Reproductive Medicine Network

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Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation

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1 Acronyms

Advisory Board	AB	Institutional Review Board	IRB
American College of Obstetricians and Gynecologists	ACOG	Intrauterine Insemination	IUI
Anti-Mullerian Hormone	AMH	Investigational New Drug	IND
Assisted Reproductive Technologies	ART	Logistic Regression	LR
Aromatase Inhibitors	AI	Luteinizing Hormone	LH
Clinical Report Form	CRF	National Institute of Child Health and Human	NICHD
Clomiphene Citrate	CC	Non-obstructive Azoospermia	NOA
Centers for Disease Control	CDC	Ovarian Stimulation	OS
Data Coordination Center	DCC	Ovarian Hyperstimulation Syndrome	OHSS
Data and Safety and Monitoring Board	DSMB	Principal Investigator	PI
Deoxyribonucleic Acid	DNA	Progesterone	P4
Estrogen	E	Pregnancy in Polycystic Ovary Syndrome Study	PPCOS
Estradiol	E2	Protected Heath Information	PHI
Estrogen Receptor	ER	Quality of Life	QOL
Follicle Stimulating Hormone	FSH	Reproductive Medicine Network	RMN
Female Sexual Distress Scale	FSDS	Serious Adverse Event	SAE
Female Sexual Function Index	FSFI	Sex Hormone Binding Globulin	SHBG
Health Insurance Portability and Accountability Act	HIPAA	Single-Nucleotide Polymorphism	SNP
Human Investigation Committee	HIC	Specialized Cooperative Center Programs in Reproductive Research	SCCPIR
Human Chorionic Gonadotropin	hCG	Thyroid-Stimulating Hormone	TSH
Hysterosalpingography	HSG	Total and Free Testosterone	T, FT
Identification	ID	Ultrasound	U/S
International Index of Erectile Dysfunction	IIEF	World Health Organization	WHO
Intent-to-Treat	ITT		
Intramuscular	IM		

2 Study Synopsis

2.1 Objectives

The objective of this study is to examine whether treatment of infertile women with an aromatase inhibitor (AI) results in a lower rate of multiple gestations than the current standard ovulation induction medications of clomiphene citrate (CC) or gonadotropin. The central hypothesis is that prescribing AIs to infertile ovulatory women undergoing ovarian stimulation (OS) and intrauterine insemination (IUI) will result in an ample rate of pregnancy, while significantly reducing the number of multiple gestational pregnancies seen with the current standard treatments. Reducing the multiple gestation rate using AIs could significantly reduce maternal and neonatal morbidity and mortality, and reduce societal and personal health care costs. When exploring the potential merits of AI, however, it is important to acknowledge use of CC or gonadotropins as standard treatment and the genuine clinical uncertainty about AI's efficacy in OS; thus, the three treatment arms are in a legitimate state of equipoise. This study seeks to provide the reproductive medicine community with sufficient data to evaluate aromatase inhibitors for infertility treatment.

2.2 Patient Population

The population will consist of 900 women desirous of conceiving, ages ≥18 to ≤40 years (at time of consent), who will be recruited over approximately a two year period from the Reproductive Medicine Network (RMN) clinical sites and possibly from the Specialized Cooperative Center Programs in Reproductive Research (SCCPIR) sites, through public notification programs.

2.3 Study Design

This will be a multi-center, prospective, clinical trial of aromatase inhibitors vs. clomiphene citrate vs. gonadotropin. The randomization scheme will be coordinated through the data coordination center (DCC) and the randomization will be stratified by each participating site and within each site for age groups 18-34 and 35-40.

2.4 Treatment

Nine hundred (900) patients will be equally randomized via computer-generated randomization schedule to receive: A) gonadotropin (Menopur®) by subcutaneous injection, or B) clomiphene citrate by oral ingestion of overencapsulated pills in double-blinded fashion, or C) aromatase inhibitor (Letrozole) by oral ingestion of overencapsulated pills in double-blinded fashion. Treatment assignments will be randomized within each site, and further randomized within age group by a varying-block-size design. Treatment in each of the arms will begin on cycle day 3 to 5.

2.5 Primary Efficacy Parameter

The primary efficacy parameter will be the multiple gestation rate following recruitment of multiple follicular development with an AI, as compared to CC and gonadotropins.

2.6 Secondary Efficacy Parameters

The secondary efficacy parameters will be the pregnancy rate, live birth rate, live birth rate of multiple gestational pregnancies, and time to pregnancy following administration of an AI as compared to CC and gonadotropins.

2.7 Statistical Analysis

To assess the treatment effects on the primary outcome of multiple gestations we will use the test for the linear trend for binomial populations. Specifically we will test a null hypothesis of H_0: $\pi_1=\pi_2=\pi_3$ against an alternative hypothesis of H_1: $\pi_1>\pi_2>\pi_3$ where π_1, π_2, and, π_3 are the population proportions of multiple gestations in the gonadotropin, CC and AI groups, respectively. For the power analysis, we assume pregnancy rates of 30%, 27% and 27% for the gonadotropin, CC and AI groups, respectively, and a pregnancy loss rate of 25% for each group. Beginning with 240 women in each group, under these assumptions we would have 54, 49 and 49 births in the three groups for the multiple gestation comparison analysis. For the power analysis we assume that under the alternative hypothesis, the multiple gestation rates would be 25%, 12.5% and 6.25% for the gonadotropin, CC and AI groups, respectively. Under these assumptions, the power by using the exact test at $\alpha=0.05$ would be 0.84.

For the secondary outcome of pregnancy rate, the non-inferiority analysis will compare the differences among the pregnancy rates in the three groups. As a basis for the null-hypothesis, we assume a 25% reduction in the pregnancy rate in the AI population compared to the combination of the gonadotropin and CC groups. This value is the margin ($\delta_0=0.25$) that represents the maximum acceptable reduction as "clinically unimportant". The null hypothesis states that δ, the difference between the combined gonadotropin and CC population rate and the AI population rate, is $\geq \delta_0$. This null hypothesis will be tested against an alternative hypothesis, which states that $\delta < \delta_0$. The resulting non-inferiority hypothesis will be tested using a z-statistic. We note that the assumptions about the pregnancy rates for the non-inferiority test of the treatment groups differ from those used for calculating the sample sizes needed to achieve the sufficient power in testing the primary hypothesis concerning the multiple gestation rates. We further note that a pregnancy rate of 30% over 4 (independent) cycles corresponds to a pregnancy rate of 8.5% per cycle.

A further set of analyses will make use of logistic regression (LR) and include, in addition to the dummy coded variable representing treatment, those variables expected to be associated with becoming pregnant. Such patient characteristics would include age, day 3 serum FSH level, length of infertility, etiology of infertility, and prior ovarian surgery.

We will also include selected interaction terms for those factors that may be related to treatment differences. Evaluation of treatment differences in LR should lead to greater power or better

estimate of treatment effects by adjusting for patient characteristics affecting the likelihood of becoming pregnant.

2.8 Anticipated Time of Completion

The RMN estimates the study will take approximately two years to complete. Participants will be recruited from each of the 7 participating RMN sites, and possibly SCCPIR sites.

2.9 Regulatory Compliance

The DCC is working with The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) to ensure that clinical study data and regulatory requirements are met regarding the Food and Drug Administration (FDA) code for federal regulations and Investigational New Drug (IND) submissions. This trial is registered on http://www.clinicaltrials.gov (NCT#01044862), and has been issued IND# 107705.

3 Background and Significance

3.1 Overview

Infertility is one of the most prevalent chronic health disorders involving young adults (Stephen and Chandra 1998). Impaired fertility is thought to affect 10 to 15% of couples, but this number may be an underestimate because the inability to conceive carries a hidden stigma of shame and secrecy for some couples, whereas others are never enumerated because they cannot afford to seek medical treatment (Schroeder 1988; Downey, Yingling et al. 1989; Whiteford and Gonzalez 1995). The availability of new treatment methods, including ovarian stimulation (OS), intrauterine insemination (IUI) and other assisted reproductive technologies (ART) explain at least in part the finding of an increase of physician visits for infertility (American Society for Reproductive Medicine 1996). Combining OS with IUI has been applied empirically for treatment of different types of infertility including unexplained infertility, male-factor infertility, and anovulatory infertility. This treatment has been shown to be effective in a previous study performed by the Reproductive Medicine Network (Guzick et al, 1999). This treatment modality is used when the female partner has at least one patent tube in addition to ovarian function, and the male partner has an adequate number of motile sperm. In infertile couples meeting the above criteria, OS improves the cycle fecundity rate in part by increasing the number of follicles (and oocytes) available for fertilization and by correcting subtle, unpredictable ovulatory dysfunction; IUI is expected to allow adequate numbers of selected sperm to be deposited into the uterine cavity avoiding any potential cervical problems (Hecht and Magoon 1998; Guzick, Carson et al. 1999). Different factors are known to influence treatment outcome after OS and IUI including OS protocol (Hughes 1997; Cohlen, te Velde et al. 1998). At the present time, primarily two medications are used for OS: an oral selective estrogen receptor (ER) modulator, CC, and injectable gonadotropins (Melis, Paoletti et al. 1987; Serhal, Katz et al. 1988; Melis, Strigini et al. 1990; Franks 1995; Guzick, Carson et al. 1999).

Currently, because most patients undergoing IUI also receive OS, the main concern is not the efficacy of the treatment but the prevention of its complications (Farhi, West et al. 1996). OS is associated with various problems and drawbacks (Mitwally and Casper 2004). Particularly, the use of injectable gonadotropins is associated with the risk of life-threatening ovarian hyperstimulation syndrome (OHSS), multiple gestation pregnancies, and the need for intense treatment monitoring, in addition to the inconvenience of parenteral route of administration and significant cost.

3.2 Problem of multiple gestational pregnancies

Multiple gestational pregnancies are the most common problem associated with OS. The rate of spontaneous twin pregnancy has been estimated to range from 1%–1.35% and that of a triplet pregnancy from 0.01%–0.017%. However, with OS and IUI, the incidence of multiple gestational pregnancies are more than 10-20 times higher, ranging from 7.5%–29% per couple (Shelden, Kemmann et al. 1988; Valbuena, Simon et al. 1996). In the last decade, the significant increase in the incidence of multiple births in most countries is almost entirely attributable to the use of gonadotropins and other agents for OS (Dawood 1996). According to the National Vital

Statistics Reports for 2001, the rate of twinning has increased 33% since 1990 and 59% since 1980. Furthermore, the rate of triplets and higher-order multiples has increased more than 400% since 1980 (National Vital Statistics Reports).

The biggest concern with multiple gestations is the high rate of preterm delivery, and its consequences. In 2001, 1.6% of singletons, 11.8% of twins, 36.7% of triplets, 64.5% of quadruplets, and 78.6% of quintuplets were delivered before 32 completed weeks of gestation (National Vital Statistics Reports). Even more noteworthy, the incidence of extreme prematurity (delivery before 28 weeks) for both triplets and quadruplets may be as high as 14% (Collins and Bleyl 1990; Kaufman, Malone et al. 1998; Devine, Malone et al. 2001).

The increased incidence of maternal and neonatal complications associated with multiple gestational pregnancies has been well documented (De Muylder, Moutquin et al. 1982; Botting, Davies et al. 1987; Lipitz, Reichman et al. 1989; Lipitz, Frenkel et al. 1990; Levene, Wild et al. 1992; Jain, Missmer et al. 2004) and the greater likelihood of prematurity alone contributes substantially to neonatal risk (Newman, Hamer et al. 1989; Elster, Bleyl et al. 1991; Kiely, Kleinman et al. 1992). Additionally, hospital costs for each twin or triplet infant can be twice or three times that of a singleton, and lifetime costs to the healthcare system and community may be 100 to 200 times that of a singleton (Callahan, Hall et al. 1994; Bergh, Ericson et al. 1999). After controlling for variables known to affect hospital charges, the predicted total charges to the family in 1991 for a singleton delivery were $9,845, as compared with $37,947 for twins ($18,974 per baby) and $109,765 for triplets ($36,588 per baby) (Callahan, Hall et al. 1994). Notwithstanding these facts, currently there is substantial economic pressure and demands from patients for infertility-treatment programs to increase their success rates.

3.3 Treatment Strategies and Approaches to reduce multiple gestational pregnancy risks

Although viewed as a blessing by some longstanding infertile couples who now have "two for the price of one," the considerable human and financial costs of multiple births warrant a re-evaluation of the protocols of OS. It is obvious that the best strategy is preventing the occurrence of multiple gestational pregnancy rather than dealing with the problem after its occurrence (e.g., selective multi-fetal pregnancy reduction). Selective multi-fetal reduction presents an ethical problem for many couples, entails the risk of losing all fetuses being carried, and increases psychological stress for couples who have struggled through years of infertility (Howie 1988; Wapner, Davis et al. 1990; Berkowitz, Lynch et al. 1993; Braude and Rowell 2003). An ovulation induction agent that would achieve ovarian mono-follicular development in most cycles, thereby reducing multiple gestations, with a comparable pregnancy success rate to OS with gonadotropins, would be an exciting approach for ameliorating the burden of multiple gestational pregnancies following OS with IUI.

3.4 The development of aromatase inhibitors (AIs)

The aromatase cytochrome P450 (P450arom, product of *CYP19* gene) is a microsomal member of the cytochrome P450 superfamily that catalyzes estrogen (E) biosynthesis. This heme protein

is responsible for binding of the C_{19} androgenic steroid substrate and catalyzing the series of reactions leading to formation of the phenolic A ring characteristic of estrogens. This is the terminal and rate-limiting step in the synthesis of E, i.e., the conversion of androstenedione and testosterone via three hydroxylation steps to estrone and estradiol (E_2), respectively.

The most successful, third-generation AIs are now licensed mainly for breast cancer treatment (Santen, Manni et al. 1990; Lonning 1996; Goss 1999; Buzdar and Howell 2001). AIs have been classified in various ways, including as first-, second-, and third generation; steroidal and nonsteroidal; reversible (ionic binding) and irreversible (suicide inhibitor, covalent binding).

The third-generation commercially available AIs include two nonsteroidal preparations, anastrozole, ZN 1033, (Arimidex®), letrozole, CGS 20267, (Femara®), and a steroidal agent, exemestane (Buzdar, Jonat et al. 1996; Dowsett and Lonning 1997; Marty, Gershanovich et al. 1997; Winer, Hudis et al. 2002). These agents are reversible, competitive AIs that are highly potent and selective. Their intrinsic potency at doses of 1 to 5 mg/day, inhibit E levels by 97 to >99%, which results in E concentrations below detection by most sensitive immunoassays. AIs are completely absorbed after oral administration, with mean terminal half-life $t_{1/2}$ of approximately 45 hours (range, 30-60 hours).

They are cleared from the systemic circulation mainly by the liver. Gastrointestinal disturbances account for most of the adverse events, although these have seldom limited therapy. Other adverse effects are asthenia, hot flashes, headache, and back pain (Buzdar, Jonat et al. 1996; Dowsett and Lonning 1997; Marty, Gershanovich et al. 1997). They are well tolerated on daily administration for years, have few adverse effects, are very safe without significant contraindications, and are relatively inexpensive.

3.5 Mechanism of OS by AIs

The blocking of E production from all sources by inhibiting aromatization releases the hypothalamic-pituitary axis from E negative feedback, thereby increasing FSH secretion and resulting in stimulation of ovarian follicular development. In addition, use of AIs is not expected to cause adverse effects on E target tissues given that no ER down-regulation occurs, in contrast to the ER depletion observed with CC treatment. In addition, because aromatase inhibition does not antagonize ERs in the brain, the initiation of follicle growth results in increasing concentrations of both E_2 and Inhibin (Anderson, Groome et al. 1998; Lockwood, Muttukrishna et al. 1998), resulting in a normal secondary feedback loop that limits FSH response to aromatase inhibition, thereby theoretically reducing the risk of multiple ovulation and OHSS. An alternative mechanism of action of the AIs in OS is that AIs also act locally in the ovary to increase ovarian follicular sensitivity to FSH. This may result from accumulation of intraovarian androgens because conversion of androgen substrate to E is blocked by aromatase inhibition. It may be that a relatively small rise in FSH, because of a normal Inhibin/E feedback loop as already described, leads to single or low multiple follicle development, thus avoiding the occurrence of OHSS. One may speculate that aromatase inhibition, with suppression of E concentrations in the circulation and in peripheral target tissues, results in up-regulation of ERs in the endometrium, resulting in rapid endometrial growth once E secretion is restored. In addition, E has been shown to decrease the level of its own receptor by stimulating ubiquitination of ERs, resulting in rapid degradation of the receptors. In the absence of E, ubiquitination is decreased allowing up-regulation of the ER and increasing sensitivity to subsequent E administration (Nirmala and Thampan 1995). It is

possible that both mechanisms could increase endometrial sensitivity to E, resulting in more rapid proliferation of endometrial epithelium and stroma and improved blood flow to the uterus and endometrium (Rosenfeld, Roy et al. 2002).

As a result, normal endometrial development occurs by the time of ovarian follicular maturation, even in the face of the observed lower than usual E_2 levels in AI-treated cycles (Mitwally and Casper 2000; Mitwally and Casper 2001; Mitwally and Casper 2002; Fatemi, Kolibianakis et al. 2003; Healey, Tan et al. 2003; Mitwally and Casper 2003; Al-Fozan, Al-Khadouri et al. 2004; Goswami, Das et al. 2004; Mitwally and Casper 2004; Cortinez, De Carvalho et al. 2005; Garcia-Velasco, Moreno et al. 2005; Mitwally, Biljan et al. 2005; Mitwally and Casper 2005; Oktay 2005; Oktay, Buyuk et al. 2005; Ryan, Moss et al. 2005; Al-Fadhli, Sylvestre et al. 2006; Atay, Cam et al. 2006; Bayar, Tanriverdi et al. 2006; Elnashar, Fouad et al. 2006; Sohrabvand, Ansari et al. 2006).

A major advantage of an AI used alone is its ability to restore mono-follicular ovulation particularly in anovulatory infertility (e.g., PCOS). Single doses as high as 60 mg of anastrozole and letrozole have been administered without significant adverse effects observed (Package insert of Letrozole Femara®; Package insert of Anastrozole Arimidex®). The success of aromatase inhibition for ovulation induction, similar to CC, depends on the presence of enough endogenous E activity that a tonic negative feedback effect is present on FSH release as occurs in women with World Health Organization (WHO) type II anovulatory infertility as well as ovulatory women with unexplained infertility.

3.6 Limitations of Prior Reports

Women with hypothalamic anovulation or ovarian failure (WHO type I & III anovulatory infertility) are not likely to benefit from AIs. It is also important to mention that anovulation due to specific underlying endocrine disorders, e.g., hyperprolactinemia, should be managed first with treatments that correct the underlying endocrine problem. It is interesting that when the AI was used alone, the response in most of the women was predictable and almost all women developed one or two mature follicles, without the development of other smaller sized follicles on the day of hCG ovulation triggering. This suggests the potential for mild OS associated with a significantly reduced risk for OHSS and multiple gestational pregnancies. The encouraging results of data, including our own, have led other investigators from different centers worldwide to study the use of AIs for OS and in general have reported findings supporting ours.

A major limitation of prior reports of utilizing AIs for OS is that most of the reports were non-randomized, thus introducing the potential for bias, or without sufficient sample size, thus introducing the potential for beta error. This study would be the first appropriately powered randomized study examining the efficacy of AIs for ovulation induction in couples with unexplained infertility examining the rate of multiple gestations as the primary endpoint. Additionally, prior studies with CC and AIs have not evaluated live birth rates in successive cycles (up to 4 cycles), and have failed to identify if there is a point at which additional cycles leads to diminished success in initiating pregnancies.

3.7 Additional Considerations

There are few published data comparing the third-generation AIs with each other. Moreover, almost all the available studies were done in postmenopausal women. All three of the newer AIs (letrozole, anastrozole, and vorazole) reduce E levels below detection levels of most clinical assays.

Geisler (Geisler, Haynes et al. 2002) recently compared letrozole and anastrozole. The study found a small but significantly higher suppression of the aromatase enzyme with letrozole compared with anastrozole (>99.1% suppression vs. 97.3% suppression). The clinical relevance of such small differences remains questionable.

Data suggest that anastrozole may be slightly more selective for the aromatase enzyme than is letrozole. Studies have shown no impact on cortisol or aldosterone levels in patients being treated with 3 to 10 mg/d anastrozole for up to 3 months (Yates, Dowsett et al. 1996; Goswami, Das et al. 2004). In contrast, some studies have shown significant declines in either or both cortisol and aldosterone levels in patients treated with 2.5 or 5 mg letrozole daily for 2 to 3 months. However, cortisol and aldosterone levels did not fall below the lower limits of normal and patients did not develop symptoms of adrenal insufficiency (Buzdar and Howell 2001). Thus, letrozole may be less selective for the aromatase enzyme.

There are potential concerns about using AIs for OS, mainly related to direct adverse effects or possible deleterious effects of low ovarian follicular E on oocyte development. Other concerns include the effects of accumulating androgens on oocyte development, fertilization, or embryogenesis. Third generation AIs are generally well tolerated with minor adverse events including hot flashes and gastrointestinal events (nausea, vomiting) and leg cramps. Overall, very few patients withdrew from first- or second-line comparative Phase III trials because of drug-related adverse events (Goss 1999; Hamilton and Piccart 1999).

Palter (Palter, Tavares et al. 2001) has shown that an E-free (or at least deficient) intrafollicular environment is compatible with ovarian follicular development, ovulation, and corpus luteum formation concluding that markedly reduced to absent intrafollicular levels of E are compatible with ovarian follicular “expansion,” retrieval of fertilizable oocytes, and apparently normal embryo development. The authors drew their conclusion from clinical “experiments of nature” including cases of deficiency of 17α-hydroxylase/17-20 lyase, (Araki, Chikazawa et al. 1987; Geier, Lunenfeld et al. 1987; Rabinovici, Blankstein et al. 1989; Pariente, Rabinovici et al. 1990; Yanase, Simpson et al. 1991) 3ß-hydroxysteroid dehydrogenase (3ß-HSD) (Mannaerts, Uilenbroek et al. 1994; Zelinski-Wooten, Hess et al. 1994), and P450 aromatase enzymes (Ito, Fisher et al. 1993; Conte, Grumbach et al. 1994; Morishima, Grumbach et al. 1995; Bulun 1996; Mullis, Yoshimura et al. 1997) in addition to cases of severe hypogonadotropism (Couzinet, Lestrat et al. 1988; Shoham, Balen et al. 1991; Schoot, Coelingh Bennink et al. 1992; Shoham, Mannaerts et al. 1993). Regarding the effect of an E-free/poor intrafollicular environment on gametogenic maturation, Palter (Palter, Tavares et al. 2001) concluded there may be a negative effect based on a number of primate studies suggesting associations between an E-free/poor intrafollicular environment and decreased rates of meiotic maturation and fertilization (Zelinski-Wooten, Hess et al. 1994).

However, the high success rates of ovulation and achievement of pregnancy in our reports despite low peripheral E levels suggest no adverse outcome associated with the use of aromatase inhibition for OS.

This could be because the administration of the AI occurs early in the follicular phase and for a limited period of time, which allows rapid clearance of the AI. Accumulation of androgens will be limited by the rapid clearance of the AIs due to their short half-life, and the reversible nature of the aromatase enzyme inhibition in the face of rising levels of FSH (which induces the expression of aromatase enzyme).

A key issue is the outcome of pregnancies achieved after the use of AIs for OS. Safety studies have not observed teratogenic or clastogenic effects in animal embryo development from exposure to anastrozole (Tiboni 2004), but there have been some concerns regarding teratogenic effects of letrozole (Biljan, Tkalec et al. 2005). Based on the short half-life of AIs (~40 hours), administration in the early follicular phase should result in clearance of AIs before implantation takes place. Three large studies have assessed pregnancy outcome in pregnancies after infertility treatment with letrozole. A cohort study compared the outcome of pregnancies achieved after letrozole treatment to other OS agents (CC, gonadotropins, and combination of both) with a control group of pregnancies spontaneously conceived without OS.

Pregnancies conceived after letrozole treatment had similar miscarriage and ectopic pregnancy rates compared to all other groups, with a significantly lower rate of multiple-gestation compared to CC. The second study, presented as an abstract at the American Society of Reproductive Medicine in 2005, compared the outcome of 150 births after treatment with letrozole to outcomes in a database of 36,050 normal deliveries (Biljan, Tkalec et al. 2005).

There was not a statistically significant difference in the overall incidence of congenital malformations for the two groups. However, letrozole-induced pregnancies had a higher incidence of locomotor malformations and cardiac anomalies. A careful review of the abstract demonstrates major methodological flaws that weaken the data and the conclusions including the inappropriate choice of the control group that included women taken from a database of spontaneously conceiving women (n= 36,050), with significantly lower mean age (30.5 years), presenting to a low-risk hospital. In the abstract presented, 15% of the letrozole pregnancies were complicated by gestational diabetes with higher incidence of multiple gestations than the controls.

