis C and Syphilis labs if not documented within 12 months of screening.

7. Participant completes FertiQoL, EHP-30, and COVID questionnaire.

8. Physical exam (heart/lung/abdomen/pelvis) including blood pressure, height, and weight measurements, including waist and hip measurements.

9. Record all current medications including supplements and OTC medications.

10. Administer the Columbia-Suicide Severity Rating Scale (C-SSRS, see Appendix D) for suicide risk assessment. Should a participant have a positive screen for suicidal ideation contact the clinic physician and implement site-specific SOC suicide prevention risk management protocol.

11. Source documentation for any inclusion/exclusion criteria that has been extracted from the participant's chart or obtained from other sources will be kept in the participant's record or have available for study monitor. This could include:

    - Uterine cavity assessment with no known cavity abnormalities and assessment by either hysteroscopy or sonohysterogram prior to embryo transfer
    - Transvaginal ultrasound report.
    - Cervical screening results based on The American College of Obstetricians and Gynecologists (ACOG) guidelines and patient age at time of informed consent signing which meet eligibility criteria.
    - Hormonal or Safety labs within the allowed time frame.
    - Urine or cervical swabs for gonorrhea and chlamydia within the allowed time frame.
    - Physical exam.
    - Participants will receive counseling on double barrier methods of contraception.
    - Either diagnosis by surgical visualization of endometriosis (laparoscopy or
    - laparotomy) or diagnosis by pathology within the last 10 years before the initial trial entry visit.
    - OR documentation of ovarian endometrioma >2 cm or two or more smaller endometriomas that total >2 cm in diameter. If entry is based on the presence of an endometrioma, transvaginal ultrasound evaluation must document the same unambiguous endometrioma on two separate occasions in more than one menstrual cycle.

9.3.2 Randomization Visit – Visit 1

To take place after eligibility is determined and signed consent obtained. Within 2 business days of participant visit, participants will be randomized to blinded study treatment and will be assigned medication

1. Urine pregnancy test performed.

2. Dispense 37-day study medication and instructions on how to take medication. Can dispense up to 81 day supply for remote referral site patients.

3. Collect blood for MicroRNA and other exploratory biomarkers.

4. Query participant on any medication changes since last visit.

5. Schedule Study Visit 2 with coordinator (30 days, with window up to 37 days).

6. Administer the Columbia-Suicide Severity Rating Scale (C-SSRS, see Appendix D) for suicide risk assessment. Should a participant have a positive screen for suicidal ideation

contact the clinic physician and implement site-specific SOC suicide prevention risk management protocol.

9.3.3 Study Visit 2

Participants will be scheduled for the next study visit at 30 days (within +7 days). They will need to be reminded to bring their study drug with them to the visit. Can be virtual visit for referral site patients.

1. Urine pregnancy test performed.

2. Conduct remaining study medication pill count and record on CRF. Review instructions on how to take study medication.

3. Dispense sufficient up to 44-day supply of assigned study medication with instructions on how to take the medication.

4. Query subject on any Adverse Events or medication changes.

5. Schedule study Visit 3 (30 days, with window up to 37 days).

6. Administer the Columbia-Suicide Severity Rating Scale (C-SSRS, see Appendix D) for suicide risk assessment. Should a participant have a positive screen for suicidal ideation contact the clinic physician and implement site-specific SOC suicide prevention risk management protocol.

9.3.4 Study Visit 3/Baseline IVF Cycle Start

Participants will be scheduled for the next study visit at 30 days, 60 days post-randomization (within +14 days). They will need to be reminded to bring their study drug with them to the visit. This visit may be performed up to 81 days post-randomization, depending on timing of IVF cycle start.

1. Urine or beta hCG pregnancy test performed.

2. Conduct remaining study medications pill count.

3. Collect blood for MicroRNA and other exploratory biomarkers if onsite.

4. Query participant on any Adverse Events or medication changes.

5. Participant completes FertiQoL and EHP-30 questionnaire.

6. Administer the Columbia-Suicide Severity Rating Scale (C-SSRS, see Appendix D) for suicide risk assessment. Should a participant have a positive screen for suicidal ideation

contact the clinic physician and implement site-specific SOC suicide prevention risk management protocol.

7. Perform transvaginal ultrasound measuring uterine and ovarian characteristics including antral follicle count. Quantify any visible endometriomas and fibroids.

8. Run or record CMP Safety Labs.

Participants will then undergo IVF-ET as per the usual standard of care protocols determined clinically at each site (Section 9.3.7).

Cycle start will be based on LMP in normally cycling women. In amenorrhoeic women, either spontaneous or study drug induced, cycle start will be random after assuring a negative beta hCG, progesterone <1, endometrial thickness of <7 mm and estradiol of under 80 picograms/ml; if estradiol level is ≥80 pg/ml (unless on luteal Estrace) and or endometrial thickness is ≥7mm, participants will receive a 7-day course of oral treatment with Medroxyprogesterone acetate (MPA) 10mg daily to initiate withdrawal bleeding to allow IVF cycle start. Participants may receive up to an additional 14 days of intervention (ORILISSA™ (elagolix) or placebo) beyond the minimum 60 days of pre-IVF treatment, such that the last dose of study intervention (ORILISSA™ (elagolix) or placebo) is received as close to but no less than 24 hours before start of IVF treatment protocol.

9.3.5 IVF Cycle Planning, Management, and Monitoring

Protocols for IVF will be per standards of clinical care as applicable at each participating site (Section 9.3.8).

9.3.6 End of Study (EOS) - Study Visit 4

This visit will occur when one of the following timepoints have occurred:

- Ongoing pregnancy at time of discharge to Obstetrics.
- Negative pregnancy test following embryo transfer
- Spontaneous pregnancy loss prior to 10 weeks gestation following embryo transfer

1. If pregnant, record obstetric ultrasound results.

2. Subject completes FertiQoL and EHP-30.

3. Query participant on any medication changes since last visit.

4. Administer the Columbia-Suicide Severity Rating Scale (C-SSRS, see Appendix D) for suicide risk assessment. Should a participant have a positive screen for suicidal ideation contact the clinic physician and implement site-specific SOC suicide prevention risk management protocol.

5. Conduct remaining study medications pill count as applicable.

9.3.7 Pregnancy Follow-up

Pregnancies will be followed through delivery or pregnancy loss. Participants who become pregnant will be asked to sign a release of prenatal records from their treating physician and of delivery records from their labor and delivery hospital (these will include both maternal and infant hospital records).

9.3.8 IVF Treatment

Participants will undergo IVF-ET as per the usual protocols determined clinically at each site. Prior RMN studies have used local IVF protocols. Here we will use each center's routine IVF protocols with minimal standardization that all centers have agreed upon as outlined below. The use of multiple centers without significant protocol modification will assure that our findings are broadly generalizable.

All sites will use standard FSH stimulation and GnRH antagonist in each cycle with the exception that additional LH activity will always be supplied at the outset of stimulation, since half of the participants will have been on GnRH antagonist and will be expected to have suppressed LH. Embryo transfers will follow ASRM guidelines allowing single or double embryo transfer. Preimplantation Genetic Testing for aneuploidy (PGT-A) and ICSI will be allowed. Frozen embryo transfers (FET) are included but must be preceded by pre-treatment with GnRH antagonist or placebo initially assigned at randomization.

The standard IVF protocol for the study will be a GnRH antagonist protocol, (Cetrotide or Antagon). Gonadotrophin stimulation with FSH (Gonal-F, Follistim). Each patient will receive at least 75 IU of Menopur as part of the initial stimulation start protocol (not a flexible start throughout a participant's cycle) to counteract the pituitary suppression by the GnRH antagonist. The last dose of oral GnRH antagonist (elagolix) will be as close to but no less than 24 hours before the start of IVF stimulation; addition of subcutaneous injections of GnRH antagonist (Cetrotide or Antagon) or of GnRH agonist will be based on the sites' standard IVF protocol.

A transvaginal ultrasound scan is scheduled to confirm a clinical pregnancy, detected by the presence of fetal heart activity and to determine number of gestations. Women are discharged from the care of the IVF clinic to their obstetrician for further prenatal care and delivery. The participants will have been consented for access to comprehensive pregnancy outcome and birth data at the time of enrollment.