The authors did not address the definition of locomotor malformations and how it was assessed. Additionally, the abstract reported a higher incidence of cardiac anomalies in the experimental group. A low incidence of cardiac anomalies in a low-risk hospital setting is not surprising since mothers would be transferred to a tertiary-care center once such an *in utero* anomaly was detected.

A most recent study which compared the incidence of congenital malformations in 911 newborns of women who conceived after letrozole treatment (514) or CC (397) did not find a statistically significant difference in overall rate of congenital malformation (Tulandi, Martin et al. 2006). The rates of major and minor congenital malformations were not significantly different, although the risk of all congenital cardiac anomalies was higher in the CC group (1.8%) compared to the letrozole group (0.2%), [p: 0.02]. Notably, the study found a 7-fold increase in overall cardiac anomalies in the CC group compared to the letrozole treated group. The authors concluded that concerns about the teratogenicity of letrozole in the setting of ovulation induction were unfounded.

3.8 Preliminary Data

It is difficult to identify estimates of pregnancy and multiple gestation rates in infertile couples with a regularly ovulating female and male partner who meet the specified inclusion criteria. We have utilized a recent cohort report which included all three arms in which choice of treatment agent was based on the decision of the patient and her health care provider; pregnancy and multiple gestations were evaluated in this study of women who underwent 3045 cycles of ovulation induction using a variety of agents for ovulation induction, including gonadotropins alone, CC alone, and an aromatase inhibitor alone. (Mitwally, Biljan et al. 2005). That study only looked at pregnancy cycles, and did not report pregnancy rates *per se*, but instead the percentage of patients who achieved pregnancy with each modality of ovarian stimulation. Initially there were 1650 infertile patients who underwent 3045 cycles of which only the pregnant cycles were reported. Among these, 110 of 671 cycles (16.4%) in cycles where gonadotropins alone were administered resulted in a pregnancy, which is within the rates previously reported for gonadotropins (see Table 1). Among women receiving clomiphene citrate, pregnancy occurred in 80 of 994 cycles (8%), which is within the range described in the literature (see Table 1). With the aromatase inhibitor letrozole at a dose of 2.5 mg/d for five days, pregnancy occurred in 33 of 167 cycles (19.8%), while at a dose of 5.0 mg/d for five days, 70 of 432 (16.2%) conceived (Mitwally, Biljan et al. 2005). With such pregnancy rates, the cumulative pregnancy rate after four cycles of ovulation induction could be estimated to range from approximately 48% with per cycle rates of 15%, to a 34% cumulative pregnancy rate if per cycle rates were 10%; these estimated rates are within the cumulative pregnancy rates previously reported (see Table 1). We have powered this study conservatively assuming a cumulative pregnancy rate of 30% in the gonadotropins treatment arm. In order to achieve a reduction in multiple birth rates, we have decided we are willing to accept a reduction of the pregnancy rate with aromatase inhibitor (as opposed to gonadotropins) of up to 25%, but for purposes of this study, we have conducted power calculations utilizing the conservative assumption that pregnancy rates will be ten percent less in the aromatase inhibitor group.

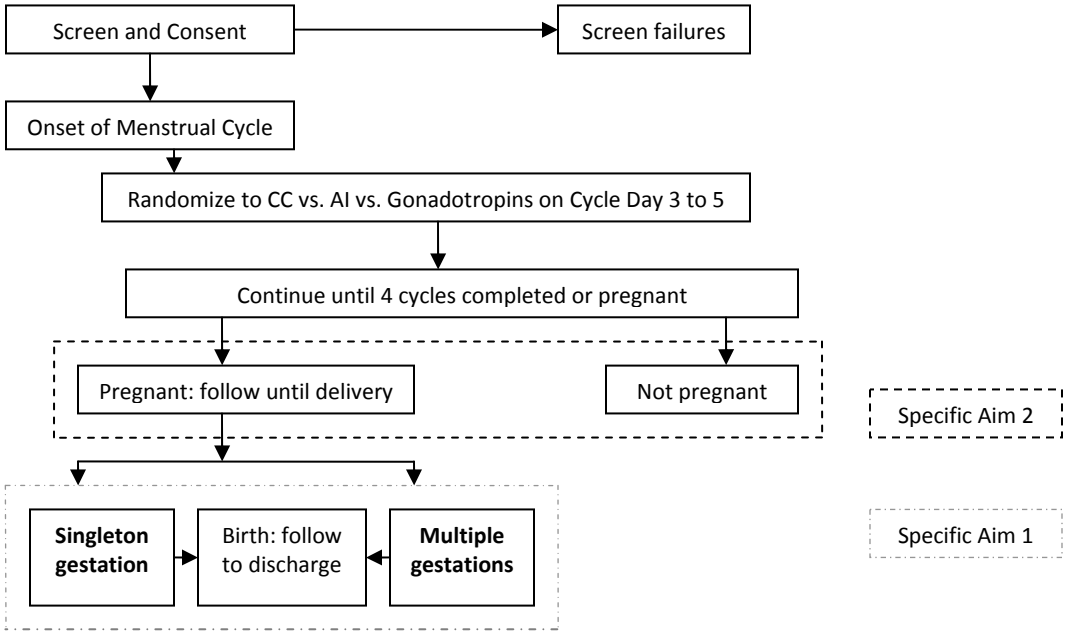
In the cohort study described above, multiple gestation rates were approximately 11% in women receiving gonadotropins, 15% in women receiving CC, and 5% in each of the aromatase inhibitor groups (Mitwally, Biljan et al. 2005). This rate for multiple gestations with gonadotropins are within the lower ranges previously described for these agents; many reports are in the 20-30% range, which is the basis for the 25% rate that we have assumed for our Primary Efficacy Parameter/Specific Aim 1 sample size and power calculations (see Table 1, below). The multiple gestation rate for the CC group in the cohort study was 15%, which is at the high end of the reports in the literature; this is the basis for the 12.5% rate we have assumed. These respective multiple gestation rates form the basis for our hypothesis in Specific Aim 1 of a 75% and 50% reduction in multiple pregnancy rates of letrozole OS compared to gonadotropins and CC, respectively. For Specific Aim 1, we have chosen the clinical pregnancy multiple gestation rate as the primary endpoint to avoid the confounding complexity of reduction in the multiple gestation pregnancy rate by selective fetal reductions. A secondary outcome will be the multiple gestational pregnancy live birth rate, which will reflect a reduction in the multiple rates not only from selective fetal reduction, but also miscarriages resulting in loss of some, or all, fetuses.

Table 1. Pregnancy rates and multiple gestation rates in non-ART cycles

Reference	Comments	FSH							CC							AI						
				Pregnancy/Cycle			Multiple Pregnancies				Pregnancy/Cycle			Multiple Pregnancies				Pregnancy/Cycle			Multiple Pregnancies	
						Cumulative/ %							Cumulative/ %							Cumulative/ %		
		#Pts	#Cycles	#	%	Years / %	#	%	#Pts	#Cycles	#	%	Years / %	#	%	#Pts	#Cycles	#	%	Years / %	#	%
Dickey		2272	4067	587	14.4%	5/60%	146	24.9%														
Kaplan		306	678	99	14.6%	6/25.4%	14	14%														
Ajossa	IUI group	138		36	10.2%	/26.1%	7	19%														
Shelden		66		52			14	27%														
Tadokoro	Un-explained	117	284	31	11%	4/38%		17%														
Gleicher	Started	1661	4035		10.9%																	
Gleicher	Completed	1661	3137	441	14.1%		127	29%														
Tur		1781		1878			401	21%														
Bedaiwy	FSH	124	283	45	15.9%	/36.3%	10	22%														
Guzick (1999)	OS + IUI	231	1299	77		/33%	22	29%														
Hughes	Review		1156	171	15%					644	42	7%										
Dankert		67		23	8.7%	/26.9%	1	4%	71		27	10%	/28%	2	7%							
Homburg										5268	1909	36%			8-13%							
Lewis	hCG group								71		23	12%	3/31%	3	13%							
Guzick (1999)												8.3%										
Holzer	Review											10-40%							20-27%			
Mitwally	AI dose 2.5 mg		671	110	16.4%		9	11%		994	80	8%		12	15%		167	33	19.8%		–	5%
Mitwally	AI dose 5.0 mg																432	70	16.2%		–	5%
Al-Fozan									80	123	11	8.7%		1	9%	74	115	13	11.5%		0	0
Bayer									25	67	8	12%		0	0	21	52	5	10%		0	0
Al-Fadhli	AI dose 5.0 mg															38		10	26.3%		0	0
RMN Protocol		167		50			13	25%	167		45			6	12.5%	167		45			3	6.25%

OS = Ovarian Stimulation
IUI = Intrauterine Insemination

Figure 1. Flowchart



The flowchart above summarizes this study with our central hypothesis, that use of aromatase inhibitors will stimulate the ovaries sufficiently to produce no reduction in the rate of pregnancy, while significantly reducing the numbers of multiple gestational pregnancies as compared to stimulation with CC or gonadotropins.

4 Objectives

4.1 Primary Aim

Our goal is to examine the incidence of multiple gestational pregnancies in infertile ovulatory females following ovarian stimulation treatment with an AI, as compared to CC or gonadotropins. This is a randomized multi-center clinical trial to evaluate the treatment efficacy of AI vs. CC or gonadotropin injection used for OS in conjunction with IUI. The primary outcome measure will be the rate of multiple gestational pregnancies initiated as determined by ultrasonographic documentation of fetal heart beats. Safety will also be evaluated by assessing the number and degree of adverse events reported in the subjects and offspring.

4.2 Secondary Aim

We will assess secondary outcomes including the time to conception, the conception rate, and the live birth rate obtained with an AI, as compared to CC or gonadotropin. We will also compare these outcomes in the three treatment arms among women with multiple gestations. The rate of cycle cancellation or discontinuation will also be a secondary endpoint.

4.3 Tertiary Aims

1. Is there a relationship between length of infertility and pregnancy occurrence and outcome?
2. Is endometrial thickness (late follicular and mid-luteal) different between the groups, and does group and overall population endometrial thickness correlate with pregnancy occurrence and outcome? Does endometrial thickness change over time with additional cycles of ovarian stimulation?
3. Are mid-luteal ultrasound and blood work predictive of who will develop symptomatic ovarian hyperstimulation syndrome, and pregnancy occurrence and outcome?
4. Do locally measured hormonal levels (E2, etc…) correlate well with core lab levels? Is variance greater with type of assay and manufacturer used?
5. Are there genetic or phenotypic determinants of success?
6. Can sperm microarray identify couples more or less likely to conceive?
7. Does perceived stress and self reported quality of life by husband and wife influence success? [Assess by SF-36 and Prime MD]
8. In the case of CC vs. AI randomization, can the physician or patient identify what arm they were randomized to?
9. Is length of luteal phase predictive of pregnancy outcome?
10. Is there a relationship between length of infertility and conception?
11. Is there a difference in pregnancy rate in the first vs. second vs. third vs. fourth cycle?

4.4 Treatment Design, Study Population, and Study Summary

4.4.1 Treatment Design

This will be a multi-center, prospective trial of gonadotropin or clomiphene citrate vs. aromatase inhibitors in the treatment of infertile ovulatory women. The study will be double-blind with respect to CC and AI use. An equal number of patients will be randomized to receive gonadotropins or CC or AI daily according to computer-generated randomization schedule. Treatment assignments will be stratified by site and age (18-34 and 35-40). The randomization scheme will be a stratified randomization with permuted blocking (the block size is permuted between 3 and 6 in the ratio of 2:1) within each stratum. Subjects will receive medication in the form of a pill (overcoated CC or AI in double-blinded fashion) or gonadotropin injection.

The appropriate study candidates will be recruited from the clinics of the Reproductive Medicine Network and possibly from the SCCPIR sites, after obtaining informed written consent from the women and their partners. Recruited subjects will meet the inclusion and exclusion criteria detailed below. Monitoring of this trial at all sites will be conducted by the RMN Data Coordination Center, with progress reports provided to the RMN Data and Safety Monitoring Board no less than every three months in order to review trial progress and subject safety. The Food and Drug Administration has issued IND# 107705 for the use of an aromatase inhibitor in ovarian stimulation.

4.4.2 Study Population

Nine hundred (900) infertile ovulatory women actively seeking pregnancy (300 per treatment arm), age 18-40 years, will be enrolled in the participating sites. The overall goal of the inclusion/exclusion criteria is to identify a population of healthy infertile women who are regularly ovulating. These will include a normal uterine cavity with at least one patent tube and a partner with motile sperm count of at least 5 million in the ejaculate. If existing medical records are used to verify inclusion or exclusion criteria, the site should keep a copy of these in the source documents. A general list of exclusionary medications requiring a washout period is found in the appendix. The list is not exhaustive and questionable medications can be looked up to see if they belong to one of the families of exclusionary medications, or the Project Leader and DCC can be queried.

4.4.3 Study Summary

Recruitment and Prescreening: see Section 5 descriptions following.

<u>Screening visit(s):</u>

1. Obtain informed, signed consent from female and partner.
    - Female and partner must specifically be made aware of potential drug complications and adverse outcomes, and partner must sign the Male Consent Form
2. Complete medical history and physical exam of female study participant.

- Vital signs, height, weight, hip and abdominal circumference, BMI
- Pap smear if necessary per current ACOG time-frame guidelines
- Standard pelvic and breast exam conducted by physician (or within past 12 months)
- Ferriman-Gallwey hirsutism scoring, acne lesion count, facial sebum scoring by Sebumeter

3. Perform radiological exams.

- Transvaginal ultrasound measuring uterine and ovarian characteristics
- Sonohysterogram or hysterosalpingogram to verify patency in at least one tube, and normal uterine cavity (or documentation within past 3 years). An uncomplicated intrauterine non-IVF pregnancy and uncomplicated delivery and postpartum course resulting in live birth within the last three years will also serve as sufficient evidence of a patent tube and normal uterine cavity as long as the subject did not have, during the pregnancy or subsequently, risk factors for Asherman's syndrome or tubal disease or other disorder leading to an increased suspicion for intrauterine abnormality or tubal occlusion.

4. Pre-conception counseling.

- Female and partner must complete Genetic Risk Factors questionnaire and RMN Standard Demographic questionnaire
    - Prenatal vitamins or folic acid prescribed. The costs for these prescriptions are not included in determining the patient care budget for this protocol.
    - Offer optional blood test for Rubella, Varicella, and HIV. The costs for these blood tests are not included in determining the patient care budget for this protocol.

5. Complete QOL Surveys.

- *Female*: FSFI, SF-36, Prime-MD, FertiQoL, Sleep Habits, FSDS
- *Partner*: SF-36, Prime-MD, FertiQoL, Sleep Habits, IIEF

6. Laboratory tests.

FEMALE LOCAL LABORATORY BLOOD TESTS		
Cycle Day 3 (+/-2)	**Day 1-10**	**Safety Screen (fasting) Labs**
prolactin	[testosterone]	Hemoglobin
FSH	progesterone	Hematocrit
TSH	βhCG	WBC
E2	Glucose (fasting)	Platelets
	[HgbA1c]	BUN
		Creatinine
		Total Bilirubin
		ALT/AST
		Total Cholesterol
		LDL-C

		HDL-C
		Triglycerides

- *Bracketed tests are not mandatory; PI discretion only*
- *Safety Screen tests must be obtained within 60 days prior to randomization*
    - *Lipid Panel (cholesterol, triglycerides, LDL/HDL)results are valid for one year*
- *Eligibility tests in Column 1 are valid for one year*
- *If Cycle Day 3 (+/- 2 days) labs are missed, or rescreening is otherwise necessary, these labs can be re-drawn on any day of the cycle*

- Males: obtain a semen specimen
    - Local lab semen analysis
    - Retain sample for future microarray analysis if Repository consent is signed

MALE CORE LABORATORY BLOOD SERUM TESTS	
testosterone	FSH
SHBG	Inhibin B
LH	TSH
glucose	insulin

- *Male core labs are not cycle-specific; may be done within three months of initiation*

Future Studies:

1. At each blood draw during the study, retain any extra blood specimen (aliquoted to at least 3 cc each) for banking for future studies as plasma and serum, stored evenly among 2 tubes, if subject has consented for optional blood collection.

Study treatment visit 1:

Patient will call on Day 1 of menstrual cycle (first day of full flow bleeding) to schedule a visit for cycle Day 3 (+/-2 days).

1. Perform physical exam, including weight and vital signs.

2. Perform transvaginal ultrasound for endometrial, uterine and ovary dimensions, and antral follicle count.

3. Collect blood from female patient.
- Local labs: serum βhCG, serum E2.
- Collect core labs (these labs will be repeated on all cycle initiation days, with the exception of the Chlamydia antibody titer):

FEMALE CORE LABORATORY BLOOD SERUM TESTS	
Fasting glucose	total testosterone
Fasting Insulin	SHBG
Inhibin A and B	DHEAS
E2	progesterone
LH	androstenedione
FSH	AMH
prolactin	TSH
17-OHP	Chlamydia antibody titer for research purposes

- Blood sample (DNA) for pharmacogenomics study if consent is signed
- Blood sample for repository if consent is signed

4. *Criteria to begin medication:*
   - βhCG is negative
   - serum E2 < 95 pg/ml
   - no ovarian cysts > 3 cm in average diameter

5. Randomization.
   - Couples randomized to the gonadotropin injection arm will have ovulation induction training to learn self- or partner-administration of injection drug, and will be coached through cycle monitoring logistics for U/S and blood draws

6. Dispense study medication.

Protocol	interval	dose	method	start	finish	notes	future cycles
Gonadotropin	daily	150 IU	SC injection	Day 3*	Until day before hCG admin.	May be increased or decreased by 37.5-75 IU/d beginning Cycle Day 7 (4 days from first injection)	Can be started at doses ranging from 75-225 IU/d
CC	daily	100 mg	pill	Day 3*	Day 7		Can be started at 50-150 mg/d= (1 to 3 pills)
AI	daily	5 mg	pill	Day 3*	Day 7		can be started at 2.5-7.5 mg/d= (1 to 3 pills)

****Menstrual cycle day 3 (+/- 2 days)***
Study treatment visit number 2:

CC/AI Group

- Within 3 days after completing 5-day drug cycle (Cycle Day 8-12)

1. Transvaginal ultrasound for endometrial and follicular monitoring.
2. E2 blood draw.
3. Adverse effects and concomitant medications query.
4. Collect female core labs.

FEMALE CORE LABORATORY BLOOD SERUM TESTS	
E2	total testosterone
FSH	

Gonadotropin Group

- Cycle Day 7-9 (or 4 days after beginning treatment)

1. Transvaginal ultrasound for endometrial and follicular monitoring.
2. E2 local blood draw.
3. Adverse effects and concomitant medications query.

Study treatment visits number 3 and beyond[1]:

CC/AI Group

Visits for subjects on oral medications will be conducted on an individualized basis until hCG administration

1. Transvaginal ultrasound examination for endometrial and follicular monitoring.
2. E2 local blood draw.
3. Adverse effects and concomitant medications query.

Gonadotropin Group

Visits for subjects in the gonadotropin arm will be conducted on an individualized basis until hCG administration, but no less frequently than every three days.

1. Transvaginal ultrasound examination for endometrial and follicular monitoring.
2. E2 local blood draw.

[1] Local E2 blood draw will be obtained from all females during each subsequent visit (Visit #4 through hCG administration day).

3. Adverse effects and concomitant medications query.
4. Collect female core labs during Visit #3 only.

FEMALE CORE LABORATORY BLOOD SERUM TESTS	
E2	total testosterone
FSH	

hCG administration day:

1. 10,000 IU in 1 cc diluent delivered IM
2. Transvaginal ultrasound examination for endometrial and follicular monitoring.
3. Draw blood labs
    - E2
    - Collect female core labs

FEMALE CORE LABORATORY BLOOD SERUM TESTS	
E2	total testosterone
FSH	progesterone

4. *Criteria for hCG administration:*
    - First occurrence of lead follicle reaching 20 mm (in average diameter in two dimensions), or
    - First occurrence of two lead follicles greater than 18 mm diameter (in average diameter in two dimensions), or
    - The day after the lead follicle reaching 18 mm (in average diameter in two dimensions), or
    - The day of detection of presumptive ovulation by ultrasound and E2 monitoring.
    - Coasting of gonadotropin administration will not be allowed.

5. *Criteria for withholding hCG:*
    - If a leading follicle does not reach a mean diameter of 18 mm after 18 days of treatment, or
    - Endogenous LH surge happens [which can lead to premature luteinization], or
    - Increased risk for OHSS and/or high-order multiple gestational pregnancy exists when more than 4 growing follicles develop (mean diameter >18 mm), or
    - Serum E2 exceeds 3000 pg/ml around the day of expected hCG administration.

5a. If cycle is cancelled, progesterone level will be measured to assess whether ovulation occurred.

5b. *Protocol medication adjustment:*

- If no ovulation or development of at least one follicle ≥ 18 mm in average diameter, then increase dosage in the subsequent cycle.
- If only one follicle ≥ 18 mm in average diameter, the dosage increase for subsequent cycles will be left to physician's discretion.
- If more than four follicles are ≥ 18 mm in average diameter, dosage will be reduced in the subsequent cycle.

6. *Cancellation criteria*: Cycles will be cancelled if significant adverse reactions develop in response to administered medications, if criteria for withholding hCG administration are encountered, or per patient's request.

Insemination day visit:

1. Collect female core labs.

FEMALE CORE LABORATORY BLOOD SERUM TESTS	
E2	Total testosterone
FSH	

2. Each site will perform its standard insemination procedure.
3. Record time of insemination.

Post-insemination visit:

To be conducted 1 week after insemination (± 1 day)

1. Ultrasound measurement of endometrial thickness, ovarian size, and follicle count.
2. Blood draws.
    - Obtain local and core P4
    - If no evidence of follicular growth by Day 21 (± 2 days), use the local serum sample for progesterone determination to confirm anovulation

Pregnancy test visits:

To be conducted 2 weeks after insemination

1. Query for adverse events, including symptoms of OHSS.
2. Patient turns in menstrual and intercourse diary.
3. βhCG pregnancy test.

Three possible outcomes:

A. No pregnancy

B. Positive test→ retest for rising level in 2 days→ no pregnancy
C. Positive test→ retest for rising level in 2 days→ positive pregnancy

A. Negative Pregnancy Test/No pregnancy

Repeat cycles until pregnancy occurs or treatment cycles conclude; women may receive hCG up to 4 times (cycles). There may be anticipated or unanticipated breaks in protocol, but none of the breaks should exceed approximately 4 weeks (allowing the subject approximately 28 weeks to complete the protocol). Subjects at sites with holiday recesses or other forced cycle breaks will have approximately 32 weeks to complete the protocol.

- *Criteria to initiate Cycles 2, 3, or 4 (*Day 3 +/- 2 days)*:*
  1. Negative serum βhCG pregnancy test (within 2 days)
  2. Day 3 (+/-2 days) serum E_2 < 95 pg/ml
  3. Day 3 (+/-2 days) vaginal ultrasound of no ovarian cyst > 3 cm

- Start New Cycle Treatment Visit 1 (see p. 22)

B. Positive Pregnancy Test (no pregnancy)

- Patient will return in 2 days to check for a rising level in serum βhCG; if there is not a rising level, patient will initiate Cycles 2, 3, or 4 (see above)

C. **Positive Pregnancy Test (pregnancy**)

Biochemical pregnancy will be defined as βhCG >5 units/ml 2 weeks after insemination followed by a rising level two days later

- Patient will return in 2 days to check a rising level in serum βhCG; threshold level of 2,000-4000 mIU/mL will be obtained
- Schedule Pregnancy Ultrasound Visit
- Schedule End of Study Drug Visit

<u>Pregnancy ultrasound(s):</u>

To be done 14-21 days after a positive pregnancy test

Clinical pregnancy rate will be defined as the identification of intrauterine sac(s) with positive fetal cardiac activity in at least one sac, 2 weeks after biochemical pregnancy identification.

1. Use to determine location of pregnancy and number of implantation sites
2. Repeat in 7-14 days if no cardiac activity detected
3. Arrange follow-up at Week 12 to check pregnancy progress

Pregnancy Follow up:

1. Prenatal records will be requested from the treating physician.
    - Copy of each prenatal visit records to be kept until delivery

2. Hospital record of delivery outcome will be obtained from patient's labor & delivery department.
3. Obtain a separate consent form to enter the patient into the pregnancy registry.