9.3.9 Schedule of Evaluation

Table 1: Schedule of Evaluation

Procedures	Screening Day -30 to -1	Randomization/ Baseline Visit 1, Day 1	Study Visit 2 30 days +7 days	Study Visit 3/Baseline IVF Cycle: 60 days +7 days, up to 14 days	Study Visit 4 End of Study
Informed Consent	X				
Demographics	X				
Transvaginal Ultrasound	X			X	
Safety Labs	X			X	
Medical History	X				
Reproductive History	X				
Physical Examination	X				
FertiQoL Administration	X			X	X
EHP-30 Administration	X			X	X
C-SSRS Administration	X	X	X	X	X
COVID Questionnaire	X				
Concomitant Medication Review	X	X	X	X	X
Randomization		X			
Study Drug Dispensing		X	X		
Biorepository Blood Collection		X		X	
Adverse Event Review		X	X	X	X
Pill Count/Compliance			X	X	X
Urine or beta hCG pregnancy test	X	X	X	X	

10 Adverse Experience Reporting

10.1 Adverse Events

10.1.1 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

10.1.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.1.3 Classification of an Adverse Event

10.1.3.1 Severity of Event

The following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

10.1.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should

be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

10.1.3.3 Expectedness

The study PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information listed in the package insert, or in the consent form.

10.1.4 Time Period and Frequency for Event Assessment and Follow-up

The occurrence of an adverse event or serious adverse event may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Site personnel will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

10.1.5 Adverse Event Reporting

Adverse events deemed non-serious will be recorded throughout study participation from the start of study drug through one week after the last dose of study medication, and reported to the DCC. Non-serious adverse events will be reported to the DSMB quarterly.

10.1.6 Serious Adverse Event Reporting

All serious adverse events that occur from randomization through thirty days after the last dose of study medication must be reported or if the patient is pregnant, 6 weeks following delivery.

The site PI will report the SAE by completing and signing the Serious Adverse Event Report Form [available in the "Study Forms" section of the PREGnant website], and then emailing the document in PDF format to dcc.c2s2@mailman.yale.edu. Participants will be identified by study number only. No other identifying information will be included on the form. The site PI must determine and record on the SAE form whether the SAE is unanticipated or anticipated, and if it is related, possibly related, or unrelated to participation in the research. The site coordinator will enter the information into the OnCore database.

The Safety Surveillance team, consisting of the DCC and lead PI of the protocol, will analyze the SAE to determine if it meets the criteria listed in the OHRP 45CFR46 and/or FDA 21CFR312.32 & 3.14.80.

These determinations will dictate timeframes for sites' submission to the DCC, and the DCC's submission to the DSMB (**Table 2**):

Table 2: Types of Serious Adverse Events and their reporting requirements

TYPE	SITE	DCC
Unanticipated and related/possibly related SAE, fatal or life-threatening	Report to DCC within 1 business day of discovery	Notify DSMB by end of next business day of receiving site report

Other unanticipated and related/possibly related SAE	Report to DCC within 1 business day of discovery	Notify DSMB 5 business days of receiving site report
Anticipated and related/possibly related SAE	Report to DCC within 5 business days of discovery	Notify DSMB 5 business days of receiving site report
Unrelated SAE (anticipated or unanticipated	Report to DCC within 10 business days (no more than 3 weeks) of discovery	Notify DSMB within 10 business days (no more than 3 weeks) of receiving site report

Upon receiving notification of an SAE, the DSMB will review it via a closed-session email or conference-call discussion. The DSMB will send a report to the DCC within two weeks; reports for life-threatening SAEs will be submitted in one week. The DSMB report will include: statement indicating what related information the DSMB reviewed; the review date; the DSMB's assessment of the information reviewed; and the DSMB's recommendation, if any, for the DCC.

The DCC will then record the DSMB report and disburse. The DCC will forward reportable events to all PREGnant investigators, NIHCD, and the FDA on behalf of the NIHCD if the protocol is under IND. The lead PI of the protocol will review, sign, and return the IND safety report to the DCC within 2 business days, and will follow up with the site PI and DCC on the SAE until it is resolved. The Protocol PI will evaluate the frequency and severity of the SAEs and determine if modifications to the protocol and consent form are required. Site PIs will report the SAE to their site IRB according to local IRB requirements. For more information, please see the PREGnant/DSMB Communication Procedure.

10.2 Unanticipated Problems

10.2.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

10.2.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

The following UPs require prompt reporting:

- Breaches of confidentiality involving risks;
- Data and Safety Monitoring Board (DSMB) reports or interim analysis altering the risk/benefit profile by identification of increased risk;
- Protocol deviations, violations, or other accidental or unintentional changes to the protocol or procedures involving risks or with the potential to recur;
- Unapproved changes made to the research to eliminate an apparent immediate hazard to a participant;
- Other problem or finding (e.g., loss of study data or forms) that an investigator or research staff member believes could influence the safe conduct of the research.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) or require prompt reporting will be reported to the IRB and to the DCC and the study sponsor according to the timeline laid out for other SAEs in Section 10.1.6, Table 2.
- Any other UP will be reported to the IRB and to the DCC and the study sponsor as part of continuing review of the study progress.

10.3 Stopping Rules Based on Safety

Study participants can withdraw from this study at any time during this study without affecting their routine clinical care.

Following randomization (Visit 1) to study drug arms (elagolix or placebo), patients will be evaluated for presence of any AEs during the course of this study. Treatment may be discontinued until further clinical assessment. These events will be reported to the DSMB as delineated in Table 2.

A primary function of the DSMB is to conduct independent assessments on the safety of the intervention, and may recommend an early termination of the trial if the excessive risks on the study patients are evident from the use ORILISSA™ (elagolix). Existing data suggest this as an unlikely event. In the unlikely event, we have established the following stopping rules to safeguard the study participants.

The following events are some of the unlikely but possibly drug related SAEs:

- Elevated liver enzymes, AST or ALT 3 times the upper limit of the reference range
- Current low trauma bone fractures
- Anaphylaxis or any serious adverse drug reaction
- Any life-threatening event or other safety event for which the investigator determines that continued treatment with Elagolix is not in the participant's best interest
- Current attempted suicide or currently reported suicidal ideations.

If the number of the SAEs either listed as above or unspecified as defined in Section 10.2.2 exceeds certain specific levels, the DSMB may consider and recommend stopping this trial. The following threshold levels may serve as a guide to the DSMB's recommendation.

The cumulative number of SAEs in the group receiving ORILISSA™ (elagolix) exceeds twice of that in the placebo group, AND either of the following occurs:

- The cumulative number of SAEs in the group receiving ORILISSA™ (elagolix) is more than 8 (about 2% of the treatment arm sample size).
- The cumulative number of SAEs in the group receiving ORILISSA™ (elagolix) is more than 5% of the enrolled patients in the group (a maximum of 20).

11 Statistical Considerations (Statistical Analysis Plan)

11.1 Statistical Hypotheses

The live birth rate per embryo transfer cycle in the GnRH antagonist treatment group is higher than that in the non-GnRH antagonist treatment (placebo or SOC IVF) group.

Primary Objective: To compare live birth rates from IVF-ET cycles in women with endometriosis treated with a 60-day course of oral GnRH antagonist (randomized or not randomized) vs not treated (placebo or SOC IVF) prior to ET.

11.2 Sample Size Determination

The 2020 SART data demonstrates a live birth rate in women with endometriosis of 39.6% per cycle in women under the age of 35 and 29.4% in those aged 35-37. Using an average live birth rate per cycle of 39% and, based on the improvement seen in randomized trials using a GnRH agonist, we predict a 15% absolute improvement in live birth rate to 54%. Using 190 participants per arm (N=380) would provide an alpha of 0.05 and power of 84%. We plan to screen approximately 2500 participants in order to randomize 400 participants (200 participants per treatment group) to account for a 5% drop out rate. As these women are already committed to IVF prior to enrollment, we expect a low dropout rate similar to that seen in the RMN PhOx IVF trial. While the dropout rate was higher in the Phase III ORILISSA™ (elagolix) trial, these women had moderate to severe pain and many were randomized to a placebo group.

To ensure the adequate power of the study without unnecessarily increasing the sample size, an interim analysis is not considered. However, as discussed in Section 10.1.6, the DCC team will provide DSMB with necessary data for the DSMB members to examine and monitor the safety and efficacy of the study. Per NICHD request, an enrollment futility interim analysis will be performed when 200 participants are enrolled.

11.3 Statistical Analyses

11.3.1 General Approach

Prior to the data analysis above, we will assess the balance of baseline characteristics between the two groups. In the event that the imbalance is of concern such as the unadjusted p-value is less than 0.05, we will examine the pertinent baseline characteristics in their potential impact on the primary outcomes.

As we have done for all RMN trials, we will make every attempt to collect complete data. Based on our previous experience, missing values is not an issue; we had a data completion rate of at least 99.5% for all the past main RMN studies (PPCOSII, AMIGOS, PhOx). For the proposed study, similar approaches will be used to ensure the completion of the data received. In the unlikely event of unexpectedly high rates of missing data, the potential mechanisms for missing data (missing completely at random, missing at random, or missing not at random) will be

examined. We will compare the available characteristics of those with missing data to those with complete data. If necessary, imputation techniques may be used (31).

Also importantly, after data cleaning, two statisticians will individually perform the analysis, and the results will be cross-checked to avoid any inconsistency and human errors. After completion of the analysis, clean datasets and all the associated programs, results (tables and figures) will be archived for both internal and external uses; and all the results will be automatically reproduced with the use of SAS programs. This strategy ensures both high quality and reproducibility of our analysis results.

Missing data: We will make every attempt to collect complete data. Based on the experience of the RMN trials in related populations, missing values were not an issue, where the data completion rates exceeded 99.5% for all the RMN completed trials (PPCOSII, AMIGOS, and PhOx). This trial is coordinated by the same DCC team as those RMN trials. For this trial, similar approaches will be used to ensure the completion of the data received. In the event of significant missing data, the mechanism for missing data (missing completely at random, missing at random, or missing not at random) will be examined prior to beginning the analyses. We will compare the available characteristics of those with missing data to those with complete data. If necessary, imputation techniques may be used (31).

11.3.2 Analysis of Primary Efficacy Endpoints(s)

For the primary hypothesis, we will use the intent-to-treat (ITT) paradigm for those who agree to be randomized where all randomized participants are considered according to their randomized treatment assignments, regardless of actual treatment received, protocol violations, etc. The primary outcome, i.e., the live birth rates, will be compared between the GnRH antagonist treatment group (randomized or non-randomized) and the non-GnRH antagonist treatment group (placebo or SOC IVF) by ITT using the Pearson chi-square test of independence. In addition, we will also conduct sensitivity analyses by considering the actual treatments and excluding dropouts in order to assess the impact of these deviations on the conclusion of the primary hypothesis. Those sensitivity analyses will be performed using regression techniques such as logistic regression or other models as appropriate and needed. Secondary analysis will also be performed within the randomized participants (elagolix vs placebo), and within the non-randomized participants (elagolix vs SOC IVF).

In short, although the primary analysis will be based on a straightforward statistical test, extensive subsequent analyses will be performed to ensure that our final conclusion is thoroughly scrutinized and appropriately reported. This strategy has been successfully applied in six high impact publications in clinical trials for infertility treatments (32, 33, 34, 35, 36, 37) for which Dr. Zhang led the DCC.

11.3.3 Analysis of the Secondary Endpoints

For secondary efficacy parameters, depending on the characteristics of the outcome and exposure(s) of interest, Student's t-test or Wilcoxon rank-sum test will be used to test the difference between the two groups. In addition, multivariable regression models will also be

performed to compare the treatment effect on the outcomes, while adjusting some other potential variables.

11.3.4 Safety Analyses

For safety analyses, based on our experience, we expect to prepare detailed descriptive tables comparing the incidents between the two groups.

12 Data Collection and Site Monitoring

12.1 Records to be kept

Data will be collected prospectively by designated research personnel at each study site, supervised by the site PI. Participant data will be entered into a web-based data management system created by the Data Coordination Center, using only a study ID number. Original source documents will be kept in the study subject folder.

12.1.1 Maintenance/Retention of site records

In order to comply with Good Clinical Practice (GCP) requirements, the investigators must maintain the master patient log that identifies all patients entered into the study for a period of two years after the study ends so that the participants can be identified by audit. The PI must maintain adequate records pertaining to participants' files and other source data for a minimum of 5 years after completion of the study.

12.2 Role of Data Management

Each clinical site and the DCC will be responsible for ensuring study personnel are trained and follow the data management guidelines of Good Clinical Practice and RMN policies.

12.3 Quality Assurance

The DCC will perform regular clinical site monitoring to assure protocol compliance, ethical standards, regulatory compliance and data quality at the clinical sites, including review of records available for inspection by monitoring authorities (see Section 12.3.10). These data will be shared with the Steering committee and the DSMB as needed. Regular face to face meetings, monthly conference calls, and phone conferences of the protocol committees and recruitment committees will be forums for addressing quality assurance issues.

12.3.1 Data Entry and Forms

Paper Case Report Forms (CRFs) will be utilized as source documentation. They will also be implemented in a Web-based OnCore and Forte data management systems. The Web data entry forms will be similar to the paper forms with the same questions. However, the Web forms usually have more flexibility than the paper forms, such as pull-down menus.

12.3.2 Features of Data Management System

Features of the data management system include study definition; different types of data entry (and complete audit trail); forms control; query capture, reporting, and resolution; dictionary coding of Adverse Events (AEs) and medical terms; and clinical data review tools. The end-user/reporting/ad hoc query front-end uses a standard Web browser, so that data entry and browsing can be done from any machine with Internet access, without purchase of special software. Login to this system will be through a secured Web server with the security under the protection of Yale Center for Clinical Investigations.

12.3.3 Data Security

A data server and Web server will be used. The data server will be managed by YNHH IT center and the servers will be managed by Forte Research Systems. The web server will be accessible through a secured login, but the data server can only be accessed through the web server. For security purposes, no login to the data server will be permitted, and access to the back end is limited to authorized individuals. Protected Health Information (PHI), including patient names and addresses, will be locked and secured at the participating sites, and data will be linked through a unique identification number, which will be assigned after a patient is screened or enrolled. Access will be limited to authorized individuals (21 CFR 11.10(d)). Each user of the system will have an individual account. The user will log into the account at the beginning of a data entry session, input information (include changes) on the electronic record and log out at the completion of the data entry session. The system will be designed to limit the number of log-in attempts and record unauthorized access log-in attempts. Individuals will work only under their own access key, and not share these with others. The system will not allow an individual to log onto the system to provide another person access to the system. Users will be asked to change their passwords at established intervals commensurate with a documented risk assessment. This plan has been adapted from the guidelines for computerized systems used in clinical investigations established by the U.S Department of Health and Human Services Food and Drug Administration.

12.3.4 Data Quality Control

12.3.4.1 *Competency to perform procedure/tests in the protocol*

The site PI will be responsible for ensuring that study related tests are performed by competent personnel. The criteria for determination of competency may vary between sites in the study. Attempts will be made to standardize protocols whenever possible to minimize inter-site variation.

12.3.4.2 *Quality Control Steps*

Quality control of data will be handled on three different levels. The first level is the real-time logical and range checking built into the web-based data entry system. The research coordinators and data entry clerks at the participating sites are required to ensure the data accuracy as the first defense. The second is the remote data monitoring and validation that is the primary responsibility of the data manager and programmer at the DCC. The data manager will conduct monthly comprehensive data checks (SAS programs run on a regular basis as a systematic search for common errors and omissions), as well as regular manual checks (within the database system). Manual checks will identify more complicated and less common errors. The data manager will query sites until each irregularity is resolved. The third level of quality control will be the site visits, where data in our database will be compared against source documents. Identified errors will be resolved between our center and clinical sites. The visits will assure data quality and patient protection.

An audit trail will be added as another security measure. This will ensure that only authorized additions, deletions, or alterations of information in the electronic record have occurred and

allows a means to reconstruct significant details about study conduct and source data collection necessary to verify the quality and integrity of data. Computer generated, time-stamped audit trails will be implemented for tracking changes to electronic source documentation.