End of Study Drug Visit:

If pregnant: perform as early in the visit as possible

If no conception within 4 cycles: perform after the pregnancy test from the fourth cycle of therapy is returned negative, showing the subject is not pregnant

Other: Study withdrawal; emergency unblinding

1. Physical exam.
    - Height, weight, waist and hip circumference
    - Ferriman-Gallwey hirsutism assessment, acne lesion count, sebum score measured with Sebumeter

2. Administration.
    - Patients will return remaining study drug
    - Patients will turn in journal logs; physician will review data
    - Query for adverse events and concomitant medications
    - Females will repeat QOL surveys
        - Pregnant women will not repeat FertiQoL

3. Laboratory tests.

BLOOD TESTS FEMALE LOCAL LABORATORY	
Pregnancy Test	**Safety Screen (fasting) Labs**
βhCG	Hemoglobin
	Hematocrit
	WBC

BLOOD TESTS FEMALE LOCAL LABORATORY	
	Platelets
	BUN
	Creatinine
	Total Bilirubin
	ALT/AST
	Total Cholesterol
	LDL-C
	HDL-C
	Triglycerides

FEMALE CORE LABORATORY BLOOD SERUM TESTS	
Fasting glucose	total testosterone
Fasting Insulin	SHBG
Inhibin A and B	DHEAS
E2	progesterone
LH	androstenedione
FSH	AMH
prolactin	TSH
17-OHP	

4.4.4 Inclusion Criteria

1. Women ≥18 to ≤40 years of age, with one or more years infertility history, desirous of conceiving, regularly ovulating (defined as 9 or more menses per year), at initiation of participation.
2. Normal uterine cavity and at least one open fallopian tube confirmed by hysterosalpingography (HSG), sonohysterography, or laparoscopy/hysteroscopy in the last three years preceding enrollment into the study. An uncomplicated intrauterine non-IVF pregnancy and uncomplicated delivery and postpartum course resulting in live birth within the last three years will also serve as sufficient evidence of a patent tube and normal uterine cavity as long as the subject did not have, during the pregnancy or subsequently, risk factors for Asherman's syndrome or tubal disease or other disorder leading to an increased suspicion for intrauterine abnormality or tubal occlusion.
3. Evidence of ovarian function/reserve as assessed by day 3 (+/-2 days) FSH ≤12 IU/L within one year prior to study initiation.
4. Normal or corrected thyroid function within one year of study initiation.
5. Normal prolactin level within one year of study initiation.
6. In general good health, not taking any medications which could interfere with the study (e.g., FSH, insulin sensitizers).
7. Ability to have inseminations following hCG administration.
8. Male partner with total motile sperm in the ejaculate of at least 5 million sperm, within one year of study initiation.

4.4.5 Exclusion Criteria

1. Currently pregnant or successful pregnancies within 12 months of initiating participation. Clinical intrauterine miscarriages prior to initiating participation, within ASRM guidelines: subjects over 35 must wait six months, while subjects under 35 must wait 12 months. No exclusion for biochemical pregnancies.
2. Undiagnosed abnormal uterine bleeding.
3. Suspicious ovarian mass.
4. Patients on oral contraceptives, depo-progestins, or hormonal implants (including Implanon). A two month washout period will be required prior to screening for patients on these agents. Longer washouts may be necessary for certain depot contraceptive forms or implants, especially when the implants are still in place. A one-month washout will be required for patients on oral cyclic progestins.
5. Known 21-hydroxylase deficiency or other enzyme defect causing congenital adrenal hyperplasia.
6. Type I or Type II diabetes mellitus, or if receiving antidiabetic medications.
7. Known significant anemia (Hemoglobin <10 g/dL).
8. History of deep venous thrombosis, pulmonary embolus, or cerebrovascular event.
9. Known heart disease (New York Heart Association Class II or higher).
10. Known Liver disease (defined as AST or ALT>2 times normal, or total bilirubin >2.5 mg/dL).
11. Known Renal disease (defined as BUN >30 mg/dL or serum creatinine > 1.4 mg/dL).
12. History of, or suspected cervical carcinoma, endometrial carcinoma or breast carcinoma.
13. History of alcohol abuse (defined as >14 drinks/week) or binge drinking of ≥ 6 drinks at one time).
14. Known Cushing's disease.
15. Known or suspected adrenal or ovarian androgen secreting tumors.
16. Allergy or contraindication to the treatment medications: AI, gonadotropins, CC or hCG.
17. Couples with previous sterilization procedures (e.g. vasectomy, tubal ligation) which have been reversed.
18. Patients with untreated poorly controlled hypertension defined as a systolic blood pressure ≥ 160 mm Hg or a diastolic ≥ 100 mm Hg obtained on two measures obtained at least 60 minutes apart.
19. Subjects who have undergone a bariatric surgery procedure in the recent past (< 12 months) and are in a period of acute weight loss or have been advised against pregnancy by their bariatric surgeon.
20. Known moderate or severe endometriosis
21. Known polycystic ovarian syndrome as evidenced by anovulation or oligovulation, hirsutism and/or elevated testosterone levels, and ovarian morphology on ultrasound examination.
22. Donated semen.
23. Couples in which either partner is legally married to someone else.

24. Medical conditions that are contraindications to pregnancy.

4.4.6 Study Termination Criteria

1. Development or suspicion of an allergic or serious adverse reaction to any of the medications in the study.
2. Uncontrolled hypertension.
3. Persistent ovarian cyst > 30 mm that does not resolve in two cycles.
4. Serious or severe Ovarian Hyperstimulation Syndrome (OHSS).
5. Spontaneous pregnancy.

5 Study Design

5.1 Type of Design

This will be a multi-center, prospective, clinical trial of gonadotropin and clomiphene citrate vs. aromatase inhibitors with a total of 900 patients in the three treatment arms. The randomization scheme will be by randomized block design with participating sites and age group (18-34 and 35-40) as the blocking strata, and the block size varies between 3 and 6 in the ratio of 2:1. The primary aim will determine whether the AI treatment results in a smaller proportion of multiple gestations than the CC or gonadotropin treatments. The proportions achieving clinical pregnancies will be calculated on an intent-to-treat basis. We will perform a non-inferiority analysis between gonadotropin, CC and AI treatments with respect to the secondary outcomes of pregnancy and live birth rates.

5.2 Rationale for Design

Aromatase inhibitors have been theorized to improve outcomes when used for induction of multiple follicular development compared to gonadotropin or clomiphene citrate, in that the rate of multiple gestations would be reduced. This design is needed to test this hypothesis and to establish the safety and efficacy of an aromatase inhibitor compared to clomiphene citrate or gonadotropin in women with unexplained infertility.

5.3 Recruitment/Informed Consent Process

Infertile couples presenting for consultation before starting ovulation induction treatment (after clinical confirmation of their eligibility for admission into the study based on inclusion & exclusion criteria) will be approached to participate by the research coordinator or non-care providing physician. In the recruitment visit, study details including interventions, as well as the experimental nature of applying AIs for OS will be explained. Risks and benefits will be thoroughly discussed and consents given to the patient and partner. A follow up visit will be scheduled if the patient and partner agree to participation in the study. At the first follow up visit, the couple's eligibility will be confirmed, questions answered, and consents signed. The female partner will undergo a physical examination within 60 days prior to randomization. All women will be given prescriptions for prenatal vitamins or folic acid. All patients and partners will complete a risk factor questionnaire for genetic diseases; if appropriate, each site will provide a referral for counseling.

Subjects will be offered optional screening for rubella and Varicella immunity. The subjects who are non-immune will be offered rubella and/or Varicella vaccination and subject entry delayed for one month prior to initiating attempts to conceive, as per the current CDC recommendations. Subjects will also be offered HIV screening and referral for treatment as necessary. Additional baseline measurements to be conducted within six months prior to initiation of cycle 1 therapy are: height (without shoes), body weight, and abdominal circumference (at the umbilicus).

Additional baseline samples which will be obtained during cycle days 1-10 preceding initiation of therapy are: 1) fasting glucose and insulin levels, 2) Serum testosterone, SHBG, DHEAS

level, and day 3 ± 1 E_2, LH, FSH, prolactin, TSH, anti-mullerian hormone, Inhibin A and B, and antral follicle count. Additionally, assessments of quality of life and stress for patient and partner to be conducted are the RMN routine demographic forms, SF-36, Prime MD, Sleep Habits, FSDS and FSFI (for females), IIEF (for males) and FertiQoL.

Additional baseline characteristics for the male partner to be assessed include semen analysis, semen (sperm) for microarray analysis, semen specimen (for DNA, RNA, micro RNA, and protein), testosterone, SHBG, LH, FSH, Inhibin B, insulin, glucose and TSH.

5.4 Recruitment

Hospital/Local Health Care Referrals
Subjects will be recruited at each site from individual practice(s) as well as faculty/resident clinics. Ongoing contact with practice and faculty members as well as with residents will be made by the investigators and coordinators, reminding them of the inclusion criteria, importance of the study, etc. In addition, the investigators will describe the study to members of other departments in the hospital, primarily family practice, medical endocrinology, urology, and gynecology who also see and treat these patients. Contact with local physicians will be made and/or grand rounds will be given to disseminate information about the study.

Local Publicity Office
Investigators will meet with their local Public Relations offices and plan a news release about the study. They will also make themselves available for any newspaper, radio, or TV stories that may increase public awareness of the study. The full gamut of local media sources should be utilized. Often there is greater yield with more extensive coverage in smaller local outlets as opposed to brief mentions in outlets with larger circulation. News release will mention the uniqueness of the study, which may improve male fertility treatment.

Local Advertisements
Advertisements will be placed in local newspapers and will be continued on a regular basis if response is good.

Contact with infertility support groups
Contact will be made with both national and local support groups to spread information about the study through informational brochures and/or participation in local meetings. The American Infertility Association also may be helpful in promoting awareness of this study.

National Professional Organizations
Contact will be made with the publicity office of The American Society for Reproductive Medicine, and other potentially helpful organizations to solicit their support and potential informational releases.

Web sites
The study will be prominently displayed on the RMN web site. Additionally each RMN center should have a web page devoted to this study with general as well as contact information. Information should also be available at the NICHD web site with links to each RMN center. An ad should also be placed at "Center Watch" on the web.

National Advertising
We would consider placing a trial ad in the health section of a select or a series of selected national publications with all our local numbers/contacts.

IRB Approval
It is expressly acknowledged that all informational material that could be construed to be advertising will be approved by the appropriate IRB prior to dissemination.

5.5 Informed Consent

Once potential couples have been identified, they will be referred to the site clinical coordinator or his/her designee. The clinical protocol will be explained to potential subjects and their partners by the physician investigator or the coordinator depending on the clinical circumstances.

Inclusion and exclusion criteria will be reviewed. After the study has been completely explained to the potential couple, they will be given the informed consent documents to review (sample consent forms, in the format of Wayne State University, are included in Section 10). Some individuals may wish to complete the informed consent process at the time of this discussion. In these cases the informed consent documents will be signed once all questions are resolved. In other cases the subjects may wish to take the consent forms home for further consideration. In these cases the coordinator will confirm the couple's willingness to be contacted, and set up a tentative timeframe to be back in touch with the subjects. The consents can be signed either with the coordinator or with a physician once all questions have been answered to the satisfaction of the potential patient and partner. A signed informed consent document, approved by the IRB at the study site, will be confirmed on all subjects prior to the baseline evaluation. The PI at each RMN site should not simultaneously be managing the care of a patient in the study and be the primary caregiver for a study participant, as specified in the NICHD clinical Research Policy guidelines.

In order to be eligible for enrollment and randomization, each member of the couple must be confirmed to meet all inclusion and exclusion criteria described above.

5.6 Randomization/Treatment Initiation

Nine hundred (900) women will be randomized to one of the three treatment conditions. Using a 1:1:1 treatment ratio, there will be 300 women assigned to each treatment group. The scheme will be a stratified randomization with permuted blocking (the block size is permuted between 3 and 6 in the ratio of 2:1) within each stratum. The two stratification variables will be site and age (18-34, 35-40). Almac (the RMN provider for the Investigational Drug Service) statisticians will generate the randomization scheme for the study subject to the final review and approval by the DCC data manager. Because this is a double-blind study, the randomization scheme (including block size) will be disclosed to the DCC data manager, and not to any RMN investigators or staff, including the Protocol Lead Investigator. Unless otherwise specified, treatment group data will be presented in a blinded fashion within DSMB reports.

The site investigator will be provided a password protected account for WebEZ, which is a web-based secured randomization service provided by Almac. After the patient has signed an

informed consent and all required baseline evaluation procedures have been completed, an Investigator or designee will login to WebEZ in order to randomize a patient into the trial.

The WebEZ will query the site for patient eligibility information. If the patient is eligible, the site will be provided with a patient identifier and a study kit number if the patient is assigned to receive CC or AI, or told to treat the patient with gonadotropin if the patient is assigned to the gonadotropin arm. The Study Coordinator at each site will be responsible for storing, dispensing, and performing pill/vial counts on the study medications.

In the event that emergency unblinding is needed, only the site PI will be able to unblind a patient to treatment by calling the WebEZ emergency unblinding number. The site PI and DCC staff will receive notification from the central randomization service when emergency unblinding has occurred. With the exception of emergency unblinding, patients will not be unblinded until study findings are released.

If a patient is randomized but never receives treatment, the patient will be considered enrolled in the study and analyzed in the group to which she was randomized (i.e., the intent-to-treat or ITT population). The randomization slot will not be re-allocated to a new patient due to the ITT nature of the study. For obvious reasons, the site investigators should try to avoid this situation by randomizing the subject immediately prior to initiation of the treatment intervention being delivered. In addition, the request should be made only after the patient has met all eligibility criteria and has completed the screening evaluation. The site investigators will be provided with a URL, available 24 hours a day and 7 days a week.

5.7 Study Specific Procedures/Visits Methodology and Intervention

Infertile couples presenting for consultation before starting ovulation induction treatment (after clinical confirmation of their eligibility for admission into the study based on inclusion & exclusion criteria) will be approached to participate. In the recruitment visit, study details including interventions, as well as the experimental nature of applying AIs for OS will be explained. Risks and benefits will be thoroughly discussed and consents given to the patient and partner. A follow up visit will be scheduled if the couple agrees to participation in the study. At the first follow up visit, the couple's enrollment eligibility will be confirmed, questions answered, and consents signed. The female partner will undergo physical examination within 60 days prior to randomization. All women will be given prescriptions for prenatal vitamins or folic acid. All patients and their partners will complete a risk factor questionnaire for genetic diseases; if appropriate, the site's principal investigator will provide a referral for counseling. Subjects will be offered optional screening for rubella and Varicella immunity. The subjects who are non-immune will be offered rubella and/or Varicella vaccination and subject entry delayed for one month prior to initiating attempts to conceive, as per the current CDC recommendations. Subjects will also be offered HIV screening and referral for treatment as necessary. Additional baseline characterizations to be conducted within six months of initiation of cycle 1 therapy are: height (without shoes), body weight, and abdominal circumference (at the umbilicus). Additional baseline samples will be obtained during cycle days 1-10 preceding initiation of therapy are: 1) fasting glucose and insulin, 2) Serum testosterone, SHBG, DHEAS level, and day 3 ± 1 E_2, LH, FSH, prolactin, TSH, anti-mullerian hormone, Inhibin A and B, and antral follicle count. Additionally, assessments of quality of life and stress for patient and partner to be

conducted are RMN routine demographic forms, SF-36, Prime MD, Sleep Habits, FSDS and FSFI (for females), IIEF (for males) and FertiQoL.

Additional baseline characteristics for the male partner to be assessed include semen analysis, semen (sperm) for microarray analysis, semen specimen (for DNA, RNA, micro RNA, and protein), testosterone, SHBG, LH, FSH, Inhibin B, insulin, glucose and TSH.

Screening visit(s): Following attaining informed, written consent, female study participants will have a physical exam, including height, weight and abdominal circumference, and pap smear as necessary per current ACOG guidelines. Subjects will also undergo Ferriman-Gallwey hirsutism scoring, an acne assessment and sebum measurements. All tests relating to data that will likely be part of the baseline data or final analyses, (i.e. physical exam, serum for the core lab, ultrasound, and QOL surveys) should be obtained on a single day (specifically, female core lab blood will be drawn during study treatment visit one of the first cycle). However, QOL surveys may be spread between the Screening and study treatment visit one of the first cycle. Blood will be obtained for inclusion/exclusion and fasting safety labs, and if desired, determination of rubella and Varicella immunity, and HIV status.

A semen specimen will be obtained from the male partner and processed for future microarray analysis. Blood will be obtained from the male for the baseline characteristics. Male partners will complete the RMN standardized demographic questionnaire and will perform the SF-36, Prime MD, and other QOL surveys.

Study treatment visit 1: Patients will call on the first day of their menstrual period to schedule a visit on cycle day 3 (+/-2 days) of their period. Patients will start treatment on Day 3 (+/- 2 days) of a spontaneous or progestin-induced period. At this time, blood for serum beta hCG level will be drawn to confirm absence of pregnancy, serum E_2, core labs, and baseline follicular ultrasound scan will be performed. Subjects will be given the medications they are to begin taking (one overcoated pill containing CC or AI or injectable solution of gonadotropin). Gonadotropin-randomized couples will undergo training to learn injectable medication self administration or partner administration, as well as logistics of cycle monitoring for performance of ultrasound exams and blood draws. Patients will have a baseline transvaginal ultrasound to determine ovarian size in three dimensions and antral follicle count, and blood will be drawn. Patients will begin the medications if beta hCG is negative, serum estradiol < 95 pg/ml and there are no ovarian cysts > 3 cm in average diameter.

Study treatment visit number 2: For patients on gonadotropin, 4 days after beginning treatment, patients will have a transvaginal ultrasound exam for endometrial and follicular monitoring, and blood will be drawn for estradiol. For patients receiving CC or AI, this visit will occur within three days after completing the five-day treatment of CC or AI. For women receiving CC or AI, core blood will be collected to send to the central lab for measurement of E_2, FSH, and testosterone. For women receiving gonadotropins, these labs will be drawn at study treatment visit number 3. These labs will be drawn again in all women on the expected day of hCG administration.

Study treatment visits number 3 and beyond: Visits for subjects on oral medications will be conducted on an individualized basis until hCG administration. The gonadotropin group will come in for visits no less frequently than every three days. All patients will have a transvaginal ultrasound examination for endometrial and follicular monitoring, and will have blood drawn for estradiol levels. The gonadotropin group will have core labs drawn on this day. From visit #4 onwards until hCG administration day, all women will have blood drawn locally for estradiol. On day of hCG administration, estradiol and core lab bloods will be drawn, and a transvaginal ultrasound will be administered.

Insemination day visit: This will occur within 44 hours following an hCG administration of 10,000 IU in 1 cc diluent administered IM. Patients will have blood drawn for core lab.

Post-insemination visit: This will be conducted one week +/- 1 day after insemination for midluteal hormonal assays for progesterone (local and core labs), and for ultrasound measurement of endometrial thickness. For women who do not have evidence of follicular growth, a day 21 ± 2 local serum sample will be obtained for progesterone determination, to confirm anovulation.

Pregnancy test visits: A serum beta hCG pregnancy test will be conducted two weeks after insemination. Patients will also be queried about any adverse events, including signs or symptoms of ovarian hyperstimulation syndrome. Pregnancy will be confirmed, if suspected, by measurement of serum hCG (baseline serum beta hCG followed in 2 days by the serial rise of serum hCG to threshold level of 2,000-4,000 mIU/mL).

Pregnancy ultrasound: Once pregnancy is confirmed chemically, ultrasound will be utilized to determine location of the pregnancy and number of implantation sites. This will be done 14-21 days after a positive pregnancy test.

Repeated pregnancy ultrasound: This will be done approximately 7-14 days after the first one if no cardiac activity is detected in all pregnancy sacs. Follow up during pregnancy will be arranged with the treating obstetricians; additionally, the subject will be called at 12 weeks to see how the pregnancy is progressing.

Follow up visit for initiation of cycles 2-4 (if negative pregnancy test):

- The subject will have a brief physical exam consisting of weight, vital signs including blood pressure, and Sebumeter measurements.
- The subject will turn in her menstrual and intercourse diary. She will report any adverse events she has experienced during the study as well as any concomitant medications she is taking.
- Subject will be issued new course of study drug.
- A transvaginal ultrasound will be performed.
- A serum pregnancy test before beginning medication again.
- If the subject has a positive pregnancy test, she will be scheduled for a pregnancy follow up visit and a transvaginal ultrasound will be performed to assess how the pregnancy is progressing.

Pregnancy Follow up:
Prenatal records will be requested from the treating obstetrician. A copy of each prenatal visit will be kept after each prenatal encounter, until delivery. Delivery outcome records will be obtained from the labor & delivery department where the patient gives birth to her baby(s).

5.7.1 End of Study Drug Visit:

An end of study drug visit will be performed after the pregnancy test at the fourth cycle for women who do not conceive during the trial, or as early in the pregnancy as possible if women do conceive. A brief exam with the addition of a repeat of acne and Sebumeter assessment and hirsutism will be collected. Subjects will return remaining study drug, their journal logs, and a final assessment of adverse events and concomitant medications will be done. Baseline measures will be repeated in all subjects including safety labs and QOL surveys, (FertiQoL will not be repeated in pregnant women). A final collection of blood for the core lab will also be collected.

5.8 Treatment Protocols

Randomization will ideally be done Day 3 (+/- 2 days) of the initial treatment cycle visit, but may be done earlier if deemed by the site PI or coordinator to be administratively necessary.

♦ Gonadotropin protocol: A daily injection of 150 IU of gonadotropin will be administered subcutaneously starting on Day 3 (+/- 2 days) of the menstrual cycle and continuing until the day of hCG administration. Dosage will be able to be increased or decreased 37.5-75 IU/d beginning cycle day 7. Future cycles can be started at doses ranging from 75-225 IU/d. The same type of gonadotropin injections will be used. Coasting of gonadotropin administration will not be allowed.

♦ AI protocol: A daily dose of 5 mg of the AI, letrozole, will be administered orally for five days starting on Day 3 (+/- 2 days) of the menstrual cycle. Future cycles can be started at 2.5-7.5 mg/d.

♦ CC protocol: CC will be administered at a dose of 100 mg/d for five days starting on cycle Day 3 (+/- 2 days). Future cycles can be started at 50-150 mg/d.

Women may undergo a total of up to four cycles culminating in hCG administration. Patients may begin subsequent cycles immediately following failed cycles, as long as they meet baseline criteria of a negative serum pregnancy test (within four days), and day 3 (+/- 2 days) serum $E_2 <$ 95 pg/ml and day 3 (+/- 2 days) vaginal ultrasound of no ovarian cyst > 3 cm.

Administration of Treatment Drugs: An equal number of patients will be randomized to one of the three treatment arms; thus each patient will receive either injections of gonadotropins or active pill (either CC or AI). Investigators may increase or decrease the dose of the fertility medication in subsequent cycles. Following cycles without ovulation or without development of at least one follicle ≥ 18 mm in average diameter, the dose of injection and pills will be increased in the subsequent cycle. For cycles in which greater than four follicles ≥ 18 mm (in average diameter), the dose of injectable medication and pills will be reduced in the subsequent cycle.

Administration of hCG: In all groups, hCG will be administered at a dose of 10,000 IU IM upon the first occurrence of a) the lead follicle reaching 20 mm (in average diameter), b) two lead follicles greater than 18 mm diameter (in average diameter), or c) the day after the lead follicle reaches 18 mm (in average diameter), or on the day of detection of presumptive ovulation by ultrasound and estradiol monitoring. Core labs will be drawn on this day.

Withholding hCG: hCG will be withheld, and the cycle cancelled if a leading follicle does not reach a mean diameter of 18 mm after 18 days of treatment, endogenous LH surge happens, or increased risk for OHSS and/or high-order multiple gestational pregnancy exists when more than 4 growing follicles develop (mean diameter >18 mm) or the serum E2 exceeds 3000 pg/m around the day of expected hCG administration. Progesterone level will be measured if the cycle is cancelled to assess whether there was an ovulation.

Insemination protocol: One insemination will be performed within 44 hours after hCG administration, and time of insemination from hCG administration will be recorded. For inseminations, each site will utilize its standard semen preparation method and catheter.

Hormonal assays: Patient blood will be drawn, serum separated, and kept at $-70^{O}C$ for processing later at a central laboratory. The following hormonal assays will be conducted each initiation visit: serum pregnancy test and serum progesterone level (if no spontaneous menses after the prior cycle) in the local lab, serum to central core lab for Total testosterone (T), estradiol (E2) and follicle stimulating hormone (FSH).

Cancellation criteria: Cycles will be cancelled if significant adverse reactions develop in response to administered medications, if criteria for withholding hCG administration are encountered, or per patient's request. If a cycle is cancelled prior to hCG administration, the subject may have one additional cycle of study medication, for no more than a total of five cycles of study medication.

Diagnosis of pregnancy: Quantitative beta hCG blood test will be done 2 weeks after the insemination day, and transvaginal ultrasound will be performed 2 weeks after a positive pregnancy test. Biochemical pregnancy will be defined as hCG >5 units/ml 2 weeks after insemination followed by a rising level two days later. Clinical pregnancy rate will be defined as the identification of intrauterine sac(s) with positive fetal cardiac activity in at least one sac, 2-4 weeks after chemical pregnancy identification.

Future Studies: At each blood draw, any remaining blood specimen will be evenly retained in two tubes for banking for future studies as plasma and serum, if patient has signed the appropriate consent.