Controls will be established to ensure that the system's date and time are correct. This is a multi-center clinical trial and will be located in different time zones. System documentation will explain time zone references as well as zone acronyms. Dates and times will include the year, month, day, hour, and minute to the date provided by international standard-setting agencies (e.g. US National Institute of Standards and Technology). The ability to change the date or time will be limited to authorized personnel, and such personnel will be notified if a system date or time discrepancy is detected.

In addition to internal safeguards built into the computerized system, external safeguards will be implemented. Data will be stored at the Data Coordination Center. Records will be regularly backed up, and record logs maintained to prevent a catastrophic loss and ensure the quality and integrity of the data. This plan has been adapted from the guidelines for computerized systems used in clinical investigations established by the U.S Department of Health and Human Services Food and Drug Administration.

12.3.5 Obligation of the Investigator

12.3.5.1 *IRB Review*

The site PI is responsible for submitting the approved John's Hopkins protocol and master consent form to their local IRB. The participating sites local IRB must review and approve the site-specific consent prior to its submission to the DCC. The DCC will then submit this consent to John's Hopkins single IRB of record for stamped approval. It is anticipated that there will be minor site-specific changes in the site-specific consent form. The single IRB will periodically review the status of the study at appropriate intervals not exceeding one year. The site PI will be responsible for submitting any updated consent and continuing review forms to the DCC as well as their local IRB. The site PI will also be responsible for submitting revisions to the protocol, communicating serious adverse events and unanticipated problems as required by the local IRB.

12.3.6 Regulatory Requirements

The site PI will be responsible for reporting adverse events and unanticipated problems to the DCC as required in Sections 10.1.5, 10.1.6, and 10.2.2 of the protocol. They will ensure that required regulatory documents are sent in a timely manner to the DCC. They will also maintain a Regulatory Binder which will be kept up to date throughout the course of the study. The DCC will assist by providing lists of required documents.

The DCC will work with NICHD staff by providing them with clinical study data, reports, and other support as required for AE Reporting. The Project Managers will work with NICHD colleagues in meeting all regulatory requirements including compliance with ICH and HIPAA requirements, FDA code for federal regulations (Title 21). For example, the DCC Project

Managers have registered this clinical trial with ClinicalTrials.gov via the Protocol Registration System (NCT04173169).

12.3.7 Protocol Amendments

Once the protocol amendment is approved by the PREGnant PIs, it is then reviewed by the Data and Safety Monitoring Board (DSMB). After all approvals, the DCC will finalize the protocol document that serves as the agreement among all members of the PREGnant protocol. In the meantime, because the DCC administers all patient care costs for the protocol, the DCC will promptly issue subcontracts to the participating sites based on the cost agreements made by the PREGnant PIs.

If the PREGnant PIs decide that changes are necessary for scientific or clinical reasons, the DCC will facilitate the procedure in a timely and diligent fashion. The investigators and key personnel will participate in teleconferences and meetings, discuss, vote, and document circumstance and rationales for the changes and the implementation procedure for the changes. These include revising study hypotheses, designs, sample sizes, data entry forms, and appropriate statistical analyses. Once the amendments are finalized and agreed to by the PREGnant PIs, they will be submitted to the Johns Hopkins IRB and DSMB for reviews and approvals.

12.3.8 Safety Oversight

The overall Principal Investigator (PI) of the clinical study may suspend or prematurely terminate the study at any time for significant and documented reasons. These would include but not limited to, safety concerns and failure to meet enrollment numbers. The PI will assure that the NIH and that proper Regulatory Authorities per local reporting requirements have met.

If monitoring of a clinical site reveals repeated non-compliance with the study protocol and cannot be rectified in a timely manner, the overall PI will be suspended or terminate the site. Every effort will be made to retrain the sites and prevent reoccurrences from protocol deviations from occurring. The PI will assure that the NIH and that proper Regulatory Authorities per local reporting requirements have met.

12.3.9 Data Monitoring

The DCC team will constantly check the data quality through onsite visits and database. The DCC statisticians will provide the Data and Safety Monitoring Board (DSMB) with regular update of the data reflecting the efficacy and safety of the trial and report serious adverse events as they occur in a timely manner.

12.3.10 Study Monitoring

A monitoring plan that satisfies the ICH/GCP guidelines for clinical monitoring will be used. A Project Manager from the DCC will lead this effort, and report findings to the DCC PI. The Project Manager will have full knowledge of the study protocol, Manuals of Procedures, and is familiar with the database system and is trained to review patient charts. The Project Manager will be responsible for training and supervising other personnel.

Once personnel at participating site are trained to recruit patients, the Project Manager will be sent to the site to help initiate the study according to the study protocol, and to ensure that the clinical site meets the scientific, clinical, and regulatory requirements. For example, the Project Manager will review all signed and dated forms (such as financial disclosure forms), the curriculum vitae and certifications of the investigators and personnel, CRF training, and the written IRB approval of the protocol and consent form.

The on-site monitor will return to the clinical site after a defined number of patients are recruited (can be as early as the recruitment of the 2nd patient) or a certain time period has passed, depending on the duration of the protocol execution. The schedule of visits will be discussed and agreed by the Steering Committee and we anticipate that the Project Manager will visit each participating site at least once.

During the site visit, the clinical sites should provide to the monitor a space and access to all relevant records including medical records and regulatory binders, and there would be immediate verbal feedback provided to the site after original source documents are compared to entries in the CRF. The clinical sites must agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved. The on-site monitor will conduct an audit of a random sample of entered information against the source documents, a review of all regulatory documents, a review of all informed consents, and a review of all pharmacy logs. The clinical site PI and coordinator should be available to meet the monitor during the visit. The monitor will review electronic data from all sites, providing a method for identifying systematic errors or problems.

To assure Good Clinical/Laboratory Practice, the monitor will control adherence to the protocol at the clinical sites and evaluate the competence of the personnel at the clinical sites including the ability to obtain written informed consents and record data correctly. The monitor will inform the DCC PI and lead study PI regarding problems relating to facilities, technical equipment, or medical staff. A thorough written report will follow each site-visit and will include a detailed itemization of discrepancies and items requiring follow-up or reconciliation. The monitor will be responsible for maintaining regular contacts between the investigators in the clinical sites and the PREGnant Consortium. When the study ends, the monitor will also visit the clinical site to provide assistance for close-out.

13 Human Subjects

13.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent documents (see Appendix) and any subsequent modifications will be reviewed and approved by the Johns Hopkins IRB responsible for oversight of the study. A signed consent form will be obtained from the participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant and this fact will be documented in the participant's record. The consent form, which will be scanned into the site's EMR, will be coded with an alphanumeric code provided by the Data Coordinating Center. This code will be the participant's unique identifier that will carry through the entire study. Participants records are maintained in the EPIC EMR and in paper charts that are kept in a locked cabinet within a locked office that is secured at all times.

13.1.1 Informed Consent Process

Informed consent will be obtained by study personnel who are qualified to obtain informed consent, who have current Human Subjects Protection Training and Good Clinical Practices certification, been trained on the protocol, and who are delegated the task on the Delegation Log by the PI. A full explanation of study procedures will be provided to the potential participants. All potential participants will be given the opportunity to ask questions. All questions will be answered to the best of the ability of study personnel, and if any questions are asked that cannot be addressed at that time, the local site investigator and or lead protocol PI will be asked to respond to the potential participant. The participant will be given a copy of the signed consent which will include the IRB contact information should she have any questions.

13.2 Subject Confidentiality

All hard copy data contained in the participants study binder which includes, but not limited to: consent, CRF's, laboratory data, ultrasound reports and AE forms will be maintained in a locked office. Whenever possible the participant will be identified only by the Study Identification Number (SID) to maintain subject confidentiality. All other study records will be kept in a locked file cabinet. Patient data entered into the YNHH Oncore system is a secure password protected database system which meets all the HIPAA required security. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the IRB, the DCC, OHRP, the sponsor, or the sponsor's designee.

13.3 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the PI, IRB, the NICHD, the OHRP, or other government agencies as part of their duties to ensure that research participants are protected.

14 Publication and Data Sharing Policy

14.1 Overall Policy

The publications policy proposes guidelines for publications that originate from our collaborative PREGnant consortium. Decisions concerning publications shall be determined by consensus (majority vote) of the collaborating principal investigators (or designate) noted below as the "Consortium". This policy is designed to promote prompt, exact, quality publications and presentations of Network studies with appropriate academic recognition of those with significant contributions. Protocols are classified into three types: 'Main Study' (which may include major and minor publications), 'Ancillary Study', and 'Pilot Study'. Additionally, there may be publications from concepts or ideas generated by the PREGnant ("Related Publications") or from other groups utilizing PREGnant data and/or specimens "Outside Studies" (those utilizing data and/or specimens from the PREGnant studies). Abstract submissions to national meetings will also follow the publications policy below. The progress of publications (including presentations) will be a standing agenda note on all phone conferences and meetings. The Steering Committee will make the final disposition regarding disputes with respect to analysis request approval, prioritization, presentation, authorship and/or manuscript submission.

14.2 Main Study

A Main Study is a consortium study designed prospectively by an investigator independent of other studies. At the end of each Main Study, a primary analysis resulting in the primary manuscript and a number of secondary analyses is produced based on the research questions stated in the protocol. The Protocol leader is the primary author of the primary analysis. A main study can generate major (related to the major hypotheses) and minor publications (relating to secondary hypotheses).

14.3 Major Publications

A major publication is defined as one reporting results of the major hypotheses tested. (For example, does hMG/IUI increase cyclic fecundity in couples with unexplained or male factor infertility?)

1. Authorship: Publications will include the names of investigators from each PREGnant site and the DCC. Each PREGnant site and the DCC will have up to two authors per publication, ordinarily the PI and the Co-PI, but this may at times involve another investigator who has contributed to the study at their site, in lieu of the PI or Co-PI. The principal investigator at each PREGnant site will be responsible for submitting the names of the two authors from that unit and designating them as either the primary or secondary authors of the unit. No more than 2 authors may represent a PREGnant site. An ancillary site may only have 1 investigator.

2. First Author: The lead investigator initiating the protocol will be the first author. The first author would always be expected to prepare the initial draft of the manuscript, after receiving approval from the Consortium to proceed. The author will prepare the first draft of the manuscript in a timely fashion after receiving all the relevant data analyses from the DCC. The primary author will circulate the final draft to all authors prior to submission, with a timely turnaround of comments from other authors expected. Final decision of the manuscript

content will be determined by the consortium. In the event that the initiating protocol investigator declines first authorship or fails to meet the timeline determined by PREGnant (as determined by majority vote) and monitored monthly, the next PREGnant investigator in the rank order of authors (described below) will be the first author.

3. Authorship Order: All authorships are expected to meet reasonable criteria as set forth by the International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals, http://www.icmje.org. Updated February 2006. Accessed April 4, 2007. The overall authorship order will be 1) the primary author, 2) PREGnant investigators, 3) a DCC investigator, additional outside investigators with a limit of one author per site, and end with the DCC PI.

Authorship Order Category	Description
1	Lead Investigator of the Protocol (N =1)
2	Primary PREGnant Investigators of the Protocol (N = 6); DCC investigator (N = 1)
3	Other Investigators (N to be determined)
4	DCC PI (N = 1)

The authorship order of the PREGnant and outside sites will be based upon participant recruitment, data accuracy and promptness of data report according to the chart below:

Investigative Sites	# Participants Rank	Accuracy Rank	Total Rank	Authorship Order
A	1	4	5	3
B	2	7	9	6
C	3	1	4	2
D	4	2	6	4
E	5	3	8	5
F	6	5	11	7
G	7	6	13	8

Data accuracy will be ranked according to the rate of missing or false data entries/randomized participant at each site. Inquires that show data was accurately entered will not count against this rate of data inaccuracy. Each site's PI will be responsible to document the contributions to the study of that site's authors. In the event the journal editor requires fewer authors even after written documentation of the authors' contribution has been provided, the steering committee will vote on the authorship order which will include at a minimum the Lead Investigator and PI of the DCC (or his/her designate) in the positions listed above. The other authors will be referenced in the footnote and listed in the title page.

4. Acknowledgement Section: The acknowledgement section will include other investigators and study personnel who contributed substantially to the study by site, as well as members of the Data and Safety Monitoring Board. The designation will list the initials of the individual followed by their highest degree (e.g. C. L. Gnatuk, J.A. Ober, R.N., etc.). Significant contributions include but are not limited to protocol review, initiation and participation at each site, participant recruitment and enrollment, study conduct, data analysis, and preparation of the manuscript.

14.4 Minor Publications

Minor studies are defined as those in which the hypotheses would not be the main elements of consortium studies, but in which the study data base would be utilized to test secondary hypotheses. (One example would be testing whether metformin use spares the dose of clomiphene resulting in lower dose needs). Ideas for "minor studies" will, in general, be proposed by a single individual, who would direct all efforts leading to publication and representation. The results from minor studies would be handled similarly to those from major studies. The “Protocol” is defined as the Concept Protocol/study design of the hypothesis resulting in the publication.

Authorship will follow the Major publications guidelines above with the exception that the individual leading the minor study would be the first author, followed by the ranked primary PREGnant investigators involved in developing the Concept Protocol. The Lead Investigator of the minor publication can propose additional investigators who contributed to the study, whose inclusion in the authorship will be voted on by the PREGnant investigators (majority vote of PREGnant investigators required for inclusion in authorship). Centers may wish to withdraw inclusion from authorship of publications of minor studies in which only data are contributed, and this will be the decision of the individual site PI.

14.5 Ancillary Study

An Ancillary Study is an observational study, conducted as a supplement to a Main Study. By definition, an Ancillary Study involves all or a subset of patients enrolled in a Main Study. An Ancillary Study does not involve any additional participants. To be defined as an Ancillary Study, there must be a need for collection of additional data not already collected in the Main Study. An Ancillary Study may also be designed by another consortium investigator, who would serve as the lead investigator and primary author of the paper. Ancillary Studies may be a “single-center” or “multi-center”.

A “single-center” Ancillary Study is a study in which all data are collected, stored and analyzed at a single center. The center bears the additional cost of such a study. The study requires approval of the PREGnant investigators. The center conducting the study is responsible for the analysis and reporting of the results. Abstracts and manuscripts resulting from data from the single-center Ancillary Study are not subject to the PREGnant Publications Policies.

A “multi-center” Ancillary Study is defined as one for which data or material (such as specimens) are collected at more than one center, or additional funds for conduct of the study

are provided by the PREGnant and the DCC provides data analysis. Multi-center Ancillary Studies require the approval of the PREGnant consortium.

Authorship will be as per Major publications above with the exception that the individual leading the ancillary study and writing the paper would be the first author, followed by ranked PREGnant primary investigators, etc. A Center not participating in the ancillary study would not receive authorship unless by majority vote of the steering committee.

14.6 Related Publications

A related publication is one that has had significant input from members of the PREGnant at formal meetings in terms of study significance and design. It is distinct from an ancillary publication in that a related publication reports on a study, concept or new methodology that has not been subjected to formal DSMB review and approval. Generally, "Related Publications" will arise from ideas and studies discussed with the PREGnant consortia, but not voted upon to become formal protocols.

The investigator who initiates, conducts and writes the study and those who (s)he names will be the sole authors. The authors should acknowledge the contribution of the PREGnant consortia in the author line of the publication according to the format of the journal.

14.7 Outside Studies

Outside studies will result from the sharing of data and/or specimens with investigators whose protocols have been approved by the steering committee, and who comply with all components of those policies. All publications will acknowledge the assistance of the PREGnant consortia in making the database available on behalf of the project. In addition, however, a disclaimer will need to be included stating, "the contents of this report represent the views of the authors and do not represent the views of the PREGnant."

14.8 Presentations

PREGnant data should be presented before national organizations by the lead investigators of Main Studies, Ancillary, and Pilot studies. Organizations that might be appropriate include the American Society of Reproductive Medicine, the Society for Gynecologic Investigation, the American College of Obstetricians and Gynecologists, the American Urology Society and other urology or andrology societies. All presentations will be approved by the PREGnant consortium. Once data are published in at least abstract form, all members of the PREGnant can cite them publicly in lectures.