5.9 Physical Exam

A physical exam with standard pelvic and breast exam will be performed on all patients by a study physician. Height, weight and waist and hip circumferences will be recorded to the nearest 0.1 cm, 0.1 kg and 1 cm, respectively. Waist will be measured at the level of the umbilicus and hip circumference will be measured at the widest diameter. Participants will be weighed while

dressed in light clothing, without shoes. Weight will be collected at each cycle initiation visit, however height, waist and hip circumferences are only collected at the screening and end of study drug visits. Blood pressure will be determined in the right arm in the sitting position. Large cuff will be used as necessary. Blood pressure will be assessed at each visit. Elevated blood pressures (≥160/100) will be repeated following acclimation to the study environment. All patients aged 21 and older should have had a normal Pap smear in accordance with current ACOG guidelines. If not, one should be performed at the screening exam. Patients with cytological abnormalities will need to have these resolved prior to study entry. A hirsutism assessment will be made via the modified Ferriman-Gallwey hirsutism score (Figure 2) by trained study personnel (Hatch, Rosenfield et al. 1981 Aug 1). An acne assessment will be made by trained personnel using a standard acne lesion assessment (count) diagram and definitions (Table 2). Photographic examples of each grade will be provided to investigators as well as training to study personnel. When counting facial acne lesions, it is important that all lesions be counted, both non-inflammatory and inflammatory, examining areas of the forehead, cheeks, and chin and avoiding the nose. Additionally we will measure facial sebum with a Sebumeter (Leyden, Shalita et al. 2005; Thiboutot, Shalita et al. 2005; Leyden, Thiboutot et al. 2006; Pariser, Thiboutot et al. 2006; Thiboutot, Pariser et al. 2006; Thiboutot, Shalita et al. 2006). Androgens can also cause increased sebum production and abnormal keratinization in the pilosebaceous unit, contributing to the development of acne (Chen, Thiboutot and Zouboulis 2002). Patients with complete inactivation of the androgen receptor in type I androgen resistance syndrome do not develop hirsutism and acne (Hargreave 2000; Rosenfield, 2005). Acne and sebum levels may, in addition to hirsutism be a significant prognostic factor for success in the trial.

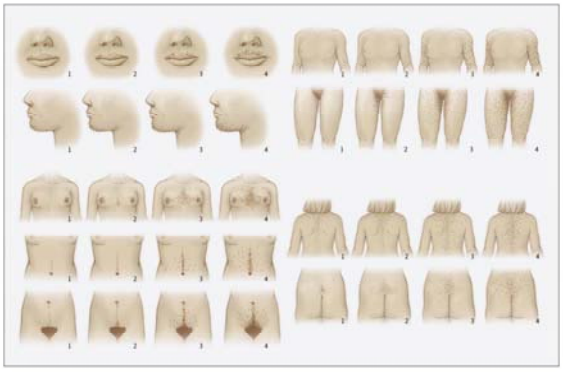


Figure 2. Modified Ferriman Gallwey Hirsutism Scale

Table 2. Acne Lesion Definitions

Name	Description
Open Comedone (Blackhead)	Results when residual skin oil, makeup, dirt, dead skin, and small hairs impact a sebaceous follicle and prevent the pore from functioning correctly. If the pore is open, the comedone will be dark in appearance and is thus called a blackhead.
Closed Comedone (Whitehead)	Non-inflammatory comedone with a white center.
Papule	An inflammatory comedone that resembles a small red bump on the skin.
Pustule	An active infection of the skin that consists of dead skin cells and bacteria. These lesions are spherical in appearance and are filled with pus. Often reddish is color, pustules may be painful and will break open easily if scratched or bumped.
Nodule	A natural progression of a papule. They appear very similar to papules, but are inflamed and penetrate deep into the skin. They are often very painful.

5.10 Transvaginal Ultrasound Exam

An ultrasound exam will be performed with a transvaginal probe. The following measures will be obtained: uterine dimensions, leiomyoma presence and size, other uterine abnormalities, endometrial thickness, ovarian size in three dimensions, the size of the largest ovarian follicle, follicle count in the largest plane and ovarian morphology. Ovarian size is determined by measuring the largest plane of the ovary in two dimensions and then turning the vaginal probe 90 degrees and obtaining a third measurement. Endometrial thickness is the largest anterior-posterior measurement of the endometrium in the sagittal plane. Ovarian volume is determined by the formula for a prolate ellipsoid (length x width x height x $\pi/6$)(Pache, Hop et al. 1991). If the patient has had no prior test of tubal patency, this may be the desired time to perform a sonohysterogram to determine tubal patency.

5.11 Laboratory Exam

Women will present fasting for 12 hours (e.g., overnight) at the initial screening visit. Blood work will be sent as described above in the inclusion and exclusion criteria to identify appropriate study subjects. This blood work is found in Table 3 below and will be run in the local lab. An aliquot of serum from this visit and each subsequent visit will be frozen and maintained for core lab determinations (serum from two 7.5 cc red top tubes at baseline and from each subsequent visit). 1 ml of serum from these visits will be aliquoted into 1.5 cc microfuge tubes and will be stored at –20 to –80 degrees C and batched for periodic shipping to the central core lab facility for eventual assay. The purpose of aliquoting is to preserve basal levels of

potential analytes in a frozen state until assay to avoid the deleterious effects of thawing and re-freezing.

Table 3. Screening labs of AMIGOS study women (run in local labs)

FEMALE LOCAL LABORATORY BLOOD TESTS		
Cycle Day 3 (+/- 2)	**Day 1-10 Fasting***	**Safety Screen (fasting) Labs**
prolactin	[testosterone]	Hemoglobin
FSH	progesterone	Hematocrit
TSH	βhCG	WBC
E2	glucose*	Platelets
	[HgbA1c]	BUN
		Creatinine
		Total Bilirubin
		ALT/AST
		Total Cholesterol
		LDL-C
		HDL-C
		Triglycerides

5.12 Biologic Repository

We will establish a serum bank at baseline prior to randomization. This serum bank will serve a two-fold purpose. One, the serum bank can serve as a repository to run additional serum assays for novel markers of infertility or treatment success that are discovered while the study is ongoing. Second, it will serve as a source of samples for further studies including proteomics, metabolomics, etc.

Baseline serum samples (5cc), DNA, (in the form of two 4.5 cc vials of frozen whole blood, blood spots on FTA cards, and blood clot), and semen (aliquoted into 5 separate NUNC 1.2 cc cryovials, in equal volume) will be collected for storage and eventual DNA extraction at the baseline visit. We anticipate that the clinical sites will collect the serum, separate into 5 to 10 1cc aliquots in cryovials, labeled with study ID, sample type, the date of draw and a unique identifier (in the form of a freezer safe barcode label). The whole blood will also be collected by the sites, and frozen in 2 labeled 4.5cc cryotubes. The FTA collection cards, with 4 125µl dried blood spots, will be stored at the sites at 4^{o} in sealed plastic bags with a desiccant. Semen will be collected at the sites, aliquoted into 5 separate NUNC 1.2 cc cryovials and placed into liquid nitrogen for storage in a dewer at the site until shipment to the repository. The serum and whole blood will be stored at -20 ^{o} C or -80^{o} C at the clinical sites until they are transferred to the repository site, likely on a yearly basis. The FTA blood spot cards will be stored at room temperature.

A detailed repository protocol may be submitted for ethics approval if a clinical site's IRB requires it. This protocol would cover the establishment of the repository, the shipment of the samples off site, the potential uses for the biological materials, and confidentiality safeguards. As such, no samples collected during the course of this study would be removed from the clinical site until the repository location has been established and individual site IRB approvals have been obtained. When shipping the samples to the repository, they will be couriered on dry ice

from the clinical sites to the repository site at infrequent intervals— at most, quarterly, but as infrequently as yearly. The proposed repository will have alarmed and monitored storage, with appropriate back-up -80^{o} C freezer capacity in the event of freezer failure. Alternate uninterruptible power supplies will also be a requirement to prevent catastrophic sample loss. A computerized inventory system with a back-up system is also required, as well as a way for the DCC to get immediate access to the inventory data, preferably on line. The repository site must conform to HIPAA, the NCI statement on best practices for biospecimen resources and to the International Society for Biological and Environmental Repositories (ISBR) best practices for repositories 2008. Additionally, the repository should conform to the NIH statement "NIH Policy Framework on Legal and Ethical Issues Associated with Human Specimen and Data Collections," which is in the final stages of approval. Storage of these samples at the repository will be a minimum of 5 years, and perhaps further into the future. We would expect that DNA extraction of the whole blood would be performed at the repository, in a batch fashion, once the study has been closed.

Subjects will be able to opt in or opt out of these studies via separate signature on the consent form. We will also store leftover serum samples for additional post hoc studies. Study subjects will be separately consented to store and use their leftover serum samples from the study and will similarly be able to opt out.

5.13 Central Core Laboratory

Screening labs to determine eligibility will be run in the local RMN site labs. Given the variability of assays between labs, secondary analyses of baseline predictive factors and response variables will be performed in a central lab at the Ligand Assay Core lab at the University of Virginia. Glucose, insulin, serum androgens (Total T, Androstenedione, DHEAS, as well as estradiol, progesterone SHBG, etc.) will be measured at the Ligand Assay Core according to established assays. We have successfully used this lab, with excellent quality and low pricing due to NICHD supporting the PPCOS study (Legro, Myers et al. 2006; Legro, Barnhart et al. 2007). We coordinated shipment of samples (both baseline and monthly visits) from the RMN sites to this lab without difficulty. These assays all have <10% interassay coefficients of variation (http://www.healthsystem.virginia.edu/internet/crr/ligand.cfm). We have obtained approval to use this facility from the head of the Reproductive Sciences Branch at NICHD, Dr. Lou DePaolo. We will also measure AMH (Jonard, Pigny et al. 2005; Pigny, Jonard et al. 2006) and other assays as needed (for instance, Inhibin A and B) at this core facility, which offers a wide variety of custom and fixed assays. Samples are labeled with a unique patient identifier, type of the visit and date of the visit. Samples are likely to be shipped to the Core lab on quarterly basis (unless mutually agreed otherwise by the Core lab and RMN).

5.14 DNA Core Facility

We will obtain blood for DNA at the Baseline Visit, since all subjects will undergo a thorough and consistent phenotyping process. We have had long term experience in this process (through the NIH sponsored U54 SCCPIR studies on the genetics of PCOS at Penn State and U Penn and through the PPCOS trial). In the first PPCOS trial, the collection of specimens was instituted as an addendum long after the study had begun; thus, half of the completed subjects and dropouts were lost to follow up. Therefore, DNA blood collection will be a part of the initial protocol, though subjects will have the option to opt out of this segment of the study or limit the use of their specimen on the consent

form. Blood drawn in EDTA tubes will be transferred to centrifuge tubes and labeled with a unique patient identifier and the date of draw. These samples will be stored in the RMN Biological Storage Facility until it is sent to a core facility where DNA will be extracted and stored for the future analyses. DNA will be extracted as reported (Urbanek, Legro et al. 1999 Jul 20). Our primary purpose in obtaining DNA is to explore genetic markers that predict response, via pharmacogenomic studies. Our secondary aim is to serve as repository to participate in genome-wide association studies. In both cases there will be no release of personal identifiers and we will obtain a Certificate of Confidentiality as we did in prior studies. In the previous RMN study we successfully utilized the lab of Dr. Richard Spielman, a U54 SCCPIR supported geneticist, who participated in our pharmacogenomic protocol part of PPCOS that identified a novel SNP in a metformin response gene STK11 (Legro, Barnhart et al. 2007). Examples of genes to be tested are found in the table below.

Table 4. Proposed SNP and microsatellite markers

GENE	MARKER ID	ALLELES	MAF [1]	MAF [2]	LOCATION
ESR1	rs2234693	C/T	C: 0.41	C: 0.44	Intron: IVS-401/*Pvu*II 14)
CYP2C9	rs1934963	C/T	C: 0.15	C: 0.16	Intron
CYP2C9	rs1799853	C/T	T: 0.10	T: 0.10	Cys144Arg
CYP2D6	rs3892097	C/T	T: 0.18	T: 0.16	Acceptor Splice Site: 1846G>A

[1] Minor Allele Frequency (MAF) was taken from dbSNP (http://www.ncbi.nlm.nih.gov/SNP).
[2] MAF estimated.

We propose to ship blood on a regular basis to a core lab for DNA extraction and storage or to the RMN Biorepository to pursue pharmacogenomic protocols upon the completion of the trial. We will genotype subjects for a variety of candidate genes, (including estrogen response genes such as the estrogen receptor and P450 metabolizing enzymes) using high-multiplex single-nucleotide polymorphism (SNP) genotyping on an Illumina platform as was done with the PPCOS I Study.

5.15 Quality of Life Measures (QOL)

Mood, quality of life, and sexual function will be assessed at baseline and at the end of the study visit. Quality of life will be assessed by the Medical Outcomes Survey (Prime MD-PHQ), Short Form 36 (SF-36) (Ware JE 1993). Female sexual function will be assessed by the Female Sexual Function Inventory (FSFI) along with the Female Sexual Distress Scale (FSDS) (Rosen, Brown et al. 2000). This measure is considered the "gold standard" paper and pencil assessments of sexual function and has excellent psychometric properties (Rosen, Brown et al. 2000). Male sexual response will be assessed by the International Index of Erectile Function (IIEF), a multidimensional scale for assessment of erectile dysfunction. The measure addresses the relevant domains of male sexual function (erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction) (Rosen et al, 1997). We will assess quality of life relating to infertility with the FertiQoL survey. There may also be some impact on fertility and we will investigate this in our study. The Sleep Habits questionnaire which was the standard measure used to collect data for the 10-year long multi-center NHLBI Sleep Heart Health Study will be administered (Kump, Whalen et al, 1994).

6 Data Analysis

6.1 Data Analysis

Data will be collected prospectively by designated research personnel at each study site, supervised by the site PI. Subject data will be entered into a web-based data management system created by the Data Coordination Center, using only a study ID number.

6.2 Primary Outcome Measurements

The multiple gestation rate per patient in women who receive AI, CC or gonadotropin for up to four cycles will be the primary outcome measurement. We expect near comparable pregnancy rates between the AI, CC, and gonadotropin groups. We will also calculate the pregnancy rate per cycle, cumulative pregnancy rate per patient, and individual cycle pregnancy rate (i.e., the pregnancy rate per cycle). The primary outcome measurement will be the rate of multiple gestational pregnancies (twins or higher order multiple gestational pregnancies) among the women who conceive. We expect the rate of multiple gestational pregnancies to be significantly lower with AI ovarian stimulation, as compared to women who receive CC or gonadotropin stimulation. Twins and high order multiple gestational pregnancy rates will be looked at together and separately. Multiple gestational pregnancies will be diagnosed as the identification of more than one positive fetal cardiac activity in one or more than one sac. Twins or higher order multiple gestations will be defined according to the number of fetuses with cardiac activity. This will be done about 2 to 4 weeks after a positive beta hCG blood pregnancy test. The ultrasound with the maximum number of fetal cardiac activities will be considered.

6.3 Secondary Outcome Measurements

We will analyze the time to conception, the conception rate and a live birth rate obtained with an aromatase inhibitor, as compared to CC or gonadotropins, as well as the multiple gestation pregnancy live birth rate. The rate of cycle cancellation or discontinuation will also be a secondary endpoint.

6.4 Additional Tertiary Endpoints to be Assessed

1. Is there a relationship between length of infertility and pregnancy occurrence and outcome?
2. Is endometrial thickness (late follicular and mid-luteal) different between the groups, and does group and overall population endometrial thickness correlate with pregnancy occurrence and outcome? Does endometrial thickness change over time with additional cycles of ovarian stimulation?
3. Are mid-luteal ultrasound and blood work predictive of who will develop symptomatic ovarian hyperstimulation syndrome, and pregnancy occurrence and outcome?

4. Do locally measured hormonal levels (E2, etc…) correlate well with core lab levels? Is variance greater with type of assay and manufacturer used?
5. Are there genetic or phenotypic determinants of success?
6. Can sperm microarray identify couples more or less likely to succeed?
7. Does perceived stress and self reported quality of life by husband and wife influence success? [Assess by SF-36 and Prime MD]
8. In the case of CC vs. AI randomization, can the physician or patient identify what arm they were randomized to?
9. Is length of luteal phase predictive of pregnancy outcome?
10. Is there a relationship between length of infertility and pregnancy occurrence?
11. Is there a difference in pregnancy rate in the first vs. second vs. third vs. fourth cycle?

6.5 Statistical Analyses

The proportions achieving clinical pregnancies will be calculated on an intent-to-treat basis.

To assess multiple gestation rate differences among the three treatment groups we will use the Trend Test (Armitage, 1955) for ordered binomials. The H_0 of equal population proportions is tested against the alternative ordered hypothesis of H_1: $\pi_1>\pi_2>\pi_3$ for the gonadotropin, CC and AI populations, respectively (see power section below).

For the secondary outcome of pregnancy rate the non-inferiority test will compare the differences among the overall pregnancy rates in the three groups using a 25% reduction in the AI population pregnancy rate compared to the combination of the gonadotropin & CC groups as a basis for the null-hypothesis, a value ($\delta_0=0.25$) that represents the maximum value acceptable as "clinically unimportant" (see power section below).

A further set of analyses will make use of logistic regression (LR) and include, in addition to the dummy coded variable representing treatment, those patient and medical variables expected to be associated with becoming pregnant. Such patient characteristics would include factors such as age, day 3 serum FSH level, length of infertility, and history of prior ovarian surgery.

We will also include selected interaction terms for those factors that may be related to treatment differences. Evaluation of treatment differences in LR should lead to greater power or better estimate of treatment effects by adjusting for prior patient characteristics affecting the likelihood of becoming pregnant.

Treatment effects for a number of tertiary outcomes will also be assessed. These include: 1) average number of ovarian follicles developed per cycle, 2) intrauterine insemination rate (IUI), 3) hormone levels, 4) endometrial thickness or change development, 5) number of adverse events, 6) length of treatment cycle, and 7) cost of treatment. To compare these outcomes among the treatment groups, chi square tests will be used for categorical variables. For continuous outcomes which are approximately normally distributed, t tests will be used. Mann-Whitney tests will be used for ordinal or highly skewed dependant variables. Within-treatment-group

correlations will also be used to investigate the relations of these outcomes to relevant patient characteristics.

To evaluate effects of treatment on number of cycles needed to achieve pregnancy we will use Kaplan-Maier curves evaluated by the log-rank test. Assuming proportional within-group rates over time (cycles), Cox regression analysis will be used to evaluate additional medical or patient factors related to this outcome as well as possible interactions of these factors with treatment.

To assess the power for the primary outcome of multiple births we are conservatively assuming 30%, 27%, and 27% pregnancy rates for the gonadotropin, CC and AI populations, respectively, and a 25% pregnancy loss for each group. In the power analysis we will assume the rates of multiple pregnancies will be 25% in the gonadotropin group, 12.5% in the CC group, and 6.25% in the AI group. The evaluation of power then will be based on ordered binomial H_0 of $\pi_1=\pi_2=\pi_3$ at a significance level of $\alpha = .05$. Here π_1 ,π_2 and π_3 refer to the population proportions of multiple gestations in the gonadotropin, CC and AI groups, respectively. Under the above assumptions, in order to have 80% power to detect the hypothesized differences in multiple gestation rates, we will need 240 subjects in each group (see Table 5); assuming a 20% dropout rate would require 300 subjects in each of three arms, or a total of 900 subjects.

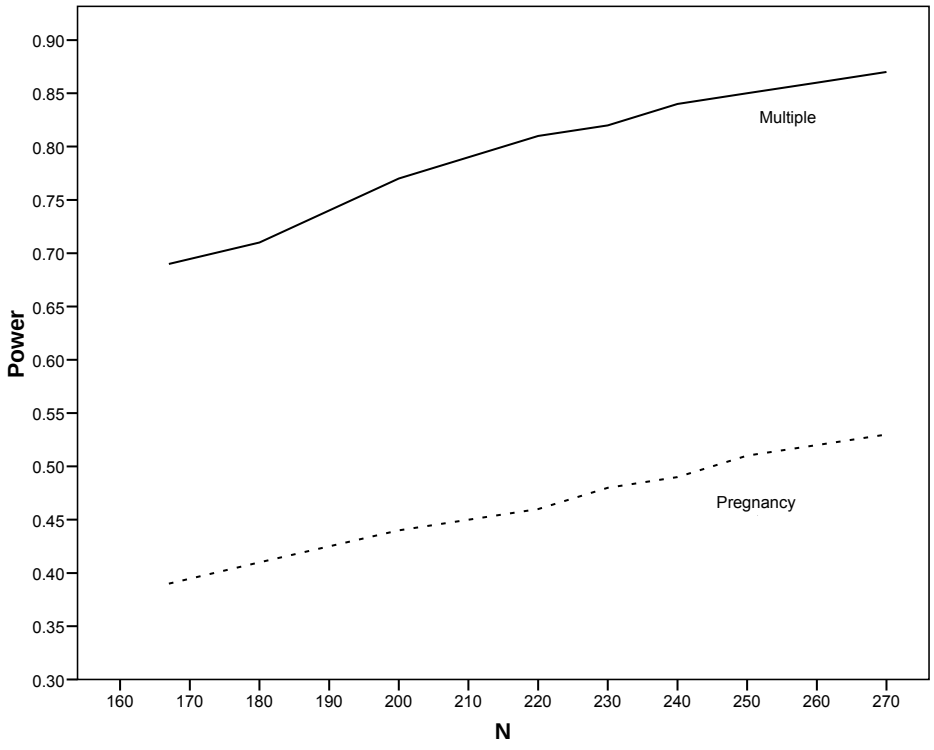
We will also perform a non-inferiority analysis among the gonadotropin, CC and AI treatments with respect to the secondary outcomes of pregnancy and live birth rates. The power for the non-inferiority test for group differences in pregnancy rates assumes 25% reduction in the AI population pregnancy rate compared to the combination of the gonadotropin and CC groups' rates (28.5%). This value is the margin ($\delta_0 = 0.25$) that represents the maximum acceptable reduction as "clinical unimportant". Under H_0 δ, the difference between the combination of the gonadotropin & CC populations' rates (28.5%) and the AI population rate (27%), is $\geq \delta_0$; Under H_1 $\delta < \delta_0$. If we have 240 subjects in the AI group and 480 subjects in the combined gonadotropin & CC group and a one-sided alpha of 0.05, power is approximately 49%. It should be pointed out that when we do the comparisons among the three groups we will adjust for various other predictive factors, e.g., site, age, etc, which should reduce the error term. Consequently, these power figures are conservative.

An interim analysis is planned at the mid-point of the study to assess the overall pregnancy rate (i.e., the three groups combined) while maintaining blinding of treatment assignment in order to assess whether this pregnancy rate approximates the predicted rate of 30-40%, and whether additional subjects may be needed to meet power targets. Since treatment assignments will not be identified, it is not thought that adjustments in significance levels will be required.

Table 5. Pregnancy and Multiple Rate Power Table

N (each arm)	Multiple Rate Test –Exact	Pregnancy Rate Test– Score test
167	0.69	0.39
180	0.71	0.41
200	0.77	0.44
220	0.81	0.46
230	0.82	0.48
240	0.84	0.49
250	0.85	0.51
260	0.86	0.52
270	0.87	0.53

Figure 3. Pregnancy and Multiple Power Graph



7 Technical Aspects

7.1 Study Agent Preparation

We propose to purchase study medication from generic manufacturers or low cost providers. We will overencapsulate the AI and the clomiphene in a double-blinded fashion study. The dose will also allow for individual titration. The gonadotropin and dilutant vials will be kitted, and distributed to clinical sites as needed. Additional information will be provided in the trial-specific manuals of procedures and operations. The study coordinator at each site will be responsible for distributing the supply drug kits, verifying pill/vial counts, and determining that there are adequate medication supplies for existing patients and new patients to be randomized. The PI will ultimately be accountable for administration and accountability of the medication used in this study.

7.2 Concomitant Medications

An inquiry into concomitant medications will be made at the screening visit as well as each subsequent visit.

7.3 Reporting Adverse Events

All serious adverse events (SAEs) that occur from the start of study drug through thirty days after the last dose of study medication must be reported or if the patient is pregnant, 6 weeks following delivery. A serious adverse event is defined as: fatal or immediately life-threatening; severely or permanently disabling; requiring or prolonging inpatient hospitalization; overdose (intentional or accidental); congenital anomaly; pregnancy loss after 20 weeks gestation; neonatal death up to 6 weeks after delivery; or, any event adversely affecting the study's risk/benefit ratio. Additionally, any event that, based on appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above is considered an SAE.

If an SAE occurs and is thought to be related to the study medication, the study medication will be discontinued. Twenty-four hour unblinding will be available through the web-based randomization system to break the randomization code for the individual patient if this is required by the PI for proper treatment of the patient.

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 RMN members-only website], and then emailing the document in PDF format to rmn-dcc@panlists.yale.edu. Subjects 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.

DCC staff will enter the SAE information in the central database and the Safety Surveillance will analyze the SAE to determine if it meets the criteria listed in the OHRP 45CFR46 and/or FDA 21CFR312.32 & 3.14.80.