However, investigators should avoid citing specific numbers in review articles and chapters, for this could jeopardize peer review publication. Authorship, First Author, and Author Order are as described for Major Publications, and if there is an authorship limit to the abstract we will follow the plan above under Major Publications. Oral and poster presentations, including those resulting from secondary analyses at professional societies, must list all authors and participating institutions.

14.9 Resources Sharing Plan

We have multiple levels/layers for resources sharing. Public and Secure Websites: We will create a well-functioning user-friendly members-only website with secured login interface. We will utilize this website to coordinate program activities, post meeting and teleconference

announcements, meeting documents and minutes, share protocol versions, study forms, procedural manuals and other written materials, distribute regulatory documents, provide access to the databases for data sharing, and some unpublished results that are restricted to the program affiliates. An online contact information directory will be created and continually maintained.

In addition to the members-only website, we will also create and maintain a public website with links to information for the general public. This public site is the portal for dissemination of information regarding our clinical trials, study publications, and posting of limited access data files for public use. The same website will also serve as the outlet for data sharing one year after the completion of any study. We will periodically archive data by study and variables of interest as described above. We will organize these datasets and other public-use files according to NIH policies and share them with the scientific community after the review and approval of the PREGnant consortia. The tasks will be shared between the Data Manager and Project Manager. The DCC has created and managed such websites successfully for the RMN in the past ten years.

We will use similar strategies to support data and resource sharing within and outside the Initiative. We will create, maintain, and distribute Central and Standardized Datasets. We have accomplished this goal for previous trials. We have developed an innovative, user-friendly, and portable system that allows investigators to explore our variable list and select variables of interest for further study or for use in scientific manuscripts. Their response can then be read by our SAS program to generate datasets instantaneously, dramatically reducing the lag time in data preparation.

We will not only facilitate sample shipping, and reconciliation of discrepancies, but also provide assistance to identify missing samples and erroneous lab results. We will follow existing strategies to manage the bio-samples and facilitate the sharing of data and samples.

We have a plan to submit data and samples collected by the trial to NICHD DASH. The informed consent will include permission to bank these samples. We have experience submitting data to dbGaP and DASH, both of which are well-known federally compliant online infrastructures for data sharing. The processes included initial data and documentation preparation (e.g., codebooks, protocols, informed consent for data sharing), data quality control, and submission. We have successfully submitted the databases to the NICHD DASH for completed trials.

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16 Appendix A: Human Subjects/Informed Consent/Female

The Informed Consents are in separate documents.

17 Appendix B: FertiQoL

FertiQoL International

Fertility Quality of Life Questionnaire (2008)

For each question, kindly check (tick the box) for the response that most closely reflects how you think and feel. Relate your answers to your current thoughts and feelings. Some questions may relate to your private life, but they are necessary to adequately measure all aspects of your life.

Please complete the items marked with an asterisk (*) only if you have a partner.

	For each question, check the response that is closest to your current thoughts and feelings	Very Poor	Poor	Nor good nor poor	Good	Very Good
A	How would you rate your health?	☐	☐	☐	☐	☐
	For each question, check the response that is closest to your current thoughts and feelings	Very Dissatisfied	Dissatisfied	Neither Satisfied Nor Dissatisfied	Satisfied	Very Satisfied
B	Are you satisfied with your quality of life?	☐	☐	☐	☐	☐
	For each question, check the response that is closest to your current thoughts and feelings	Completely	A Great Deal	Moderately	Not Much	Not At All
Q1	Are your attention and concentration impaired by thoughts of infertility?	☐	☐	☐	☐	☐
Q2	Do you think you cannot move ahead with other life goals and plans because of fertility problems?	☐	☐	☐	☐	☐
Q3	Do you feel drained or worn out because of fertility problems?	☐	☐	☐	☐	☐
Q4	Do you feel able to cope with your fertility problems?	☐	☐	☐	☐	☐
	For each question, check the response that is closest to your current thoughts and feelings	Very Dissatisfied	Dissatisfied	Neither Satisfied Nor Dissatisfied	Satisfied	Very Satisfied
Q5	Are you satisfied with the support you receive from friends with regard to your fertility problems?	☐	☐	☐	☐	☐
*Q6	Are you satisfied with your sexual relationship even though you have fertility problems?	☐	☐	☐	☐	☐
	For each question, check the response that is closest to your current thoughts and feelings	Always	Very Often	Quite Often	Seldom	Never
Q7	Do your fertility problems cause feelings of jealousy and resentment?	☐	☐	☐	☐	☐
Q8	Do you experience grief and/or feelings of loss about not being able to have a child (or more children)?	☐	☐	☐	☐	☐
Q9	Do you fluctuate between hope and despair because of fertility problems?	☐	☐	☐	☐	☐
Q10	Are you socially isolated because of fertility problems?	☐	☐	☐	☐	☐
*Q11	Are you and your partner affectionate with each other even though you have fertility problems?	☐	☐	☐	☐	☐
Q12	Do your fertility problems interfere with your day-to-day work or obligations?	☐	☐	☐	☐	☐
Q13	Do you feel uncomfortable attending social situations like holidays and celebrations because of your fertility problems?	☐	☐	☐	☐	☐
Q14	Do you feel your family can understand what you are going through?	☐	☐	☐	☐	☐
	For each question, check the response that is closest to your current thoughts and feelings	An Extreme Amount	Very Much	A Moderate Amount	A Little	Not At All
*Q15	Have fertility problems strengthened your commitment to your partner?	☐	☐	☐	☐	☐
Q16	Do you feel sad and depressed about your fertility problems?	☐	☐	☐	☐	☐
Q17	Do your fertility problems make you inferior to people with children?	☐	☐	☐	☐	☐
Q18	Are you bothered by fatigue because of fertility problems?	☐	☐	☐	☐	☐
*Q19	Have fertility problems had a negative impact on your relationship with your partner?	☐	☐	☐	☐	☐
*Q20	Do you find it difficult to talk to your partner about your feelings related to infertility?	☐	☐	☐	☐	☐
*Q21	Are you content with your relationship even though you have fertility problems?	☐	☐	☐	☐	☐
Q22	Do you feel social pressure on you to have (or have more) children?	☐	☐	☐	☐	☐
Q23	Do your fertility problems make you angry?	☐	☐	☐	☐	☐
Q24	Do you feel pain and physical discomfort because of your fertility problems?	☐	☐	☐	☐	☐

18 Appendix C: EHP-30

ENDOMETRIOSIS HEALTH PROFILE QUESTIONNAIRE (EHP-30)

PART 1: CORE QUESTIONNAIRE

During The Last 4 Weeks
How Often, Because Of Your Endometriosis, Have You...

		Never	Rarely	Sometimes	Often	Always
1.	Been unable to go to social events because of the pain?	☐	☐	☐	☐	☐
2.	Been unable to do jobs around the home because of the pain?	☐	☐	☐	☐	☐
3.	Found it difficult to stand because of the pain?	☐	☐	☐	☐	☐
4.	Found it difficult to sit because of the pain?	☐	☐	☐	☐	☐
5.	Found it difficult to walk because of the pain?	☐	☐	☐	☐	☐
6.	Found it difficult to exercise or do the leisure activities you would like to do because of the pain?	☐	☐	☐	☐	☐
7.	Lost your appetite and/or been unable to eat because of the pain?	☐	☐	☐	☐	☐

Please check that you have ***ticked one box for each question***
before moving onto the next page.

Baseline v1.1 date 25.02.14 .

During The Last 4 Weeks

How Often, Because Of Your Endometriosis, Have You...

		Never	Rarely	Sometimes	Often	Always
8.	Been unable to sleep properly because of the pain?	☐	☐	☐	☐	☐
9.	Had to go to bed/lie down because of the pain?	☐	☐	☐	☐	☐
10.	Been unable to do the things you want to do because of the pain?	☐	☐	☐	☐	☐
11.	Felt unable to cope with the pain?	☐	☐	☐	☐	☐
12.	Generally felt unwell?	☐	☐	☐	☐	☐
13.	Felt frustrated because your symptoms are not getting better?	☐	☐	☐	☐	☐
14.	Felt frustrated because you are not able to control your symptoms?	☐	☐	☐	☐	☐

Please check that you have ***ticked one box for each question***
before moving onto the next page.