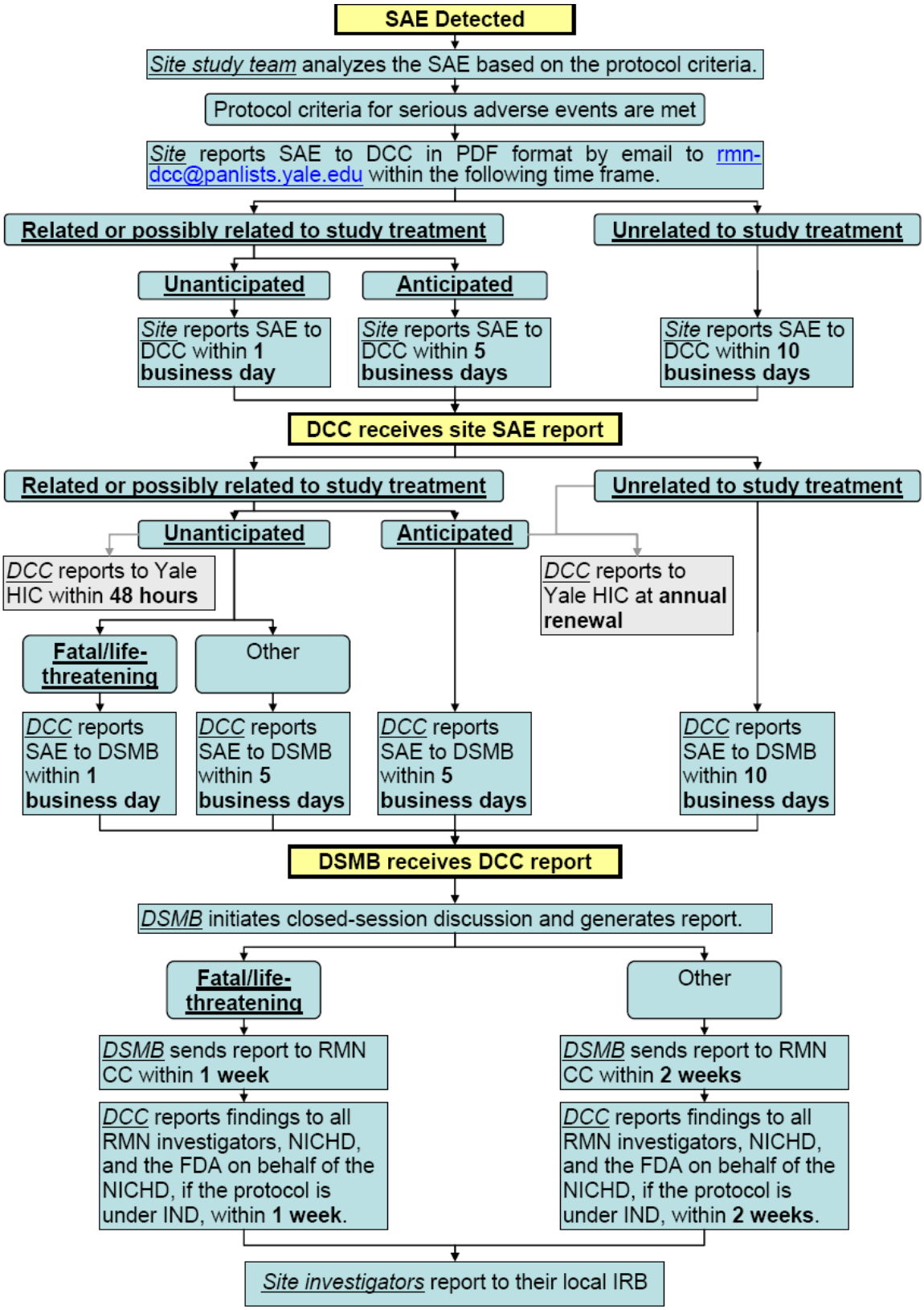
These determinations will dictate timeframes for sites' submission to the DCC, and the DCC's submission to the DSMB:

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 within 5 business days of receiving site report
Anticipated and related/possibly related SAE	Report to DCC within 5 business days of discovery	Notify DSMB within 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 arranged by the NICHD RMN Committee Coordinator [RMN CC]. The DSMB will send a report to the RMN CC 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 RMN CC will then forward the DSMB report to the DCC for the record and appropriate disbursal. The DCC will forward reportable events to all RMN investigators, NIHCD, and the FDA on behalf of the NIHCD if the protocol is under IND. The NIHCD Project Scientist 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 RMN/DSMB Communication Procedure.

Adverse events deemed non-serious will also 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. If an anticipated serious adverse event occurs at a frequency greater than expected, the DCC will notify the DSMB by the end of the next business day of discovery and follow the procedures for reporting serious and unanticipated and related adverse events. The DCC will forward relevant safety information to the DSMB. If an adverse event not initially determined to be reportable to the FDA under 21CFR312.32 is so reportable, the DCC will report the adverse event to the FDA within 15 calendar days after the determination is made.



CFR= Code of Federal Regulations

7.4 Data Collection and Management (including quality assurance/compliance measures)

7.4.1 Data Entry and Forms

Case Report Forms (CRFs) will be developed as the protocol is developed. They will also be implemented in a Web-based Oracle data management system. 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.

7.4.2 Features of Data Management System

Features of the data management system include study definition; different types of data entry (including double entries and complete audit trail); forms control; query capture, reporting, and resolution; dictionary coding of Adverse Events (AEs) and medical terms; clinical data review Tools; 21 CFR Part 11 and CDISC compliant; and prepares data and CRF images to FDA e-Submission Standards. 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 Data Center.

7.4.3 Data Security

A data server and Web server will be used. These two servers will be separated and managed by Yale University ITS Data Center. 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. 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. Access keys will be changed 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.

7.4.4 Data Quality Control

7.4.4.1 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.

7.4.4.2 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.

7.5 Study Monitoring

A monitoring plan that satisfies the Guideline for Monitoring of Clinical Investigations of the National Cancer Institute 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 required by the FDA (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 in 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, the Steering Committee, and NICHD 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. This report will also be forwarded to the Steering Committee for review. The monitor will be responsible for maintaining regular contacts between the investigators in the clinical sites and the RMN. When the study ends, the monitor will also visit the clinical site to provide assistance for close-out.

7.6 Data and Safety Monitoring Board

The NICHD has established an independent Data and Safety Monitoring Board (DSMB) to review and interpret data generated from RMN studies and to review protocols prior to their implementation. Its primary objectives are to ensure the safety of study subjects, the integrity of the research data and to provide NICHD with advice on the ethical and safe progression of studies conducted in the RMN. The DSMB advises on research design issues, data quality and analysis, and research participant protections for each prospective and on-going study. A copy of the DSMB Charter can be found in the appendix.

The DSMB members are appointed by the Director of NICHD in accordance with established NIH and NICHD policies. DSMB members are experts in and represent the following fields: biostatistics, epidemiology, infertility, gynecology, andrology and ethics. The NICHD Committee Coordinator is responsible for scheduling regular committee meetings, recording all meeting minutes and summarizing the committee recommendations for the Steering Committee and NICHD. Steering Committee members are prohibited from attending closed sessions of the

DSMB. Open sessions may be attended by Steering Committee members or Chairperson when requested by NICHD and the DSMB.

The DSMB meets regularly at a time and place of their choosing to review Network randomized trial protocols with respect to ethical and safety standards, monitors the safety of on-going clinical trials, monitors the integrity of the data with respect to original study design, and provides advice on study conduct. The DSMB periodically monitors data quality, including protocol adherence and adverse events. As outlined in the protocols, the DSMB will conduct interim evaluations of the data. It may recommend protocol modifications based on concern for subject welfare and scientific integrity.

7.7 Reporting

Administrative Reports will be prepared by the DCC, and they include monthly and quarterly reports to the RMN on accrual, data quality and study compliance and reports presented in the packet produced for each Steering Committee and DSMB. Statistical reports include reports to the SC and AB from the data analysis, and special reports for scientific manuscripts.

Statistical Reports will be generated in SAS. Reports are provided for DSMB reviews, and for final analysis of study results in preparation for scientific publications. The content of the interim reports will be very complete, and will serve as the template for the final report of each study, which in turn will form the basis of the publication of the results. Our proposed reports to the DSMB would include the following: a protocol description and history; accrual rates; site performance in terms of accrual; eligibility; protocol violations; data accuracy and minority representation; patient characteristics by treatment and site; and the rate of adverse experiences.

7.8 Obligation of the Investigator

7.8.1 IRB Review

The site PI is responsible for submitting the approved protocol and consent form to the local IRB for review. The IRB must approve all aspects of the study as detailed in the protocol, including the patient informed consent form. It is anticipated that there will be minor site-specific changes in the consent form. The IRB must periodically review the status of the study at appropriate intervals not exceeding one year. The site PI will also be responsible for submitting revisions to the protocol to the IRB, as directed by the DCC, and promptly communicating serious adverse events that result during the study, to both the local IRB and the DCC. After the approval, the informed consent and IRB approval (or amendment) letters must be forwarded to the DCC.

7.8.2 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 subjects can be identified by audit. The PI must maintain adequate records pertaining to subjects' files and other source data for a minimum of 5 years after completion of the study.

7.8.3 Establishment of Pregnancy Registry

As per the recommended guidelines we intend to establish a pregnancy registry for this trial to establish outcomes of pregnancy. We will track the outcomes of all randomized subjects who have a positive serum pregnancy screen during the course of this study. We will record biochemical pregnancies (defined as positive serum pregnancy screens without ultrasonically detected pregnancies), ectopic pregnancies, and all intrauterine pregnancy losses both before and after 20 weeks including missed abortions, spontaneous abortions, elective abortions, fetal demises, and stillbirths. We will review pregnancy and birth records of the mother and of the fetus to establish neonatal morbidity and mortality and the presence of fetal anomalies. The infant will be examined at each site within 60 days of birth by a dysmorphologist for potential congenital anomalies.

Fetal anomalies will be classified using the CDC birth defects code list (http://www.cdc.gov/ncbddd/bd/documents/MACDPcode%200807.pdf). We will extract from these records concomitant medical and obstetrical conditions, exposure information on all other medical products used, including prescription products, over-the-counter (OTC) products, dietary supplements, vaccines, and insertable or implantable medical devices. We will file individual case reports for all congenital anomalies which will be considered a serious adverse event. Additionally we will provide to the FDA a written annual status report of the pregnancy registry as specified in the guidelines above. We intend at a minimum to perform an annual parent directed screening questionnaire to assess the infant's developmental milestones for the first three years after birth as recommended by the FDA and to review the child's CDC growth curve and medical records. The registry will follow children until age 3. Additionally, babies will be evaluated by a dysmorphologist within the first 60 days of birth. A survey will be administered to the mother annually that will screen for cognitive, and neurodevelopment up to age 3. If medical issues arise from the survey, a medical record review will be performed for more extensive assessment.

7.9 Regulatory Requirements

The DCC will work with NICHD staff by providing them with clinical study data, reports, and other support as required for AE Reporting and IND submissions. 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), and IND applications. For example, the DCC Project Managers will register this clinical trial in a timely manner with ClinicalTrials.gov via a web based data entry system called the Protocol Registration System (PRS).

7.10 Protocol Amendments

Once the protocol is approved by the Steering Committee, it is then reviewed by an Advisory Board and 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 Network. In the meantime, because the DCC administers all patient care costs for the RMN, the DCC will

promptly issue subcontracts to the participating sites based on the cost agreements made by the Steering Committee and NICHD.

After the protocols are approved by the RMN and the Steering Committee decides that changes are necessary for scientific or clinical reasons, the DCC will facilitate the procedure timely and diligent fashion. The RMN 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 RMN, they will be submitted to the IRB and DSMB reviews and approvals.

8 Publication Policy

8.1 Overall Policy

The publications policy proposes guidelines for publications that originate from our collaborative Reproductive Medicine Network. Decisions concerning publications shall be determined by consensus (majority vote) of the collaborating principal investigators (or designate) noted below as the "Network". 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 RMN ("Related Publications") or from other groups utilizing RMN data and/or specimens "Outside Studies" (those utilizing data and/or specimens from the RMN 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.

8.2 Main Study

A Main Study is a Network study designed prospectively by an investigator independent of other studies. Generally that investigator becomes Lead investigator of the protocol and Chair of the Protocol Subcommittee. 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 Subcommittee Chair 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).

8.2.1 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 RMU and the DCC rather than merely identify the "Reproductive Medicine Network". Each RMU and 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 RMU will be responsible for submitting the names of the two authors from that unit and designating them as either the primary and secondary authors of the unit. No more than 2 authors may represent a RMN site. An ancillary site (such as a SCCPIR) may only have 1 investigator.
The Steering Committee Chair and NIH Project Scientist will be authors. Occasionally, additional authors, both within and outside the RMN may be appropriate. In these cases, the final decision will be by Network consensus (majority vote of the steering committee required).

2. First Author: The lead investigator initiating the protocol, chairing the Protocol Subcommittee 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 Network 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 Protocol Subcommittee. In the event that the initiating protocol investigator declines first authorship or fails to meet the timeline determined by the Steering Committee (as determined by majority vote) and monitored monthly, the next RMU 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) RMU investigators, additional outside investigators with a limit of one author per site (e.g. SCCPIR investigators if applicable), followed by the Steering Committee Chair, NIH Project Scientist, and then the authors of the DCC.

Authorship Order Category	Description
1	Lead Investigator of the Protocol (N =1)
2	Primary RMN Investigators of the Protocol (N = 6); DCC investigator (N = 1)
3	Outside Investigators (i.e. Primary Investigator of SCCPIR sites) (N to be determined)
4	Additional Investigators (by Steering Committee vote) (N to be determined)
5	Secondary RMN Investigators (N = 7)
6	Steering Committee Chair (N = 1)
7	NIH Project Scientist (N = 1)
8	DCC PI (N = 1)
9	"for the NICHD Reproductive Medicine Network"

It is anticipated there will be up to 18-25 authors per major manuscript. The authorship order of the RMUs and outside sites will be based upon subject recruitment, data accuracy and promptness of data report according to the chart below:

Investigative Sites	# Subjects 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 subject 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 with the authorship order ending with the footnoted statement "for the Reproductive Medicine Network". 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 Advisory Board and 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, subject recruitment and enrollment, study conduct, data analysis, and preparation of the manuscript.

8.2.2 Minor Publications

Minor studies are defined as those in which the hypotheses would not be the main elements of Network 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 RMN 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 Steering Committee (majority vote of SC 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 (RMU) PI.

8.2.3 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 Network 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 Main Study Protocol Subcommittee and the Steering Committee. 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 RMN 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 NICHD RMN and the DCC provides data analysis. Multi-center Ancillary Studies require the approval of the Main Study Protocol Subcommittee and the Steering Committee.

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 RMN primary investigators, etc. A center not participating in the ancillary study would not receive authorship unless by majority vote of the steering committee.

8.2.4 Pilot Study

A Pilot Study is a preliminary study that generates data to help in the design of a Main Study and is the responsibility of the Main Study Protocol Subcommittee. The DCC collaborates with the Protocol Committee to complete the analysis, which may or may not generate an abstract for presentation and/or a manuscript for publication. The DCC writes a Final Report if there is sufficient data to justify one. It is not expected there will be any secondary analyses resulting from a Pilot Study.

8.2.5 Related Publications

A related publication is one that has had significant input from members of the RMN Steering Committee 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 Steering Committee, 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 NICHD Reproductive Medicine Network in the author line of the publication according to the format of the journal.

8.2.6 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 NICHD, the RMN, and the Protocol Subcommittee 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 NICHD Reproductive Medicine Network." The authors will be requested to cc the submitted manuscript to the NICHD program official to ensure compliance. These policies apply to both Network centers and outside centers.

8.2.7 Presentations

Network 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 P & P committee. Once data are published in at least abstract form, all members of the Network 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. In addition, they must include both the NICHD RMN logo and NIH Department of Health and Human Services logos that can be found on the Network web site.

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10 Human Subjects/Informed Consent/Female

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

Consent Version: April 5, 2011

Female Subjects

Title of Study: Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation

Principal Investigator (PI): *[insert name of principal investigator]*

Funding Source: NICHD: Reproductive Medicine Network

Purpose

You are being asked to be in a research study designed to look at three medications — gonadotropin (hMG) vs. clomiphene citrate (CC) vs. aromatase inhibitors (AI) — to determine whether AI will produce rates of ovulation, pregnancy, and successful live birth in infertile women that are comparable to gonadotropin and CC treatments, while reducing the rates of multiple gestation often seen with those drugs. The gonadotropin that will be used in this study is hMG (Menopur®), a combination of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH). This drug has been approved by the United States Food and Drug Administration (FDA) for the treatment of infertility. Clomiphene Citrate (CC) has also been approved by the FDA and is also used for the treatment of infertility. The aromatase inhibitor (AI) that will be used in this study is Letrozole, which is an FDA approved medication for breast cancer. This medication has recently been used to induce ovulation (causing you to release an egg from the ovary to increase your chance of pregnancy), but is not yet FDA approved for this use. You have been asked to participate because you and your partner have not been able to conceive. This study is being conducted at *[insert institution name]* and its affiliated clinics. The estimated number of study participants to be enrolled at *[insert institution name]* is about *[insert site specific number]* as well as about 900 throughout the United States.

In this research study, you will be asked to come to the clinic to visit your study doctor and/or the study coordinator approximately eight times in each of the four treatment cycles, for a total of approximately 32 times if you compete all four cycles. If you conceive prior to the last cycle, the number of visits will be fewer. You should know that this number of visits is similar to the number of visits which would occur with standard care of women receiving gonadotropins. Your participation in this study will last approximately 20 weeks. If you conceive, we will monitor you throughout the entire length of your pregnancy through six weeks beyond delivery. We will continue to follow you and your offspring for 3 years by written survey and phone via the RMN Pregnancy Registry if you consent to this additional monitoring.

Please read this form and ask any questions you may have before agreeing to be in the study.

STUDY PROCEDURES

If you agree to take part in this research study and before any study-related procedures are performed, you and your partner will each be asked to read and sign an informed consent form stating that you wish to participate.

Description of Procedures

If you agree to participate in this study, you will go through a screening process to determine if you are eligible to participate. The study doctor or coordinator will obtain this signed informed consent form from you and will obtain personal information about you as well as emergency contact information. Blood work and other tests will be done to determine if you are eligible. This blood work will consist of hormone levels to evaluate you for specific causes of infertility. If no reason for your infertility is identified, then you will be considered to have unexplained infertility. You will also have blood work done to ensure your kidneys and liver are functioning normally and that you are not anemic. You will be asked to have your partner provide a sample of his semen for testing, for which he will sign an informed consent document beforehand. You will also provide any results of any tests you have had to see if your tubes are open (such as a hysterosalpingogram, sonohysterogram). These tests are needed to assess other possible infertility factors.

If you and your partner qualify for this study and wish to participate, you will be randomized into a medication group. Below is a description of each visit and the requirements in further detail.

Screening Visit

The screening visit will be done before you begin the trial. At this visit, we will be sure that you have read, understood, and signed the informed consent. If you have any questions these will be answered before you sign the consent form. You will be asked a number of questions about your general medical health and your reproductive history, and will be asked to list the medications you are taking or have taken in the last 30 days. You may still participate in the study if you have taken Clomiphene, Letrozole or gonadotropins previously.

- You will provide a blood sample for a pregnancy test.
- You will have a complete physical examination including vital signs, height, weight, BMI, hip and waist measurements, and pelvic and breast exam. You will have a pap smear done if you are twenty-one or older and have not had one done within the time period specified by current ACOG guidelines.
- The amount of acne lesions on your face will be counted as well as measuring the oil on your forehead with a Sebumeter will be performed.
- You will have a Hysterosalpingogram (HSG) or Sonohysterogram (SHG) if there has not been previous documentation or suitable alternative (successful pregnancy) in the past three years.
- A hirsutism (excessive hair growth) assessment will be completed
- A transvaginal ultrasound will be done to measure your uterus and look at your ovaries.

- You will also have blood drawn (about 8 tablespoons) for hormonal testing, including FSH, TSH, prolactin, progesterone, estradiol, and be tested for safety labs such as a blood cell count, fasting glucose level, lipid panel, and kidney/liver tests.
- You will be given questionnaires to complete. A female sexual function index (FSFI) and female sexual distress scale (FSDS) will assess your sexual function. A Medical Outcomes Survey (Prime MD-PHQ) and the Short Form-36 (SF-36) assess your daily activities. FertiQoL will assess how your infertility affects your thoughts and feelings. The Sleep Habits survey will assess your sleep habits. You will be free to skip any questions that you would prefer not to answer.
- You will also have pre-conception counseling done during this visit to identify any problems that may lead to complications during your pregnancy.
- You will fill out a questionnaire to identify if there are any genetic diseases in your family and will receive counseling if this is the case.
- Additionally, you will be offered optional blood tests to determine if you are immune to rubella (German Measles) and varicella (chickenpox), or to see if you are infected with the HIV virus. If these tests are abnormal, you will be referred for appropriate treatment and counseling, however, they will not prevent you from being eligible for this study.
- Your partner will need to provide a semen sample for analysis.
- You will be given a prescription for either prenatal vitamins or folic acid, which you will take daily.
- You will be given instructions to complete menstrual and intercourse diaries and these will be dispensed at this time.
- You will be instructed to have insemination with your partner's/spouse's sperm within 44 hours after you receive the hCG injection.

Randomization

When you have met all of the criteria above for participation, you will be instructed to call on the 1st day of your period to schedule your Visit 1 (treatment visit). You will be randomized on day 1 to 5 of your menstrual cycle to the study medication. You will be randomized into a research group by a procedure similar to the toss of a coin. Neither you nor your physician will be able to decide to which group you are assigned. You will receive kits containing either one type of pill (Clomiphene Citrate, or Letrozole) or injectable gonadotropin (hMG). All of the pills will look identical. If you are randomized to take a pill, neither you nor the doctors in the study will know which treatment you have received until the study has been completed. You and your partner will be given instructions to learn injectable medication self administration or partner administration, as well as logistics of cycle monitoring for performance of ultrasound exams and blood draws. You will have a 1 in 3 chance of receiving either of the three study drugs.

Treatment protocol:

- If you are randomized to injectable gonadotropin, you will need to do a daily injection of gonadotropin starting on day three to five of the menstrual cycle and continuing until the day of hCG administration. The injection training will teach you and your partner how to do these injections and how to adjust the dose. If you are randomized to take a pill you will take a daily oral dose of 5 mg of the AI or 100 mg

of CC for five days starting on day three to five of the menstrual cycle. This dose may be adjusted for cycle 2, 3, and 4.

A decision will be made by your study doctor whether to increase or decrease dosages. You may undergo a maximum of 4 cycles.

Visit 1 (Treatment Visit) Baseline (Day 3 +/- 2 days of the menstrual cycle)
You will have fasting blood drawn (approximately 2 tablespoons) to confirm absence of pregnancy, and to look at your hormone levels. Blood for testing Chlamydia antibodies will also be obtained; however, Chlamydia titers would not be run until the study closes, and results would not be made available to your doctor for the purposes of clinical care. If you have a concern about a recent or previous pelvic infection, including Chlamydia, you should discuss this with your gynecologist. You will have a transvaginal ultrasound. Your study medications will be dispensed at this time if your Estradiol (hormone) level is at the appropriate level, your ultrasound results are within a normal range, and your serum pregnancy test is negative. You will receive either over-coated pills containing CC or AI, or a kit of gonadotropin for injection. You will be instructed to start your pills or injections that day.

Visit 2 (Gonadotropin Group= Cycle Day 7-9, CC/AI Group= Cycle Day 8-12)
A transvaginal ultrasound will be performed and you will have blood drawn (approximately 2 tablespoons) to look at your hormones. You will report any adverse events you have experienced during the study.

Visit 3 and above
These visits will be conducted on an individualized basis until hCG administration. A transvaginal ultrasound will be performed and you will have blood drawn (approximately 2 tablespoons) to look at your hormones. You will report any adverse events you have experienced during the study.

hCG visit:
When your main follicle (cyst which contains an egg) gets to a certain size, you will stop taking the study medication and will be told to self- or partner-administer an injection of hCG at a dose of 10,000 IU. You will also need to get blood tests and an ultrasound exam. This visit may not occur and the cycle may need to be cancelled if the lead follicles become too large or too small after 18 days of treatment, or if your hormones levels are not in the appropriate range.

Insemination day visit: The visit may happen the day after hCG administration if your hormones are at the appropriate level for conception. You will have blood drawn (approximately 2 tablespoons) to look at your hormones. You will report any adverse events you have experienced during the study.

Post-insemination visit:
This visit will happen one week after insemination. A transvaginal ultrasound will be performed and you will have blood drawn (approximately 2 tablespoons) to look at your hormones. You will report any adverse events you have experienced during the study.

Pregnancy test visits:

Two weeks after insemination a blood pregnancy test will be done (1/2 tablespoon). You will report any adverse events you have experienced during the study.

Cycle 2-4

If your pregnancy test is negative after a cycle, you may start another cycle of treatment. You may participate for a maximum of 4 completed cycles. Each cycle will be a repeat of visits 1 through the pregnancy test visit. A cycle may be cancelled if any significant adverse reactions develop in response to the medications, if you are unable to have hCG, or if you request the cycle to be cancelled. If there are residual cysts of the ovaries larger than 3 cm then you may be asked to skip the next cycle. If you do not complete a cycle, you may be allowed to participate in a fifth cycle.

Pregnancy ultrasound:

If you have a positive pregnancy test at any point during this study, you will have an ultrasound done 14-21 days after the positive test.

Repeated pregnancy ultrasound:

You may need additional ultrasounds done to evaluate the progress of the pregnancy. After delivery, we will request the hospital records of the labor & delivery department where you gave birth to your baby(s).

Follow up during your pregnancy will be arranged with your regular doctor for prenatal care. If you don't have a doctor who delivers babies, you will be referred to one.

End of Study Drug Visit

All patients will return for an End of Study Drug Visit, during which the baseline measurements you gave during screening visit will be repeated. If you do not conceive, this visit will take place at the end of the 4th treatment cycle. If you do conceive, the visit will take place as soon after pregnancy as possible. A complete physical exam will be performed. You will bring any remaining study medications. Fasting blood will be drawn for hormones, and to repeat your safety labs to be sure the medications haven't changed anything (about 4 tablespoons). You will be asked to complete the SF-36, Prime MD-PHQ, FSFI, FSDS, FertiQoL and Sleep Habits questionnaires, as you did at the screening visits. If you do conceive, you will also be followed throughout the pregnancy by phone consultations. If you consent to take part in the RMN Pregnancy Registry, you will be asked to bring the baby in for an exam within 60 days of birth to check the baby for congenital malformations, and you will also be contacted every year for three years to collect information for a registry of babies.

Certificate of Confidentiality To help us further protect your privacy, the researchers have obtained a Certificate of Confidentiality from the National Institutes of Health (NIH) / National Institute of Child Health and Human Development (NICHD). This Certificate means that the researchers cannot be forced (for example by court order) to disclose any information that might identify you to any federal, state, or local court. A Certificate of Confidentiality does not prevent you from voluntarily giving information to others about yourself or your involvement in this research. You should know that we may provide information to your health care providers if we suspect that you may harm yourself or others. We will not release any information collected as part

of the research regarding use of illicit drugs and testing for drugs done on samples collected for the research.

BENEFITS

The possible benefit to you for taking part in this research study is the medication(s) and treatments of ovarian stimulation and intrauterine insemination may help you to become pregnant. The information from these blood tests will let you know more about your health such as the levels of hormones involved in reproduction in your blood. The initial ultrasound examination will evaluate your pelvic anatomy, which may identify abnormalities such as ovarian cysts or abnormalities of the uterine lining. Additionally you may experience regular menstrual bleeding and normal ovulation on these medications. No benefit is guaranteed.

RISKS/DISCOMFORT AND INCONVENIENCES

Below is a table listing all tests or procedures involved in this research and their related discomforts and risks.

Test or Procedure	Discomforts and Risks
Standard venipuncture for blood work	Slight pinch or pin prick, discomfort, black and blue mark at the site of puncture, small blood clot, infection or bleeding at the site, and fainting during the procedure
Transvaginal ultrasound	Abdominal or pelvic discomfort
Sonohysterogram or Hysterosalpingogram	Pain, bleeding, damage to the uterus, pelvic infection, interrupting an unrecognized pregnancy, small amount of radiation exposure, allergic reaction to the radioactive dye
Clomiphene Citrate	Visual changes (such as blurring of vision, double vision, floaters), abdominal pain, nausea, vomiting, constipation, mood changes, headache, hot flashes, fatigue, abnormal endometrial thickening, multiple pregnancies, formation of ovarian cyst, breast discomfort, abnormal uterine bleeding, and bloating
Letrozole	Fatigue, dizziness, nausea, hot flashes, arthritis pain in your joints, back pain, increased cholesterol levels, formation of ovarian cysts, multiple pregnancies

Gonadotropin	Pain at the injection site, ovarian cysts, abdominal pain, nausea, vomiting, fatigue, multiple pregnancy, ovarian hyper-stimulation syndrome (which can cause massive enlargement of your ovaries, with collection of fluid in your abdominal cavity and around your heart and lungs. This may become so severe that it requires hospitalization and even admission to the intensive care unit, or death).
Insemination	Vasovagal response (feeling lightheaded, dizzy, sweating); possible infection.
Infertility treatment	Emotional distress at various degrees.

It is not expected that patients will have all of these side effects. If you are feeling fatigue or dizziness associated with these medications, caution should be taken while driving or operating machinery. You will be assigned to a treatment group by chance. The treatment you receive may prove to be less effective or to have more side effects than the other research treatments or other available treatments.

Side effects are usually temporary and manageable. However, it is possible they could be more serious. In addition to the risks described above, there may be unknown risks we cannot predict while participating in this research. It is important that you notify your study coordinator if you experience any of these symptoms listed above and keep accurate documentation of these side effects on your daily journal logs. The investigators will let you know if they learn anything that might make you change your mind about participating in this research. You should check with your study doctor before starting any new prescription, over the counter medications, vitamins or herbal supplements.

Knowledge of treatment assignment

If you have been randomized to a pill treatment group, you will not be able to learn which treatment you received until after the conclusion of the study and analysis of the results.

PREGNANCY/FETAL RISK

Although these drugs may result in pregnancy, there is no guarantee that this will result in a live birth. Clomiphene has been associated with a 12.5% multiple pregnancy rate. Multiple pregnancies are more likely to end early in preterm labor and are more likely to experience most pregnancy complications including diabetes and hypertensive disorders of pregnancy. The multiple pregnancy rate with Letrozole is not known, but is probably more than the natural rate (~1%) but less than clomiphene. The multiple pregnancy rate with gonadotropins is 25%. The pregnancy may also lead to a miscarriage or may implant outside the uterus (i.e. a tubal or ectopic pregnancy) and require further therapy including surgery to treat. Finally the use of these drugs may be associated with an increased risk for fetal malformations, though no specific

pattern has been associated with either drug. Letrozole has been shown in laboratory animals to be embryotoxic (cause death of embryos), fetotoxic (cause death of fetuses), and possibly teratogenic (cause congenital malformations, i.e., "birth defects). Letrozole and clomiphene citrate have been shown to be genotoxic (cause abnormalities to genes) in *in vitro* laboratory tests.

The study also may include risks that are unknown at this time. It is important that you promptly report any side effects to your study coordinator or study physician.

If you become pregnant during the study, you should inform the study doctor immediately. The study doctor and sponsor will follow the progress of your pregnancy and will request access to you and/or your infant's medical records for up to at least delivery, if applicable.

UNKNOWN RISKS

Since the study drug is investigational when taken alone or in combination with other drugs, there may be other risks that are unknown. All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life-threatening.

If at any time during the study there is concern that you have a reportable communicable disease (i.e., certain sexually transmitted diseases or HIV), this information will need to be reported to the State Health Department.

ALTERNATIVE TREATMENTS

You may elect not to participate and talk to your doctor about other therapies for inducing (causing) ovulation to help you conceive. Clomiphene Citrate and gonadotropin can be obtained without being a part of this study, as can Letrozole (although Letrozole use would be for a non-FDA approved use of this medication).

STUDY COSTS

The physical exam, ultrasound(s), blood tests, and medications that are required parts of the study will be provided at no cost to you if not covered by your insurance company. All study procedures once you have started the medication, if performed for the purpose of the study, will be paid for by the study. You will not incur any additional costs as a participant in this study. The costs of the semen analysis, the test to determine if your tubes are open (SHG), and prescriptions for prenatal vitamins (or folic acid) and the cost of the medications will be provided if not covered by your insurance company.

You or your insurance will be responsible for paying for the blood tests not related to the study, any further testing or treatment related to the pre-conception counseling, as well as the cost of the prenatal vitamins (or folic acid). You or your insurance company will also be responsible for the costs of any additional tests, monitoring or treatment for ovarian hyper-stimulation syndrome, and all pregnancy related costs which occur while in this study.

You will receive no monetary compensation for participating in the study. If you conceive, pregnancy care (whether for a normal intrauterine pregnancy, a pregnancy which results in a miscarriage, or an ectopic pregnancy outside the uterus) will not be provided as part of the study and you will need to find a doctor to provide this care, or one will be recommended to you. The costs of your prenatal care after this point and costs of your delivery and any complications of your pregnancy will not be covered by this study. Therefore you, or your insurance carrier, will be responsible for these costs.

COMPENSATION

You will not be paid for taking part in this study.

RESEARCH RELATED INJURIES

In the event that this research-related activity results in an injury, treatment will be made available including first aid, emergency treatment, and follow-up care as needed. Cost for such care will be billed in the ordinary manner to you or your insurance company. No reimbursement, compensation, or free medical care is offered by *[insert institution name]* or its affiliated agencies. If you think that you have suffered a research related injury, contact *[insert name of principal investigator]* right away at xxx-xxx-xxxx.

CONFIDENTIALITY

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. You will be identified in the research records by a code name or number. Information that identifies you personally will not be released without your written permission. However, the study sponsor, the Human Investigation Committee (HIC) at *[insert institution name]*, or federal agencies with appropriate regulatory oversight [e.g., Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), Office of Civil Rights (OCR), etc.] may review or copy your confidential study-related records which may identify you by name. Therefore, absolute confidentiality cannot be guaranteed. If the results of this study are published or presented at meetings, you will not be identified.

When the results of this research are published or discussed in conferences, no information will be included that would reveal your identity.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

VOLUNTARY PARTICIPATION/WITHDRAWAL

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you decide to take part in the study you can later change your mind and withdraw from the study. You are free to only answer questions that you want to answer. You are free to withdraw from participation in this study at any time. Your decisions will not change any present or future

relationship with *[insert institution name]* or its affiliates, or other services you are entitled to receive.

Any time your participation is ended or if you withdraw voluntarily from the study, you may be asked questions about your participation in the study. You may also be asked to have any laboratory tests and physical examinations that the study doctor considers necessary for your own safety.

NEW FINDINGS

During the course of this study, you will be informed of any significant new findings (either good or bad) that might cause you to change your mind about your continued participation. This can include changes in the risks or benefits resulting from participation in the research or new alternatives to participation in the study. If significant new information is provided to you, we will ask you and your partner to sign new consent forms that say you still want to be in the study.

QUESTIONS/EMERGENCY CONTACT/IRB CONTACT

If you have any questions about this study now or in the future, you may contact *[insert name of principal investigator]* at xxx-xxx-xxxx or one of his research team members at the following phone numbers xxx-xxx-xxxx. If you have questions or concerns about your rights as a research participant, the Chair of the Human Investigation Committee can be contacted at (xxx) xxx-xxxx. If you are unable to contact the research staff, or if you want to talk to someone other than the research staff, you may also call (xxx) xxx-xxxx to ask questions or voice concerns or complaints.

PRIMARY CARE PHYSICIAN / SPECIALIST NOTIFICATION OPTION
Please indicate below whether you want us to notify your primary care physician or your specialist of your participation in this study.

_____ Yes, I want the study doctor to inform my primary care physician/specialist of my participation in this study.

_____ No, I do not want the study doctor to inform my primary care physician/specialist of my participation in this study.

_____ I do not have a primary care physician/specialist.

_____ The study doctor is my primary care physician/specialist.

If you would like us to contact your primary care physician or specialist, please provide as much information below as possible:

Name of Primary Care Physician: _____

Address of Primary Care Physician: _____

Phone number of Primary Care Physician: _____

Optional Blood Repository Collection

As part of this study, we are obtaining a sample of your blood to be stored by the Reproductive Medicine Network for future use. If you agree, your blood will be collected at the baseline visit and shipped to a central location and stored for a minimum of 5 years, and perhaps further into the future. Your sample will be tested for DNA and to measure other substances in your blood. The results of these tests will not have an effect on your care, and neither your doctor nor you will ever receive results of these tests. If you have any questions, you should contact *[insert name of principal investigator]* at xxx-xxx-xxxx.

If you agree to allow us to collect and store a blood sample from you for future use, your sample will be labeled with study ID, sample type, the date of the blood draw and a unique identifier, in the form of a barcode label. You will not be identified on your sample and your sample cannot be directly linked back to you. These samples will be stored in a locked laboratory at the *[insert institution name]* until shipment to the repository. Your blood samples may be shipped and stored in a biological specimen repository coordinated by the Reproductive Medicine Network pending approval by the Human Investigation Committees at all the participating sites. If you consent to the collection of your blood for the repository, it will be kept indefinitely or until the sample is exhausted by the Reproductive Medicine Network.

You should initial below to indicate your preference for the collection of your blood sample for the repository:

_____ I **give my permission** for my blood sample to be collected and sent to the repository for future testing.

_____ I **decline my permission** for my blood sample to be collected and sent to the repository for future testing.

Participant: By signing below, you indicate that you have read the information written above and have indicated your choices for the optional part of the research study.

_____	_____	_____	_____
Signature of Participant	Date	Time	Printed Name

Person Explaining the Research: Your signature below means that you have explained the optional part of the research to the participant and have answered any questions she has about the research.

_____	_____	_____	_____
Signature of person who explained this research	Date	Time	Printed Name

(Only approved study personnel for this research may explain the research and obtain informed consent.)

Optional Study DNA Collection

As part of this study, we are obtaining, prior to you starting medication, a sample of your blood for DNA testing and for measure of other substances in the blood. If you agree, the researchers would like to use your DNA to identify certain sequences of key genes (called polymorphisms) that may predict a response to the medications used in this trial. If genes are identified that relate to the response to the treatment, the sample may also be used in the development of diagnostic or prognostic tests to identify those who will or who will not respond to these medications. We also may use this DNA to identify genes that cause infertility. There is no normal or abnormal result produced by the DNA and the researchers will not use the DNA to try to see if you have any genetic diseases or conditions. The testing of DNA may provide additional information that will be helpful in understanding the medications used in this trial and the effects on infertility, but it is unlikely that these studies will have a direct benefit to you. The results of these tests will not have an effect on your care. Neither your doctor nor you will receive results of these tests, nor will the results be put in your health record. If you have any questions, you should contact [insert name of principal investigator] at xxx-xxx-xxxx.

If you agree to allow your DNA sample to be collected at the baseline visit, your DNA sample will be labeled with your study identification number and the visit date. These samples will be stored in a locked laboratory at the [insert institution name] until it is shipped to the RMN Biological Storage facility or to other laboratories for processing and testing. You are free to change your mind regarding the use of your sample. You should contact [insert name of principal investigator] at xxx-xxx-xxxx and let him know you wish to withdraw your permission for your DNA to be used for testing. Your DNA sample will be destroyed at that time of withdrawal. You understand that you will not have access to the sample once it is sent to the laboratory. If you consent to the collection of your DNA, it will be kept indefinitely or until the sample is exhausted by the Reproductive Medicine Network.

You should initial below to indicate your preference for the collection of your DNA sample:

_____ I give my permission for my DNA and serum sample to be collected and tested under this study.

_____ I decline my permission for my DNA and serum sample to be collected for this study.

Participant: By signing below, you indicate that you have read the information written above and have indicated your choices for the optional part of the research study.

_____	_____	_____	_____
Signature of Participant	Date	Time	Printed Name

Person Explaining the Research: Your signature below means that you have explained the optional part of the research to the participant and have answered any questions she has about the research.

_____ _____ _____ _____
Signature of person who explained this research Date Time Printed Name
(Only approved investigators for this research may explain the research and obtain informed consent.)

Optional Blood Storage for Future Use

As part of this study, we are obtaining blood from you during the screening and cycle day visits. If you agree, the researchers would like to retain any additional blood specimen (aliquoted up to 3 cc each) for banking for future studies as plasma and serum, stored evenly in 2 tubes, so that your blood can be studied in the future after this study is over; the researchers would like to additionally store any leftover samples of your blood in the same manner. These future studies may provide additional information that will be helpful in understanding ovarian physiology, but it is unlikely that these studies will have a direct benefit to you. The results of these tests will not have an effect on your care. Neither your doctor nor you will receive results of these future research tests, nor will the results be put in your health record. Sometimes blood is used for genetic research about diseases that are passed on in families. Even if your samples are used for this kind of research, the results will not be put in your health records. It is possible that your blood might be used to develop products or tests that could be patented and licensed. There are no plans to provide financial compensation to you should this occur. If you have any questions, you should contact *[insert name of principal investigator* at xxx-xxx-xxxx.

Your leftover samples will be labeled with your study identification number, your initials and the visit date. These samples will be stored in a locked laboratory at the *[insert institution name]*. If you consent to the collection of samples of blood for future research, the period for the use of the samples is unknown. Your blood samples may be shipped and stored in a biological specimen repository coordinated by the Reproductive Medicine Network pending approval by the Human Investigation Committees at all the participating sites. If you agree to allow your blood to be kept for future research, you will be free to change your mind at any time. You should contact *[insert name of principal investigator]* at xxx-xxx-xxxx and let him know you wish to withdraw your permission for your blood to be used for future research. Any unused blood will be destroyed and not used for future research studies.

You should initial below to indicate your preferences regarding the optional storage of your leftover blood for future research studies.

a. Your sample(s) may be stored and used for future research studies to learn about, prevent, treat or cure unexplained infertility.
_____ Yes _____ No

b. Your sample(s) may be stored and use for research about other health problems.
_____ Yes _____ No

c. Your sample(s) may be shared with other investigators/groups without any identifying information.

_____ Yes _____ No

Participant: By signing below, you indicate that you have read the information written above and have indicated your choices for the optional part of the research study.

_____	_____	_____	_____
Signature of Participant	Date	Time	Printed Name

Person Explaining the Research: Your signature below means that you have explained the optional part of the research to the participant and have answered any questions she has about the research.

_____	_____	_____	_____
Signature of person who explained this research	Date	Time	Printed Name

(Only approved study personnel for this research may explain the research and obtain informed consent.)

I give permission for the results of studies on my blood to be used to develop better understanding and treatments for infertility.

_____*Yes* _____ *No* _____*INITIALS*

A representative of the physicians associated with this study may contact me in the future to take part in more research.

_____*Yes* _____ *No* _____*INITIALS*

Participant: By signing below, you indicate that you have read the information written above and have indicated your choices for the optional part of the research study.

_____	_____	_____	_____
Signature of Participant	Date	Time	Printed Name

Person Explaining the Research: Your signature below means that you have explained the optional part of the research to the participant and have answered any questions she has about the research.

_____	_____	_____	_____
Signature of person who explained this research	Date	Time	Printed Name

(Only approved study personnel for this research may explain the research and obtain informed consent.)

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

To voluntarily agree to take part in this study, you must sign on the line below. If you choose to take part in this study you may withdraw at any time. You are not giving up any of your legal rights by signing this form. Your signature below indicates that you have read this entire consent form, including the risks and benefits, and have had all of your questions answered. You will be given a copy of this consent form.

_____ _____

Signature of participant / legally authorized representative Date

_____ _____

Printed name of participant / legally authorized representative Time

PERSON EXPLAINING CONSENT STATEMENT

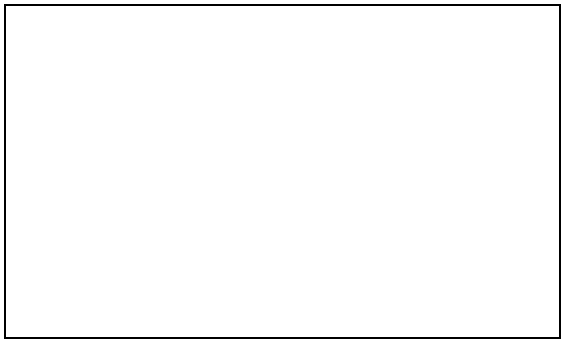
I have carefully explained to the subject the nature and purpose of the above study. The subject signing this consent form has (1) been given adequate time and place to read and review this consent form; (2) been given an opportunity to ask questions regarding the nature, risks and benefits of participation in this research study; (3) been given access to the Pregnancy Registry Consent Forms if choosing to participate in the three-year monitoring option; and (4) has verbalized understanding the nature and purpose of the study and the demands required of participation.

_____ _____

Signature of person obtaining consent Date

_____ _____

Printed name of person obtaining consent Time



Continue to HIPAA Authorization

11 Human Subjects/Informed Consent/Male

Consent to Participate in a Clinical Research Study

Consent Version April 5, 2011
Male Subjects

Title of Study: Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation

Principal Investigator (PI): *[insert name of principal investigator]*

Funding Source: NICHD: Reproductive Medicine Network

Purpose
Your partner/spouse and you are being asked to be in a research study designed to look at three medications— gonadotropin (hMG) vs. clomiphene citrate (CC) vs. aromatase inhibitors (AI) — to determine whether AI will produce rates of ovulation, pregnancy, and successful live birth in infertile women that are comparable to gonadotropin and CC treatments, while reducing the rates of multiple gestation often seen with those drugs. The gonadotropin that will be used in this study is hMG (Menopur®), a combination of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH). This drug has been approved by the United States Food and Drug Administration (FDA) for the treatment of infertility. Clomiphene Citrate (CC) has also been approved by the FDA and is also used for the treatment of infertility. The aromatase inhibitor (AI) that will be used in this study is Letrozole, which is an FDA approved medication for breast cancer. This medication has recently been used to induce ovulation (causing you to release an egg from the ovary to increase your chance of pregnancy), but is not yet FDA approved for this use. You have been asked to participate because you and your partner have not been able to conceive. This study is being conducted at *[insert institution name]* and its affiliated clinics. The estimated number of study participants to be enrolled at *[insert institution name]* is about *[insert site specific number]* as well as about 900 throughout the United States.

In this research study, three medications— gonadotropin (Menopur®), Clomiphene Citrate or Letrozole (Femara®)— will be evaluated to see which one most likely result in your partner/spouse's pregnancy. Your role in this study is to assist your partner/spouse, as well as provide a semen sample to determine her eligibility in the main study.

Please read this form and ask any questions you may have before agreeing to be in the study.

Study Procedures
If you agree to take part in this research study, we will obtain blood from you during the screening visit in order to measure your hormone levels. You will also be asked to provide a semen sample if you have not given one in the past 12 months. The study coordinator will give you a laboratory form including instructions as well as a collection cup for you to take to the collection room.

You will also be required to complete a medical history questionnaire. This questionnaire will ask you questions about your medical health, infertility history, demographic information, and family history. You will be given 5 questionnaires to complete. A Medical Outcomes Survey (Prime MD-PHQ) and the Short Form-36 (SF-36) will assess your daily activities. FertiQoL will assess how your infertility affects your thoughts and feelings. The Sleep Habits Survey will assess the quality of your sleep. The International Index of Erectile Function survey (IIEF) will assess your sexual function. You will be free to skip any questions that you would prefer not to answer.

You will be asked to assist in the giving of injections for the hCG trigger and if your partner/spouse is randomized to the gonadotropin treatment group. You may decline and remain in the study, if your partner is going to self-administer the injections.

As part of the inclusion criteria for participation in this study, inseminations (placing your sperm in your partner's/spouse's uterus) of your partner must take place at least once each cycle for up to four cycles. Both you and your partner must agree to this requirement.

For the collection of the semen analysis test and for the samples to be used for insemination, it is important to not have sex or masturbate for 48 hours prior to collecting your sample.

Collection of sample

The following are the instructions you will follow to collect your sample. There is a private room near the lab where the specimen can be collected.

1. Wash your hands and genitals in the normal way and dry thoroughly.
2. Use the cup provided by the study coordinator or the lab. Do not open the container until you are ready to produce the sample.
3. Collect the sample by masturbation, putting the entire specimen directly into the cup.
4. Do not use lubricants or condoms, as these are harmful to sperm.
5. Seal the cup immediately with the lid.
6. Write your name on the label of the cup. Fill out the bottom portion of the lab form. Return the specimen and form to the laboratory staff.

For the semen analysis, once your specimen has been tested, the study coordinator will be given your results. Your results will be reviewed with the principal investigator of the study. You will be notified of your results. If there are more than 5 million motile (moving) sperm in the ejaculate, your partner/spouse will be eligible to participate in the main study. If the results of your semen analysis are abnormal, you will be provided with that information and referred to your physician for further follow-up. If the number of motile sperm in an ejaculate is less than 5 million, your partner/spouse will be ineligible to participate in the main study at this time.

For the inseminations, the semen specimen will be washed to concentrate the sperm and remove other components of the ejaculate specimen. The sperm will then be used for insemination (placement of the sperm into the uterus) of your partner/spouse.

Optional Semen Storage for DNA analysis

You will be asked for your consent to use a small sample of semen to study the chemicals that make up all of your genes and contain your genetic information. The genetic information

obtained from your samples can be used by researchers to better understand infertility. These will be stored for future research analysis that will be limited to infertility and related conditions.

At the study visit, a portion of your semen specimen will be set aside for part of the study. Your DNA samples will be stored indefinitely. You will not learn the results of these research studies conducted on your DNA samples. All such tests and statistical analysis of data will be conducted confidentially. You will be identified by a coded study number unrelated to any of your personal information on all samples. Only coded data will be used for statistical analyses. The principal investigator and coordinator will maintain a link, through the use of this code number, that will allow linkage in the data base to questionnaire information as well as to allow withdrawal of consent at a later time**.** The results of this DNA test will not produce any results that provide information about anyone but you. We will plan to identify your DNA by a special code, and keep it indefinitely or until the sample is exhausted by the Reproductive Medicine Network scientists. Some of your DNA may be analyzed as part of other research activities in this or other institutions. If your DNA is shared with other researchers your identity will be kept anonymous. The Reproductive Medicine Network will own your samples, but you can request that the sample be destroyed if you wish. We will not provide the results of these research tests to any law enforcement or social agency.