19 Appendix D:COLUMBIA-SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE

Ask questions that are in bold and underlined.	Past month	
Ask Questions 1 and 2	**YES**	**NO**
1) ***Have you wished you were dead or wished you could go to sleep and not wake up?***		
2) ***Have you had any actual thoughts of killing yourself?***		
If YES to 2, ask questions 3, 4, 5, and 6. If NO to 2, go directly to question 6.		
3) ***Have you been thinking about how you might do this?*** e.g. "*I thought about taking an overdose but I never made a specific plan as to when where or how I would actually do it….and I would never go through with it.*"		
4) ***Have you had these thoughts and had some intention of acting on them?*** as opposed to "*I have the thoughts but I definitely will not do anything about them.*"		
5) ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?***		
6) ***Have you ever done anything, started to do anything, or prepared to do anything to end your life?*** Examples: Collected pills, obtained a gun, gave away valuables, wrote a will or suicide note, took out pills but didn't swallow any, held a gun but changed your mind or it was grabbed from your hand, went to the roof but didn't jump; or actually took pills, tried to shoot yourself, cut yourself, tried to hang yourself, etc.	**Lifetime**	
	Past 3 Months	
If YES, ask: ***Was this within the past 3 months?***		

Possible Response Protocol to C-SSRS Screening

Item 1 Behavioral Health Referral
Item 2 Behavioral Health Referral
Item 3 Behavioral Health Consult (Psychiatric Nurse/Social Worker) and consider Patient Safety Precautions
Item 4 Behavioral Health Consultation and Patient Safety Precautions
Item 5 Behavioral Health Consultation and Patient Safety Precautions
Item 6 Behavioral Health Consult (Psychiatric Nurse/Social Worker) and consider Patient Safety Precautions
Item 6 3 months ago or less: Behavioral Health Consultation and Patient Safety Precautions

20 Appendix E: The Child-Pugh Scoring System

The Child-Pugh Scoring System

- Encephalopathy: None = 1 point, Grade 1 and 2 = 2 points, Grade 3 and 4 = 3 points
- Ascites: None = 1 point, slight = 2 points, moderate = 3 points
- Bilirubin: under 2 mg/ml = 1 point, 2 to 3 mg/ml = 2 points, over 3 mg/ml = 3 points
- Albumin: greater than 3.5mg/ml = 1 point, 2.8 to 3.5mg/ml = 2 points, less than 2.8mg/ml = 3 points
- Prothrombin Time* (sec prolonged): less than 4 sec = 1 point, 4 to 6 sec = 2 points, over 6 sec = 3 points

*Frequently INR will be used as a substitute for PT, with INR under 1.7 = 1 point, INR 1.7 to 2.2 = 2 points, INR above 2.2 = 3 points

The severity of cirrhosis:
- Child-Pugh A: 5 to 6 points
- Child-Pugh B: 7 to 9 points
- Child-Pugh C: 10 to 15 points

21 APPENDIX F: DSMB Charter

Pre-IVF treatment with a GnRH antagonist in women with endometriosis – A prospective double-blind placebo-controlled trial (PREGnant)

DATA AND SAFETY MONITORING BOARD (DSMB) CHARTER

1. Purpose and Responsibilities of the DSMB

The members of the Data and Safety Monitoring Board (DSMB) identified in this Charter for the PREGnant study are responsible for safeguarding the interests of study participants, assessing the safety and efficacy of all study procedures, and shall monitor the overall conduct of the PREGnant trial. This Committee will serve as an independent advisory group to the Director of NICHD, and is required to provide recommendations about starting, continuing, and stopping the PREGnant study.

This Committee is responsible for identifying mechanisms to complete various tasks that will impact the safety and efficacy of all study procedures, and overall conduct. The table below identifies the key areas where oversight is necessary and the ways in which the Committee for the PREGnant study will complete those tasks.

Basic Responsibility of DSMB	Method DSMB for PREGnant will use to complete task
Familiarize themselves with the study protocol	· Review study protocols and informed consent forms.
Monitor adverse events	· Adverse Event: Review quarterly progress reports prepared by the DCC. · Serious Adverse Events: Review report submitted by the DCC within one week of the event if life threatening or fatal, or within two weeks otherwise. The DSMB will submit a report of their review to the DCC within 7 business days if the SAE is life threatening or fatal, or within two weeks otherwise.
Monitor data quality	· Conduct interim evaluations of the data.
Oversee participant recruitment and enrollment	· Review interim progress reports prepared by the DCC.
Develop an understanding of the Study's risks and benefits	· Review study protocols and related literatures. · Review interim reports of participant accrual and outcome measures provided by the DCC.

	· Assess the need to perform further in-depth evaluation of the benefits and risks of the study after reviewing each report.
Ensure the proper reporting occurs	· Review and approve the meeting and reporting schedule listed in Section 5 of this DSMB charter.

2. Contacts

NICHD
David Weinberg, Ph.D, Program Officer
Abisola (Abi) Tepede, Pharm.D., R.Ph., P.M.P., Program Officer

Data Coordination Center (DCC)
Heping Zhang, PhD, DCC Principal Investigator
Hao Huang, MD, DCC Data Manager

The Data Manager at the DCC will prepare and review the DSMB reports prior to submission to the DSMB, and will not be blind to treatment condition.

Lead Investigators
Hugh Taylor, MD and Heping Zhang, Ph.D.

3. DSMB Members, Organizational Chart, & Communications

Members

The DSMB for the PREGnant study is comprised of the members listed in the table below. In addition, their high level roles and responsibilities are identified in the table.

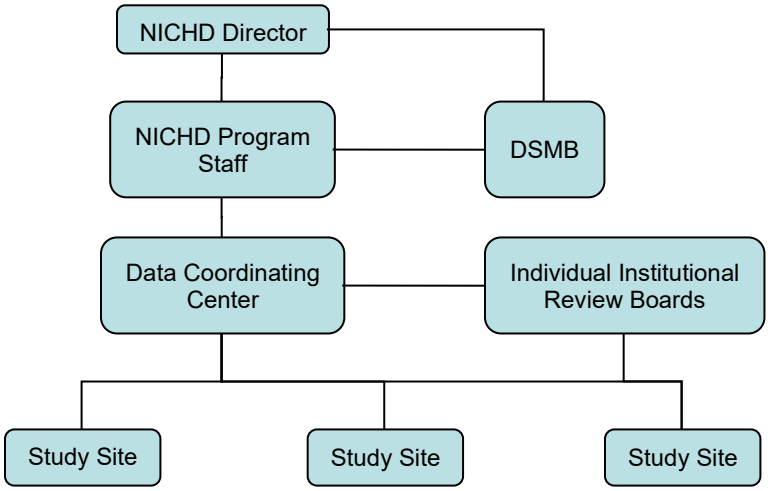
Name of Member	Role on DSMB	High Level Responsibilities
David S. Guzick, MD, PhD	Chair of DSMB Voting member	· Chair the DSMB discussion and prepare written recommendations to NICHD. · Ensure the safety of study participants, the integrity of the research data. · Provide NICHD with advice on the ethical and safe progression of studies conducted in the RMN. · Advises on research design issues, data quality and analysis, and research participant protection for each prospective and on-going study.
Peter S. Bernstein, MD, MPH	Voting member	· Ensure the safety of study participants, the integrity of the research data. · Provide NICHD with advice on the ethical and safe progression of studies conducted in the RMN.
Katherine Burns, PhD	Voting member	
Robert W. Rebar, MD	Voting member	
Ming T. Tan, PhD	Voting member	

Kim L. Thornton, MD	Voting member	· Advises on research design issues, data quality and analysis, and research participant protection for each prospective and on-going study.

Only Voting members for this DSMB may attend closed sessions for this Committee. In addition, only Voting members will have access to unblinded data points for this Committee.

Organizational Chart

The following diagram illustrates the relationship between the DSMB and other entities in the PREGnant study.



Communication

Communication for members of this DSMB will be primarily the Data Coordination Center (DCC). Investigators from the PREGnant study will not communicate directly with DSMB members about the study, except when making presentations or responding to questions at DSMB meetings or during scheduled conference calls.

4. Conflict of Interest and Compensation

It is extremely important that all members of the DSMB state any real or apparent conflicts of interests at the onset of the study. Members of the DSMB shall read the NICHD Clinical Research Guidance Document regarding Conflict of Interest and provide their signed summary of any COI for the study, at its onset, to the NICHD Committee Coordinator. A table summarizing any COI within the DSMB is provided in the Appendix.
Prior to each meeting, all members of the DSMB will have an opportunity to state whether they have developed any new conflicts of interest since the meeting. As a new COI is identified it must be documented in the table in the Appendix and a new signed summary of the COI should be provided to the DCC.

If a new conflict is reported, the Coordinator and staff will determine if the conflict limits the ability of the DSMB member to participate in the discussion.
All DSMB members will be compensated for their role in supporting the committee. Compensation will include an honorarium for meeting attendance and any travel costs.

5. Meeting Schedule

DSMB meetings will be conducted quarterly. However, the DSMB may hold a meeting at any time in accordance with their mission.

6. Blinding

All summaries for DSMB reports will be presented in a blinded fashion, unless specified by the DSMB Chair.

7. Report Schedule and Content

The type of reports (full or brief) is indicated below, followed by a description of the contents of each type.

DSMB Report	Report Submission Date	Type of Report
1.	tbd	Brief
2.	tbd	Brief
3.	tbd	Brief
4.	tbd	Full
5.	tbd	Brief
6.	tbd	Full
7.	tbd	Brief
8.	tbd	Full
9.	tbd	Brief
10.	tbd	Full
11.	tbd	Brief
12.	tbd	Full
13.	tbd	Brief
14.	tbd	Full
15.	tbd	Brief
16.	tbd	Full

Brief DSMB reports will include the following summaries:

- overall actual versus projected enrollment accrual
- overall randomization update

- overall study drop-out rate
- serious adverse events
- primary outcome measures update

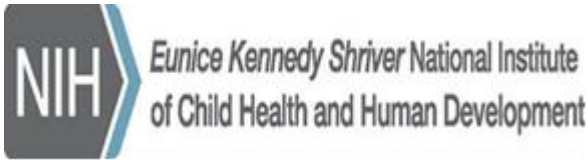
Full DSMB reports will include the following summaries:
- recruitment update (number screened) overall and by site
- enrollment update (enrolled defined as randomized to a treatment) overall and by site
- accrual status including actual enrollment compared to projections overall and by site
- randomization update (i.e., number assigned to each treatment arm)
- study drop-out rate for enrolled patients (number, reason, time point) overall and by site)
- pre-specified subset of baseline demographic data for enrolled patients
- safety data, adverse events, and serious adverse events
- number of case report forms expected
- number/percentage of expected case report forms received – overall and by site
- number of case report forms that are query clean
- primary outcome measures update

References

NIH Policy for Data and Safety Monitoring
http://grants.nih.gov/grants/guide/notice-files/NOT98-084.html
Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-supported Multi-center Clinical Trials
http://grants.nih.gov/grants/guide/notice-files/not99-107.html.

Appendix: Summary of COI within the DSMB

DSMB Member Name	Date Submitted Signed COI	Was a COI Identified?	Will the Member Remain part of the Committee?
David S. Guzick, Chair			
Katherine Burns, Ph.D.			
Robert Rebar, M.D.			
Ming T. Tan, Ph.D.			
Kimberly L. Thornton, MD			



Conflict of Interest Statement

I, _____, assuming the role of _____
(insert role, for example: DSMB member)

for the _____
(insert project or study name)

agree to the following statements.

□ I agree to:

- protect the interests and safety of study participants;
- uphold the integrity of the research process including data collection and analysis to be as free from bias and preconception as I am able;
- adhere to the highest scientific and ethical standards, to comply with all relevant regulations and to eliminate or disclose, during my involvement with the proposed clinical research project, any real or apparent conflicts of interest.

In addition:

□ I declare that I, my spouse or dependent children, or organization with which I am connected, do/does not have any financial interest in the _____ study, where financial interested is defined by the DHHS, as anything of monetary value, including but not limited to, salary or other payments for services (for example, consulting fees or honoraria); equity interests (for example, stocks, stock options or other ownership interests); and intellectual property rights (for example, patents, copyrights and royalties from such rights).
The financial interest term does not include various items which can be found in The Federal regulation, PHS, DHHS Part 50--Policies of General Applicability; Subpart F- *Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding Is Sought.*

For Federal employees, financial interests that are allowable and require disclosure are:

Financial Interest Disclosure: Financial interest that require disclosure are stock holdings in pharmaceutical firms, medical device manufacturers, and biotechnology companies

Allowable Financial Interests: In a company that produces a product that is being evaluated by a study, participants may hold up to $15,000 of stock: and up to an aggregate of $25,000 of the stock of that company and its competitors who produce that (or a similar) product. As an alternative to individual stock holdings, participants may hold up to an aggregate of $50,000 in sector mutual funds-including pharmaceutical/health care sectors.

For holdings in excess of these *de minimus* levels, a conflict of interest analysis needs to be conducted by NIH regarding the holding, the company producing the product being evaluated under the study, and its competitors, and, if a conflict exists, could lead to the need to withdraw from the study.

□ I agree to not withhold any data related to the _____ study or to interfere with the analysis or publication of the study's results.

□ I will not engage in activities that could be viewed as real or apparent COI, including but not limited to:

□ having a part-time, full-time, paid, or unpaid employee status of any organizations that are: (a) involved in the study under review; (b) whose products will be used or tested in the study under review, or whose products or services would be directly and predictably affected in a major way by the outcome of the study;

□ being an officer, member, owner, trustee, director, expert advisor, or consultant of such organizations;

□ being a current collaborator or associate of the principal investigator (applicable to potential members of data safety and monitoring boards);

□ having a scientific interest beyond that required for my role, where scientific interest is defined as having influence over the protocol, the study design, conducting the study analysis or any reporting related to the investigation (applicable to potential members of data safety and monitoring boards).

Yale SCHOOL OF PUBLIC HEALTH

Data and Safety Monitoring Board (DSMB)

Confidentiality Agreement

I agree to serve as a DSMB member for the PREGnant (Pre-IVF treatment with a GnRH antagonist in women with endometriosis - A prospective double blind placebo controlled trial) and FRIEND (Reproductive Medicine Collaborative Consortium: a randomized placebo controlled trial of EGCG to improve fertility in women with uterine fibroids) consortia for which Yale University Collaborative Center for Statistics in Science serves as the Data Coordination Center (DCC).

As a DSMB member I understand that I will be provided with and have access to documents submitted by the NICHD or the DCC as they relate to study protocols, Registries or other consortium-related materials, including proprietary and confidential information.

I shall not disclose any confidential information (oral or written) unless required to do so by law. Confidential documents may be distributed to an administrative assistant, who is not permitted to share the materials with anyone other than me.

I agree that I will not distribute or publish the study records. I further agree that I shall not make use of consortium materials except for the express purpose of advising the Consortia and the NICHD.

I have read this agreement and agree to abide by its terms.

Name (Print or Type): _____

Signature: _____ Date: _____

22 Appendix G: Investigator Signature of Agreement

Investigator Signature of Agreement

The Eunice Kennedy Shriver National Institute of Child Health and Human Development
Reproductive Medicine Network

Title: Pre-IVF treatment with a GnRH antagonist in women with endometriosis – A prospective clinical trial

Version: 1.6

Principal Investigator:

I, *[Insert PI's name]* , the Principal Investigator for *[Insert Institute Name]*, hereby certify that I have read and agree to conduct this study in accordance with this protocol on behalf of all RMN Investigators and research staff from my site.

I will conduct the clinical study as described and will adhere to the *Code of Federal Regulations,* Title 21 and Title 25, Part 46, Good Clinical Practices (GCP), International Conference on Harmonisation (ICH), and the Declaration of Helsinki. I have read and understood the contents of the Protocol.

The signature of the investigator below indicates acceptance of the protocol and a complete understanding of the investigator commitments as outlined in Form FDA 1572, Statement of Investigator.

_____

Principal Investigator's Signature Date

_____

Printed Name Date