PLEASE INITIAL

_____ I consent to have an additional portion of my semen sample set aside for future genetic analysis of infertility and related conditions.

_____ I do not consent to have an additional portion of my semen sample set aside for future, genetic analysis of infertility and related conditions.

A representative of the physicians associated with this study may contact me in the future to take part in more research.

_____Yes _____ No _____INITIALS

Participant: By signing below, you indicate that you have read the information written above and have indicated your choices for the optional part of the research study.

_____ _____ _____ _____

Signature of Participant Date Time Printed Name

Person Explaining the Research: Your signature below means that you have explained the optional part of the research to the participant and have answered any questions he has about the research.

_____	_____	_____	_____
Signature of person who explained this research	Date	Time	Printed Name

(Only approved study personnel for this research may explain the research and obtain informed consent.)

Optional Blood Storage for Future Use

As part of this study, we are obtaining blood from you during the screening visit. If you agree, the researchers would like to retain any additional blood specimen (aliquoted up to 3 cc each) for banking for future studies as plasma and serum, stored evenly in 2 tubes, so that your blood can be studied in the future after this study is over; the researchers would like to additionally store any leftover samples of your blood in the same manner. These future studies may provide additional information that will be helpful in understanding testicular physiology, but it is unlikely that these studies will have a direct benefit to you. The results of these tests will not have an effect on your care. Neither your doctor nor you will receive results of these future research tests, nor will the results be put in your health record. Sometimes blood is used for genetic research about diseases that are passed on in families. Even if your samples are used for this kind of research, the results will not be put in your health records. It is possible that your blood might be used to develop products or tests that could be patented and licensed. There are no plans to provide financial compensation to you should this occur. If you have any questions, you should contact *[insert name of principal investigator* at xxx-xxx-xxxx.

Your leftover samples will be labeled with your study identification number, your initials and the visit date. These samples will be stored in a locked laboratory at the *[insert institution name]*. If you consent to the collection of samples of blood for future research, the period for the use of the samples is unknown. Your blood samples may be shipped and stored in a biological specimen repository coordinated by the Reproductive Medicine Network pending approval by the Human Investigation Committees at all the participating sites. If you agree to allow your blood to be kept for future research, you will be free to change your mind at any time. You should contact *[insert name of principal investigator]* at xxx-xxx-xxxx and let him know you wish to withdraw your permission for your blood to be used for future research. Any unused blood will be destroyed and not used for future research studies.

You should initial below to indicate your preferences regarding the optional storage of your leftover blood for future research studies.

d. Your sample(s) may be stored and used for future research studies to learn about, prevent, treat or cure unexplained infertility.
_____ Yes _____ No

e. Your sample(s) may be stored and use for research about other health problems.

_____ Yes _____ No

f. Your sample(s) may be shared with other investigators/groups without any identifying information.

_____ Yes _____ No

Participant: By signing below, you indicate that you have read the information written above and have indicated your choices for the optional part of the research study.

_____	_____	_____	_____
Signature of Participant	Date	Time	Printed Name

Person Explaining the Research: Your signature below means that you have explained the optional part of the research to the participant and have answered any questions she has about the research.

_____	_____	_____	_____
Signature of person who explained this research	Date	Time	Printed Name

(Only approved study personnel for this research may explain the research and obtain informed consent.)

Benefits

The possible benefit to you for taking part in this research study is the medication(s) your partner takes may help her become pregnant. Information from this study may also benefit other people now or in the future.

You will be provided with your semen analysis results. Any abnormalities will be assessed by the principal investigator and followed through by your physician. The results of your semen analysis will determine eligibility for your partner/spouse to participate in the main study.

Risks

By taking part in this study, you may experience the following risks:

During the collection of the blood sample, you may experience some pain and/or bruising at the site on your arm where the blood was taken. Such bruises usually go away without treatment. Rarely, localized clot formation and/or infections might occur and would be treated by standard medical practice. There may also be risks involved in taking part in this study which are not known to researchers at this time. There is the potential of identification of communicable diseases (STDs). If you are found to have an STD, you will be notified.

If you have an infection, it is possible that this will be transferred to your partner/spouse. This possibility will be minimized by not placing the sperm into the uterine cavity of your partner/spouse if the number of white blood cells exceeds the limits allowed by your physician.

PREGNANCY/FETAL RISK

Although the drugs your partner will take may result in pregnancy, there is no guarantee that this will result in a live birth. Clomiphene has been associated with a 12.5% multiple pregnancy rate. Multiple pregnancies are more likely to end early in preterm labor and are more likely to experience most pregnancy complications including diabetes and hypertensive disorders of pregnancy. The multiple pregnancy rate with Letrozole is not known, but is probably more than the natural rate (~1%) but less than clomiphene. The multiple pregnancy rate with gonadotropins is 25%. The pregnancy may also lead to a miscarriage or may implant outside the uterus (i.e., a tubal or ectopic pregnancy) and require further therapy including surgery to treat. Finally the use of these drugs may be associated with an increased risk for fetal malformations, though no specific pattern has been associated with either drug. Letrozole has been shown in laboratory animals to be embryotoxic (cause death of embryos), fetotoxic (cause death of fetuses), and possibly teratogenic (cause congenital malformations, i.e., "birth defects). Letrozole and clomiphene citrate have been shown to be genotoxic (cause abnormalities to genes) in *in vitro* laboratory tests.

The study also may include risks that are unknown at this time. It is important that your partner promptly reports any side effects to your study coordinator or study physician.

If your partner becomes pregnant during the study, you should inform the study doctor immediately. The study doctor and sponsor will follow the progress of your partner's pregnancy and will request access to your infant's medical records for up to at least delivery, if applicable.

Unknown Risks
There may be other risks that are unknown.

If at any time during the study there is concern that you have a reportable communicable disease (i.e., certain sexually transmitted diseases or HIV), this information will need to be reported to the State Health Department.

Alternatives
You do not have to provide a semen analysis for testing. However, if you decline to do so, your partner/spouse will not be eligible to participate in the main study.

Study Costs
Your insurance company will be charged for the semen analysis, the sperm preparation for insemination, and the inseminations. If you do not have insurance or your insurance will not cover the cost, the study will cover the cost at no expense to you.

You or your/your partner's insurance company will also be responsible for the costs of any additional tests, monitoring or treatment for ovarian hyper-stimulation syndrome, and all pregnancy related costs which occur while in this study.

Neither you nor your partner will receive monetary compensation for participating in the study. If your partner conceives, pregnancy care (whether for a normal intrauterine pregnancy, a pregnancy which results in a miscarriage, or an ectopic pregnancy outside the uterus) will not be provided as part of the study and you/your partner will need to find a doctor to provide this care, or one will be recommended to you. The costs of your prenatal care after this point and costs of your delivery and any complications of your partner's pregnancy will not be covered by this study. Therefore you/your partner, or your insurance carrier, will be responsible for these costs.

Compensation
You will not be paid for taking part in this study.

Research Related Injuries
In the event that this research-related activity results in an injury, treatment will be made available including first aid, emergency treatment, and follow-up care as needed. Cost for such care will be billed in the ordinary manner to you or your insurance company. No reimbursement, compensation, or free medical care is offered by [*institution*] or its affiliated clinics. If you think that you have suffered a research related injury, contact the PI right away at XXX-XXX-XXXX.

Confidentiality
All information collected about you during the course of this study will be kept confidential to the extent permitted by law. You will be identified in the research records by a code name or number. Information that identifies you personally will not be released without your written permission. However, the study sponsor, the Human Investigation Committee (HIC) at [*institution*], or federal agencies with appropriate regulatory oversight [e.g., Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), Office of Civil Rights (OCR), etc.] may review your records.

When the results of this research are published or discussed in conferences, no information will be included that would reveal your identity.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Certificate of Confidentiality To help us further protect your privacy, the researchers have obtained a Certificate of Confidentiality from the National Institutes of Health (NIH) / National Institute of Child Health and Human Development (NICHD). This Certificate means that the researchers cannot be forced (for example by court order) to disclose any information that might identify you to any federal, state, or local court. A Certificate of Confidentiality does not prevent you from voluntarily giving information to others about yourself or your involvement in this research. You should know that we may provide information to your health care providers if we

suspect that you may harm yourself or others. We will not release any information collected as part of the research regarding use of illicit drugs and testing for drugs done on samples collected for the research.

Voluntary Participation/Withdrawal

Taking part in this study is voluntary. You have the right to choose not to take part in this study. You are free to only answer questions that you want to answer. You are free to withdraw from participation in this study at any time. Your decisions will not change any present or future relationship with [*institution*] or its affiliates, or other services you are entitled to receive. However, if you decline to participate, your partner/spouse will not be eligible to participate in the main study.

Questions
If you have any questions about this study now or in the future, you may contact [*PI*] at XXX-XXX-XXXX or one of his research team members at the following phone number XXX-XXX-XXXX. If you have questions or concerns about your rights as a research participant, the Chair of the Human Investigation Committee can be contacted at XXX-XXX-XXXX. If you are unable to contact the research staff, or if you want to talk to someone other than the research staff, you may also call XXX-XXX-XXXX to ask questions or voice concerns or complaints.

Consent to Participate in a Research Study

To voluntarily agree to take part in this study, you must sign on the line below. If you choose to take part in this study you may withdraw at any time. You are not giving up any of your legal rights by signing this form. Your signature below indicates that you have read, or had read to you, this entire consent form, including the risks and benefits, and have had all of your questions answered. You will be given a copy of this consent form.

_____ _____
Signature of participant/Legally authorized representative* Date

_____ _____
Printed name of participant/Legally authorized representative * Time

PERSON EXPLAINING CONSENT STATEMENT
I have carefully explained to the subject the nature and purpose of the above study. The subject signing this consent form has (1) been given adequate time and place to read and review this consent form; (2) been given an opportunity to ask questions regarding the nature, risks and benefits of participation in this research study; and (3) has verbalized understanding the nature and purpose of the study and the demands required of participation.

_____ _____
Signature of person obtaining consent Date

_____ _____
Printed name of person obtaining consent Time

Continue to HIPAA Authorization on next page

12 HIPAA Authorization

A federal regulation, known as the "Health Insurance Portability and Accountability Act (HIPAA)" gives you certain rights concerning the use and disclosure (sharing with others) of your Protected Health Information (PHI). This regulation provides safeguards for the privacy and security of your information. Your permission (authorization) is required for the use and sharing of any protected health information collected as part of this research study. If you are not willing to sign this authorization to use and/or disclose your PHI by the research team, you will not be eligible to take part in this research study.

The principal investigator (PI) and his research team will use your medical records and information created or collected as part of this research study. Your PHI is important for the PI and his research team in order to collect information about you during the study, to be able to contact you if needed, and to provide treatments to you during the study, if required. The PI may send out your study related health information to the sponsor or other entities involved in this study.

Your medical records, which may contain information that directly identifies you, may be reviewed by representatives from groups identified below. The purpose of these reviews is to assure the study is being conducted properly, that data is being obtained correctly or for other uses authorized by law. These reviews occur at the study site or in the PI's research office and can take place anytime during the study or after the study ends.

The PHI that will be "USED" for this research includes the following: name, address (street address, city, state and zip code), elements of dates, telephone numbers, email addresses, social security number, email addresses, and any unique identifying numbers or characteristics or code.

The PHI that will be "DISCLOSED" or shared with others for this research includes the following: elements of dates, and any unique identifying numbers or characteristics or code.

Your study information may be **used** or **shared** with the following people or groups:

- The PI, co-investigators, and key personnel of *[insert institution name]* associated with the research project
- *[insert institution name]*'s HIC and the Institutional Review Boards (IRB)
- Authorized members of *[insert institution name]*'s workforce who may need to access your information in the performance of their duties. [*For example, to provide treatment and services, ensure integrity of the research, or for accounting and/or billing matters.*]
- Other collaborating academic research institutions, which include:

Pennsylvania State University School of Medicine
Richard Legro, MD
717-531-8478

University of Colorado
Nanette Santoro, MD
William Schlaff, MD
303-724-2018

University of Michigan
Gregory Christman, MD
734-764-8142

University of Pennsylvania
Christos Coutifaris, MD, PhD
215-662-3378

University of Texas
Robert Brzyski, MD
210-567-6121

University of Vermont
Peter Casson, MD
802-847-3450

Yale University School of Medicine
Heping Zhang, PhD
203-785-5185

University of California, San Francisco
Mitchell Rosen, MD, HCLD
415-885-7870

University of Oklahoma
Karl Hansen, MD, PhD
405-271-8722

University of Medicine and Dentistry of New Jersey
Aimee Seungdamrong, MD
973-972-6480

- The study Sponsor or representative, including companies it hires to provide study related services, which include:

  NICHD
  301-435-6979

  DMC University Laboratories
  1-800-234-3508

  Data Coordination Center at Yale University (DCC) to ensure compliance with policies or monitor the safety of the study

- Federal agencies with appropriate regulatory oversight (e.g., FDA, OHRP, OCR, etc.) may review your records.

Once your information has been released according to this Authorization, it could be released again and may no longer be protected by the HIPAA regulations.

This Authorization does not expire. The research team may need to correct it or provide missing information about you even after the study has ended, and your medical records may be needed to assist in this process.

- During your participation in this research project you will not be able to access that part of your medical record involved in the research. This will be done to prevent the knowledge of the research results from affecting the reliability of the project. Your information will be available to the treating physician should an emergency arise that

would require for him to know this information to best treat you. You will have access to your medical record when the study is ended or earlier, if possible. The PI is not required to release research information that is not part of your medical record.

You may withdraw (take back) your permission for the **use** and **disclosure** of your PHI for this research at anytime, by **writing** to the PI at the address on the first page of this form. Even if you withdraw your permission, the PI for the research project may still use your PHI that was collected prior to your written request if that information is necessary to the study. If you withdraw your permission for use of your PHI, you will also be withdrawn from the research project. Withdrawing your authorization **will not** affect the health care that will be provided by the *[insert institution name]*.

Authorization to use and disclose PHI

- By signing this form, you are authorizing the PI to **use** and **disclose** PHI collected about you for the research purposes as described above.

_____ _____

Signature of participant Date

_____ _____

Printed name of participant Time

_____ _____

Signature of person obtaining Authorization Date

_____ _____

Printed name of person obtaining Authorization Time

13 Appendix A: Risk Factors for Genetic Disorders

The following questions are designed to determine if you have an increased risk of having a baby with a genetic disorder. Sometimes genetic disorders occur even when there is no history of problems in your family. The following questions are related to you and your immediate family including mother, father, sister, brother, child, or grandparent. If you answer "yes" to any of the following questions and would like more information, please discuss this with your physician.

Questions	Yes	No	Unknown	N/A
1. If you conceive during this study, will you be 35 or older when your baby is due?				
2. If you are of Mediterranean or Asian descent, does anyone in your family have thalassemia? (a blood disorder that causes anemia)				
3. Is there a family history of neural tube defects?				
4. Have you had a child with a neural tube defect?				
5. Does anyone in your family have a history of congenital heart defects? (heart problems when they were born)				
6. Does anyone in your family have a history of Down Syndrome?				
7. Have you ever had a child with Down Syndrome?				
8. If you are of Eastern European Jewish or French Canadian descent, does anyone in your family have a history of Tay-Sachs disease? (a disorder of the central nervous system)				
9. If you are of Eastern European Jewish descent, does anyone in your family have a history of Canavan disease? (a disorder of the central nervous system that leads to blindness and muscle weakness)				
10. If you are of African American descent, is there any history of sickle cell trait? (a type of anemia)				
11. If you are of African American descent, is there any history of sickle cell disease? (a type of anemia)				
12. Do you or anyone in your family have a history of hemophilia? (a disorder that causes bleeding)				
13. Do you or anyone in your family have a history of muscular dystrophy? (a neuromuscular disorder)				
14. Do you or anyone in your family have a history of cystic fibrosis? (a disorder that causes thick mucous in the lungs and other organs)				
15. Do you or anyone in your family have a history of Huntington's disease? (a degenerative brain disease)				
16. Do you or anyone in your family have a history of alpha-1 antitrypsin deficiency? (lack of a liver protein)				
17. Do you or anyone in your family have a history of mental retardation?				
17a. If yes to question 17, was this person ever tested for fragile-x syndrome? (a condition which can cause mild to severe mental retardation)				
18. Do you or anyone in your family have a history of any other genetic disease, chromosomal disorder or birth defects?				
19. Do you have any metabolic disorders such as diabetes or phenylketonuria (PKU)? (a disorder which prevents the normal use of protein foods)				
20. Have you ever had 3 or more miscarriages in a row?				
21. Have you ever had a baby that was stillborn?				

Partner Family History

The following questions are designed to determine if you have an increased risk of having a baby with a genetic disorder. Sometimes genetic disorders occur even when there is no history of problems in your family. The following questions are related to you and your immediate family including mother, father, sister, brother, child, or grandparent. If you answer "yes" to any of the following questions and would like more information, please discuss this with your physician.

Questions	Yes	No	Unknown	N/A
1. If you are of Mediterranean or Asian descent, does anyone in your family have thalassemia? (a blood disorder that causes anemia)				
2. Is there a family history of neural tube defects?				
3. Have you had a child with a neural tube defect?				
4. Does anyone in your family have a history of congenital heart defects? (heart problems when they were born)				
5. Does anyone in your family have a history of Down Syndrome?				
6. Have you ever had a child with Down Syndrome?				
7. If you are of Eastern European Jewish or French Canadian descent, does anyone in your family have a history of Tay-Sachs disease? (a disorder of the central nervous system)				
8. If you are of Eastern European Jewish descent, does anyone in your family have a history of Canavan disease? (a disorder of the central nervous system that leads to blindness and muscle weakness)				
9. If you are of African American descent, is there any history of sickle cell trait? (a type of anemia)				
10. If you are of African American descent, is there any history of sickle cell disease? (a type of anemia)				
11. Do you or anyone in your family have a history of hemophilia? (a disorder that causes bleeding)				
12. Do you or anyone in your family have a history of muscular dystrophy? (a neuromuscular disorder)				
13. Do you or anyone in your family have a history of cystic fibrosis? (a disorder that causes thick mucous in the lungs and other organs)				
14. Do you or anyone in your family have a history of Huntington's disease? (a degenerative brain disease)				
15. Do you or anyone in your family have a history of alpha-1 antitrypsin deficiency? (lack of a liver protein)				
16. Do you or anyone in your family have a history of mental retardation?				
16a. If yes to question 16, was this person ever tested for fragile-x syndrome? (a condition which can cause mild to severe mental retardation)				
17. Do you or anyone in your family have a history of any other genetic disease, chromosomal disorder or birth defects?				
18. Do you have any metabolic disorders such as diabetes or phenylketonuria (PKU)? (a disorder which prevents the normal use of protein foods)				

14 Appendix B: List of common medications excluded or requiring wash-out period

AMIGOS Excluded Medications

A patient will be excluded from study if they are taking any medication that should not be discontinued and this medication would affect reproductive function or metabolism, or would interact with either study medication.

Hormonal Medications Requiring 1 month wash-out:

Progestins (Oral or Cyclic)

- medroxyprogesterone acetate (Provera, Cycrin, Amen, Curretab)
- megestrol (Megase)
- norethindrone (Aygestin)
- progesterone gel (Crinone)
- Micronized progesterone (Prometrium)

Hormonal Medications Requiring 2 month Wash-Out Period:

GnRH Agonists/Antagonists

- Leuprolide (Lupron)
- nafarelin (Synarel)
- buserelin
- gosarelin (Zoladex)
- ganarelix (Antagon)
- cetrorelix (Cetrotide)

Gonadotropins

- Pergonal
- Repronex
- Follistim
- Gonal-F
- Fertinex
- Metrodin

Injectable Contraceptives

- medroxyprogesterone acetate (Depo Provera)

Oral Contraceptives

- Any Brand

Continuous Progestins (Not including cyclic)

- Any Brand

Other Medications Requiring 2 month Wash-out Period:

Somatostatin
- octreotide (Sandostatin)
- lanreaotide

Anti-Acne
- isotretinoin(Accutane)

Anti-androgens
- cyproterone (Cyprostat)
- spironolactone (Aldactone)
- flutamide (Eulexin)
- finasteride (Proscar, Propecia)

Anti-diabetic
- acarbose (Precose)
- Insulin
- *sulfonylureas*
- acetahexamide (Dymelor)
- chlorpropamide (Diabinese)
- tolazamide (Tolinase)
- tolbutamide (Orinase)
- glimepiride (Amaryl)
- glipizide (Glucotrol)
- glyburide (DiaBeta Micronase)
- *thiazolidinediones*
- rosiglitazone (Avandia)
- pioglitazone (Actos)

Biguanides
- metformin (Glucophage)
- Incretins : GLP-1 Analogues/DPP-IV inhibitors
- sitagliptin (Januvia)
- vidagliptin (Glavus)
- exenatide (Byetta)

Anti-obesity
- diazoxide (Proglycem)
- orlistat (Xenical)
- sibutramine (Meridia)
- diethylpropion (Tenuate)
- phendimetrazine (Bontril)
- phentermine (Adipex-P, Fastin, Ionamin)

Calcium Channel Blockers
- diltiazem (Cardizem, Dilacor, Tiazac, Diltia-XL)
- verapamil (Isoptin, Calan)
- amlodipine (Norvase)
- felodipine (Plendil)

isradipine (DynaCirc)
nicardipine (Cardene)
nifedipine (Procardia, Adalat)
nifsoldipine (Sular)

Angiotensin Converting Enzyme (ACE) Inhibitors

Prinivil (lisinopril)
Captoten (captropril)
Cozaar (losartan)
multiple others

Medications with potential longer washouts (Contact DCC)

Contraceptive Implants
Norplant (levonorgestrel implants)
Implanon
Previous clomiphene and letrozole use requires a two-month washout

15 Appendix C: SF 36 Health Survey

SF36 Health Survey

INSTRUCTIONS: This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question please give the best answer you can.

1. In general, would you say your health is: (Please tick **one** box.)
   - Excellent ☐
   - Very Good ☐
   - Good ☐
   - Fair ☐
   - Poor ☐

2. Compared to one year ago, how would you rate your health in general now? (Please tick **one** box.)
   - Much better than one year ago ☐
   - Somewhat better now than one year ago ☐
   - About the same as one year ago ☐
   - Somewhat worse now than one year ago ☐
   - Much worse now than one year ago ☐

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? **(Please circle one number on each line.)**

	Activities	Yes, Limited A Lot	Yes, Limited A Little	Not Limited At All
3(a)	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
3(b)	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
3(c)	Lifting or carrying groceries	1	2	3
3(d)	Climbing **several** flights of stairs	1	2	3
3(e)	Climbing **one** flight of stairs	1	2	3
3(f)	Bending, kneeling, or stooping	1	2	3
3(g)	Waling **more than a mile**	1	2	3
3(h)	Walking **several blocks**	1	2	3
3(i)	Walking **one block**	1	2	3
3(j)	Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	(Please circle one number on each line.)	Yes	No
4(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
4(b)	Accomplished less than you would like	1	2
4(c)	Were **limited** in the **kind** of work or other activities	1	2
4(d)	Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (e.g. feeling depressed or anxious)?

	(Please circle one number on each line.)	Yes	No
5(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
5(b)	Accomplished less than you would like	1	2
5(c)	Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick **one** box.)

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

7. How much physical pain have you had during the past 4 weeks? (Please tick **one** box.)

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very Severe ☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Please tick **one** box.)

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

9. These questions are about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that is closest to the way you have been feeling for each item.

	(Please circle one number on each line.)	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
9(a)	Did you feel full of life?	1	2	3	4	5	6
9(b)	Have you been a very nervous person?	1	2	3	4	5	6
9(c)	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
9(d)	Have you felt calm and peaceful?	1	2	3	4	5	6
9(e)	Did you have a lot of energy?	1	2	3	4	5	6
9(f)	Have you felt downhearted and blue?	1	2	3	4	5	6
9(g)	Did you feel worn out?	1	2	3	4	5	6
9(h)	Have you been a happy person?	1	2	3	4	5	6
9(i)	Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.) (Please tick **one** box.)

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

11. How TRUE or FALSE is each of the following statements for you?

	(Please circle one number on each line.)	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
11(a)	I seem to get sick a little easier than other people	1	2	3	4	5
11(b)	I am as healthy as anybody I know	1	2	3	4	5
11(c)	I expect my health to get worse	1	2	3	4	5
11(d)	My health is excellent	1	2	3	4	5

Thank You!

16 Appendix D: Female Sexual Function Index

Female Sexual Function Index (FSFI) ©

Subject Identifier _____ Date _____

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION.

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how **often** did you feel sexual desire or interest?

   - ☐ Almost always or always
   - ☐ Most times (more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (less than half the time)
   - ☐ Almost never or never

2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?

   - ☐ Very high
   - ☐ High
   - ☐ Moderate
   - ☐ Low
   - ☐ Very low or none at all

I

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

4. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very high
- ☐ High
- ☐ Moderate
- ☐ Low
- ☐ Very low or none at all

5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very high confidence
- ☐ High confidence
- ☐ Moderate confidence
- ☐ Low confidence
- ☐ Very low or no confidence

6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

10. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

13. Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

17. Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

18. Over the past 4 weeks, how **often** did you experience discomfort or pain following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Very high
- ☐ High
- ☐ Moderate
- ☐ Low
- ☐ Very low or none at all

Thank you for completing this questionnaire

17 Appendix E: Prime MD PHQ

Patient Initials:__ __ __
Study ID #: __ __-__ __ __ __
Date of Visit:__ __/__ __/__ __ __ __
Month Day Year

Patient Health Questionnaire

This questionnaire is an important part of providing you with the best health care possible. Your answers will help in understanding problems that you may have. Please answer every question to the best of your ability unless you are requested to skip over a question.

DATE _____ NAME _____ AGE _____ SEX: Female Male

1. During the last 4 weeks, how much have you been bothered by any of the following problems?	Not bothered at all	Bothered a little	Bothered a lot
a. Stomach pain	[ ]	[ ]	[ ]
b. Back pain	[ ]	[ ]	[ ]
c. Pain in your arms, legs, or joints (knees, hips, etc.)	[ ]	[ ]	[ ]
d. Menstrual cramps or other problems with your periods	[ ]	[ ]	[ ]
e. Pain or problems during sexual intercourse	[ ]	[ ]	[ ]
f. Headaches	[ ]	[ ]	[ ]
g. Chest pain	[ ]	[ ]	[ ]
h. Dizziness	[ ]	[ ]	[ ]
i. Fainting spells	[ ]	[ ]	[ ]
j. Feeling your heart pound or race	[ ]	[ ]	[ ]
k. Shortness of breath	[ ]	[ ]	[ ]
l. Constipation, loose bowels, or diarrhea	[ ]	[ ]	[ ]
m. Nausea, gas, or indigestion	[ ]	[ ]	[ ]

2. Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
a. Little interest or pleasure in doing things	[ ]	[ ]	[ ]	[ ]
b. Feeling down, depressed, or hopeless	[ ]	[ ]	[ ]	[ ]
c. Trouble falling or staying asleep, or sleeping too much	[ ]	[ ]	[ ]	[ ]
d. Feeling tired or having little energy	[ ]	[ ]	[ ]	[ ]
e. Poor appetite or overeating	[ ]	[ ]	[ ]	[ ]
f. Feeling bad about yourself - or that you are a failure or have let yourself or your family down	[ ]	[ ]	[ ]	[ ]
g. Trouble concentrating on things, such as reading the newspaper or watching television	[ ]	[ ]	[ ]	[ ]
h. Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	[ ]	[ ]	[ ]	[ ]
i. Thoughts that you would be better off dead or of hurting yourself in some way	[ ]	[ ]	[ ]	[ ]

Patient Initials:__ __ __
Study ID#:__ __-__ __ __ __

3. Questions about anxiety.

	NO	YES
a. In the last 4 weeks, have you had an anxiety attack - suddenly feeling fear or panic?	[ ]	[ ]

If you checked "NO", go to question #5.

	NO	YES
b. Has this ever happened before?	[ ]	[ ]
c. Do some of these attacks come suddenly out of the blue - that is, in situations where you don't expect to be nervous or uncomfortable?	[ ]	[ ]
d. Do these attacks bother you a lot or are you worried about having another attack?	[ ]	[ ]

4. Think about your last bad anxiety attack.

	NO	YES
a. Were you short of breath?	[ ]	[ ]
b. Did your heart race, pound, or skip?	[ ]	[ ]
c. Did you have chest pain or pressure?	[ ]	[ ]
d. Did you sweat?	[ ]	[ ]
e. Did you feel as if you were choking?	[ ]	[ ]
f. Did you have hot flashes or chills?	[ ]	[ ]
g. Did you have nausea or an upset stomach, or the feeling that you were going to have diarrhea?	[ ]	[ ]
h. Did you feel dizzy, unsteady, or faint?	[ ]	[ ]
i. Did you have tingling or numbness in parts of your body?	[ ]	[ ]
j. Did you tremble or shake?	[ ]	[ ]
k. Were you afraid you were dying?	[ ]	[ ]

5. Over the last 4 weeks, how often have you been bothered by any of the following problems?	**Not at all**	**Several days**	**More than half the days**
a. Feeling nervous, anxious, on edge, or worrying a lot about different things	[ ]	[ ]	[ ]

If you checked "Not at all", go to question #6.

b. Feeling restless so that it is hard to sit still	[ ]	[ ]	[ ]
c. Getting tired very easily	[ ]	[ ]	[ ]
d. Muscle tension, aches, or soreness	[ ]	[ ]	[ ]
e. Trouble falling asleep or staying asleep	[ ]	[ ]	[ ]
f. Trouble concentrating on things, such as reading a book, watching TV	[ ]	[ ]	[ ]
g. Becoming easily annoyed or irritable	[ ]	[ ]	[ ]

Patient Initials:__ __ __
Study ID#: __ __-__ __ __ __

6. Questions about eating.	NO	YES
a. Do you often feel that you can't control what or how much you eat?	[ ]	[ ]
b. Do you often eat, within any 2-hour period, what most people would regard as an unusually large amount of food?	[ ]	[ ]

If you checked 'NO' to either #6a or #6b, go to question #9.

	NO	YES
c. Has this been as often, on average, as twice a week for the last 3 months?	[ ]	[ ]

7. In the last 3 months have you often done any of the following in order to avoid gaining weight?	NO	YES
a. Made yourself vomit?	[ ]	[ ]
b. Took more than twice the recommended dose of laxatives?	[ ]	[ ]
c. Fasted - not eaten anything at all for at least 24 hours?	[ ]	[ ]
d. Exercised for more than an hour specifically to avoid gaining weight after binge eating?	[ ]	[ ]

8. If you checked 'YES' to any of these ways of avoiding gaining weight, were any as often, on average, as twice a week?	NO	YES
	[ ]	[ ]

	NO	YES
9. Do you ever drink alcohol (including beer or wine)?	[ ]	[ ]

If you checked "NO" go to question #11.

10. Have any of the following happened to you more than once in the last 6 months?	NO	YES
a. You drank alcohol even though a doctor suggested that you stop drinking because of a problem with your health	[ ]	[ ]
b. You drank alcohol, were high from alcohol, or hung over while you were working, going to school, or taking care of children or other responsibilities	[ ]	[ ]
c. You missed or were late for work, school, or other activities because you were drinking or hung over	[ ]	[ ]
d. You had a problem getting along with other people while you were drinking	[ ]	[ ]
e. You drove a car after having several drinks or after drinking too much	[ ]	[ ]

11. If you checked off any problems on this questionnaire, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
[ ]	[ ]	[ ]	[ ]

Patient Initials:__ __ __
Study ID#: __ __-__ __ __ __

12. During the last 4 weeks, how much have you been bothered by any of the following problems?	Not bothered at all	Bothered a little	Bothered a lot
a. Worrying about your health	[ ]	[ ]	[ ]
b. Your weight or how you look	[ ]	[ ]	[ ]
c. Little or no sexual desire or pleasure during sex	[ ]	[ ]	[ ]
d. Difficulties with husband/wife, partner/lover or boyfriend/girlfriend	[ ]	[ ]	[ ]
e. The stress of taking care of children, parents or other family members	[ ]	[ ]	[ ]
f. Stress at work or outside of the home or at school	[ ]	[ ]	[ ]
g. Financial problems or worries	[ ]	[ ]	[ ]
h. Having no one to turn to when you have a problem	[ ]	[ ]	[ ]
i. Something bad that happened recently	[ ]	[ ]	[ ]
j. Thinking or dreaming about something terrible that happened to you in the past - like your house being destroyed, a severe accident, being hit or assaulted, or being forced to commit a sexual act	[ ]	[ ]	[ ]

13. In the last year, have you been hit, slapped, kicked or otherwise physically hurt by someone, or has anyone forced you to have an unwanted sexual act?	NO	YES
	[ ]	[ ]

14. What is the most stressful thing in your life right now?

_____

_____

15. Are you taking any medicine for anxiety, depression or stress?	NO	YES
	[ ]	[ ]

16. FOR WOMEN ONLY: Questions about menstruation, pregnancy and childbirth.

a. Which best describes your menstrual periods?
___ Periods are unchanged
___ No periods because pregnant or recently gave birth
___ Periods have become irregular or changed in frequency, duration or amount
___ No periods for at least a year
___ Having periods because taking hormone replacement (estrogen) therapy or oral contraceptive

	NO	YES
b. During the week before your period starts, do you have a serious problem with your mood - like depression, anxiety, irritability anger or mood?	[ ]	[ ]
IF YES: Do these problems go away by the end of your period?	[ ]	[ ]
c. Have you given birth within the last 6 months?	[ ]	[ ]
d. Have you had a miscarriage within the last 6 months?	[ ]	[ ]
e. Are you having difficulty getting pregnant?	[ ]	[ ]

18 Appendix F: Female Sexual Distress Scale (FSDS- Revised 2005)

INSTRUCTIONS
Below is a list of feelings and problems that women sometimes have concerning their sexuality. Please read each item carefully, and circle the number that best describes HOW OFTEN THAT PROBLEM HAS BOTHERED YOU OR CAUSED YOU DISTRESS DURING THE PAST 7 DAYS INCLUDING TODAY. Circle only one number for each item, and take care not to skip any items. If you change your mind, erase your first circle carefully. Read the example before beginning, and if you have any questions please ask about them.
Example: How often did you feel: **Personal responsibility for your sexual problems.**

NEVER	RARELY	OCCASIONALLY	FREQUENTLY	ALWAYS
0	1	2	3	4

HOW OFTEN DID YOU FEEL:

1. Distressed about your sex life	0	1	2	3	4
2. Unhappy about your sexual relationship	0	1	2	3	4
3. Guilty about sexual difficulties	0	1	2	3	4
4. Frustrated by your sexual problems	0	1	2	3	4
5. Stressed about sex	0	1	2	3	4
6. Inferior because of sexual problems	0	1	2	3	4
7. Worried about sex	0	1	2	3	4
8. Sexually inadequate	0	1	2	3	4
9. Regrets about your sexuality	0	1	2	3	4
10. Embarrassed about sexual problems	0	1	2	3	4
11. Dissatisfied with your sex life	0	1	2	3	4
12. Angry about your sex life	0	1	2	3	4
13. Bothered by low sexual desire	0	1	2	3	4

19 Appendix G: 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?	☐	☐	☐	☐	☐

20 Appendix H: Sleep Habits Questionnaire

SLEEP HEART HEALTH STUDY

SLEEP HABITS QUESTIONNAIRE

ID#:

Field Center: ____ ____

Today's date: ____ ____ ____
month day year

Please complete as thoroughly as possible and to the best of your knowledge.

1 A. At what time do you usually FALL ASLEEP on weekdays or your work days?

____ ____ : ____ ____ ☐ 1 A.M. *(Midnight is 12:00 A.M.)*
☐ 2 P.M.

B. At what time do you usually FALL ASLEEP on weekends or your non-work days?

____ ____ : ____ ____ ☐ 1 A.M. *(Midnight is 12:00 A.M.)*
☐ 2 P.M.

2 How many minutes does it usually take you to fall asleep at bedtime?

____ ____ ____ *(Number of minutes)*

3 A. At what time do you usually WAKE UP on weekdays or your work days?

____ ____ : ____ ____ ☐ 1 A.M.
☐ 2 P.M.

B. At what time do you usually WAKE UP on weekends or your non-work days?

____ ____ : ____ ____ ☐ 1 A.M.
☐ 2 P.M.

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4 How many hours of sleep do you usually get at night (or your main sleep period) on weekdays or workdays?

_____ _____ *(Number of hours)*

5 How many hours of sleep do you usually get at night (or your main sleep period) on weekends or your non-work days?

_____ _____ *(Number of hours)*

6 During a usual week, how many times do you nap for 5 minutes or more? *(Write in "0" if you do not take any naps.)*

_____ _____ *(Number of times)*

7 Please indicate how often you experience each of the following. *(Check one box for each item.)*

	NEVER (0)	RARELY (1/month or less)	SOMETIMES (2-4/month)	OFTEN (5-15/month)	ALMOST ALWAYS (16-30/month)
A. Have trouble falling asleep.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
B. Wake up during the night and have difficulty getting back to sleep.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
C. Wake up too early in the morning and be unable to get back to sleep.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
D. Feel unrested during the day, no matter how many hours of sleep you had.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
E. Feel excessively (overly) sleepy during the day.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
F. Do not get enough sleep.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
G. Take sleeping pills or other medication to help you sleep.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Questions 8 through 16 are about snoring and breathing during sleep. To answer these questions, please consider both what others have told you AND what you know about yourself.

8 Have you ever snored (now or at any time in the past)?

☐ 1 YES

☐ 0 NO → *Skip to Question 14 on page 4.*

☐ 8 DON'T KNOW → *Skip to Question 14 on page 4.*

9 How often do you snore now? *(Check one.)*

☐ 0 Do not snore any more. → *Skip to Question 13 on page 4.*

☐ 1 Rarely - less than one night a week.

☐ 2 Sometimes - 1 or 2 nights a week.

☐ 3 Frequently - 3 to 5 nights a week.

☐ 4 Always or almost always - 6 or 7 nights a week.

☐ 8 Don't know.

10 How loud is your snoring? *(Check one.)*

☐ 1 Only slightly louder than heavy breathing.

☐ 2 About as loud as mumbling or talking.

☐ 3 Louder than talking.

☐ 4 Extremely loud - can be heard through a closed door.

☐ 8 Don't know.

11 For how many years have you been snoring?

____ ____ *(Number of years)* **OR** Don't know ☐ 88

12 Is your snoring: ***(Check one.)***

- ☐ 1 Increasing over time?
- ☐ 2 Decreasing over time?
- ☐ 3 Staying the same?
- ☐ 8 Don't know.

13 Have you ever had surgery as treatment for your snoring?

☐ 1 YES ☐ 0 NO

14 Are there times when you stop breathing during your sleep?

☐ 1 YES

☐ 0 NO → *Skip to Question 16 on page 5.*

☐ 8 DON'T KNOW → *Skip to Question 16 on page 5.*

15 How often do you have times when you stop breathing during your sleep?

- ☐ 1 Rarely - less than one night a week.
- ☐ 2 Sometimes - 1 or 2 nights a week.
- ☐ 3 Frequently - 3 to 5 nights a week.
- ☐ 4 Always or almost always - 6 or 7 nights a week.
- ☐ 8 Don't know.

16 A. Have you ever been told by a doctor that you had sleep apnea (a condition in which breathing stops briefly during sleep)?

☐ 1 YES ☐ 0 NO → *Skip to Question 17 below.*

☐ 8 DON'T KNOW → *Skip to Question 17 below.*

B. Do you sleep with either a pressure mask ("CPAP") or a mouthpiece as treatment for your sleep apnea?

☐ 1 YES ☐ 0 NO

C. Have you had surgery as treatment for your sleep apnea?

☐ 1 YES ☐ 0 NO

17 Do you usually use oxygen therapy (oxygen delivered by a mask or nasal cannula) during your sleep?

☐ 1 YES ☐ 0 NO

18 In the past year, how often, on average, have you been awakened with the following?

	NEVER (0)	RARELY (1/month or less)	SOMETIMES (2-4/month)	OFTEN (5-15/month)	ALMOST ALWAYS (16-30/month)
A. Coughing or wheezing.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
B. Chest pain or tightness.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
C. Shortness of breath.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
D. Sweats or hot flashes.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
E. Noise in your surroundings.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
F. Pain in your joints, muscles, or back.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
G. Heartburn or indigestion.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
H. Leg cramps or leg jerks.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I. Need to go to the bathroom.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

19 During the past year, how often have one or more members of your household been in or near the room where you have slept?

☐ 1 NEVER ☐ 2 SOMETIMES ☐ 3 USUALLY

20 What is the chance that you would doze off or fall asleep (not just "feel tired") in each of the following situations? *(Check one box for each situation. If you are never or rarely in the situation, please give your best guess for that situation.*

	NO CHANCE	SLIGHT CHANCE	MODERATE CHANCE	HIGH CHANCE
A. Sitting and reading.	☐ 1	☐ 2	☐ 3	☐ 4
B. Watching TV.	☐ 1	☐ 2	☐ 3	☐ 4
C. Sitting inactive in a public place (such as a theater or a meeting).	☐ 1	☐ 2	☐ 3	☐ 4
D. Riding as a passenger in a car for an hour without a break.	☐ 1	☐ 2	☐ 3	☐ 4
E. Lying down to rest in the afternoon when circumstances permit.	☐ 1	☐ 2	☐ 3	☐ 4
F. Sitting and talking to someone.	☐ 1	☐ 2	☐ 3	☐ 4
G. Sitting quietly after a lunch without alcohol.	☐ 1	☐ 2	☐ 3	☐ 4
H. In a car, while stopped for a few minutes in traffic.	☐ 1	☐ 2	☐ 3	☐ 4
I. At the dinner table.	☐ 1	☐ 2	☐ 3	☐ 4
J. While driving.	☐ 1	☐ 2	☐ 3	☐ 4

Field Center Use Only

☐ 0 Self administered

Interviewer administered, in:

☐ 1 English ☐ 4 Pima

☐ 2 Spanish ☐ 5 Other, specify:_____

☐ 3 Lakota ☐ 6 Unknown

Interviewer or Reviewer _____ _____ _____ Date: _____ _____ _____
month day year

21 Appendix I: International Index of Erectile Function (IIEF)

(Write the number that best describes your erectile function for the past 4 weeks in the spaces provided.)

Over the past four weeks: 1. How often were you able to get an erection during sexual activity? _____	0 = No sexual activity 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration? _____	0 = No sexual activity 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
3. When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner? _____	0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
4. During intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner? _____	0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
5. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse? _____	0 = Did not attempt intercourse 1 = Extremely difficult 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
6. How many times have you attempted sexual intercourse? _____	0 = No attempts 1 = One to two attempts 2 = Three to four attmepts 3 = Five to six attempts 4 = Seven to ten attempts 5 = Eleven or more attempts
7. When you attempted sexual intercourse, how often was it satisfactory for you? _____	0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
8. How much have you enjoyed sexual	0 = No intercourse

intercourse? _____	1 = No enjoyment 2 = Not very enjoyable 3 = Fairly enjoyable 4 = Highy enjoyable 5 = Very highly enjoyable
9. When you had sexual stimulation or intercourse, how often did you ejaculate? _____	0 = No sexual stimulation/intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
10. When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax? _____	0 = No sexual stimulation/intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
11. How often have you felt sexual desire? _____	1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
12. How would you rate your sexual desire? _____	1 = Very low/none at all 2 = Low 3 = Moderate 4 = High 5 = Very high
13. How satisfied have you been with your overall sex life? _____	1 = Very dissatisfied 2 = Moderately dissatisfied 3 = About equally satisfied and dissatisfied 4 = Moderately satisfied 5 = Very satisfied
14. How satisfied have you been with your sexual relationship with your partner? _____	1 = Very dissatisfied 2 = Moderately dissatisfied 3 = About equally satisfied and dissatisfied 4 = Moderately satisfied 5 = Very satisfied
15. How would you rate your confidence that you could get and keep an erection? _____	1 = Very low 2 = Low 3 = Moderate 4 = High 5 = Very high

*RC Rosen, A Riley, G Wagner et al. The international index of erectile dysfunction (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997 49: 822-30.

22 Appendix J: Investigator Signature of Agreement

Investigator Signature of Agreement

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

Title: Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation

Version: 6.0

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 all RMN Investigators and research staff from my site.

_____ _____

Signature Date

23 Appendix K: DSMB Charter

Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation

DATA AND SAFETY MONITORING BOARD (DSMB) CHARTER

Purpose and Responsibilities of the DSMB

The members of the Data and Safety Monitoring Board (DSMB) identified in this Charter for the AMIGOS 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 AMIGOS 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 AMIGOS 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 AMIGOS study will complete those tasks.

Basic Responsibility of DSMB	Method DSMB for AMIGOS 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 on behalf of RMN. · Serious Adverse Events: Review report submitted by the DCC on behalf of RMN 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 NICHD Committee Coordinator 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 on behalf of RMN.
Develop an understanding of the Study's risks and benefits	· Review study protocols and related literatures. · Review interim reports of subject 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 Sections 5 and 6 of this DSMB charter.

Contacts

NICHD
Charisee Lamar, PhD, Committee Coordinator
Esther Eisenberg, MD, Project Scientist

Data Coordination Center (DCC)
Heping Zhang, PhD, DCC Principal Investigator
Meizhuo Zhang, PhD, DCC Project Director
Sui Tsang, DCC Data Manager

Lead Investigator(s)
Michael Diamond, MD

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

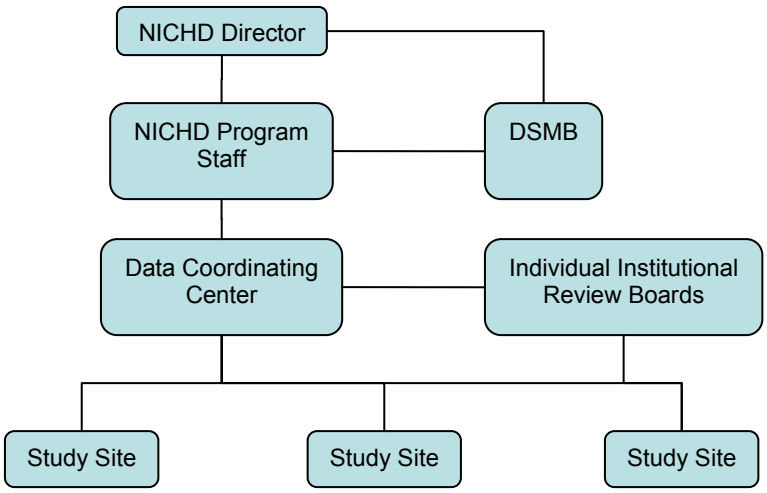
DSMB Members, Organizational Chart, & Communications

Members
The DSMB for the AMIGOS 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
Robert Rebar, MD	Chair of DSMB Voting member	· Chair the DSMB discussion and prepare written recommendations to NICHD. · Ensure the safety of study subjects, 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.
Vivian Lewis, MD	Voting member	· Ensure the safety of study subjects, 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.
Rev. Phillip Cato, PhD	Voting member	
Vanja Dukic, PhD	Voting member	
Frank Witter, MD	Voting member	
Peter Schlegel, MD	Voting member	

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 AMIGOS study.



Communication

Communication for members of this DSMB will be primarily through the NICHD Program Office and, where applicable, the Data Coordination Center (DCC). Investigators from the AMIGOS 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.

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 (COI) and provide their signed summary of any COI for the study, at its onset, to the NICHD Committee Coordinator, Dr. Charisee Lamar. A table summarizing any COI within the DSMB is provided in the Appendix.

Prior to each meeting, all members of the RMN 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 NICHD Committee Coordinator. The Coordinator will forward the COI documentation to the DCC for record-keeping purposes.

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.

Meeting Schedule

DSMB meetings will be conducted quarterly. However, the DSMB may hold a meeting at any time in accordance with their mission. The NICHD Committee Coordinator will notify the DCC of any change in schedule.

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.	December 15th, 2010	Brief
2.	March 15th, 2011	Brief
3.	June 15th, 2011	**Full**
4.	September 15th, 2011	Brief
5.	December 15th, 2011	**Full**
6.	March 15th, 2011	Brief
7.	June 15th, 2011	**Full**
8.	September 15th, 2011	Brief

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

Blinding

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

Efficacy Outcome Summary

An interim analysis is planned at the mid-point of the study to assess the overall pregnancy rate (i.e., the three groups combined) while maintaining blinding of treatment assignment in order to assess whether this pregnancy rate approximates the predicted rate of 30-40%, and whether additional subjects may be needed to meet power targets. Since treatment assignments will not be identified, it is not thought that adjustments in significance levels will be required.

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?
Robert Rebar, MD			
Vivian Lewis, MD			
Rev. Phillip Cato, PhD			
Vanja Dukic, PhD			
Frank Witter, MD			
Peter Schlegel, MD			

Reproductive Medicine Network

Conflict of Interest Statement

Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation

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).

DSMB Confidentiality Agreement

I understand that I will be provided with information from the Data Coordination Center or Study sites or similar organizations for the AMIGOS study, including proprietary and confidential information.

I understand that I will have access to these records in order to participate in the Independent Data Monitoring Committee for the AMIGOS study.

In my role as a member of the DSMB, I _____, *[insert name]* hereby agree that I shall not release, publish, or reproduce these records. I further agree that I shall not make any use of these records except for the limited purpose of participation in the Independent Data Monitoring Committee for the AMIGOS study.

I will take reasonable precautions to prevent access by any other persons to these confidential records or to work products that result from review of those records. I will retain any confidential documentation until the conclusion of the Study and will return the documents and all related materials to the Executive Secretary for this Study.

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

Signed: _____ Date: _____
[Name], [Title]