NICHD
NATIONAL REPRODUCTIVE MEDICINE NETWORK PROTOCOL

Ovulation Induction/Insemination Trial
Revised Protocol, February, 1993

DATA COORDINATING CENTER

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Preface

Initially, the Steering Committee of the NICHD National Reproductive Medicine Network proposed to evaluate the efficacy of ovulation induction with Metrodin and/or intrauterine insemination in two simultaneous randomized controlled trials, one focused on couples with unexplained infertility and the other on couples diagnosed with pure male-factor infertility. By June of 1992, 60 couples had been randomized to treatment according to this design -- 36 with unexplained infertility and 24 with pure male factor infertility.

Experience in designing and implementing the initial study protocol showed, however, that distinguishing these two diagnostic groups was problematic. The distinction was based on arbitrary cut points in the semen parameters by which male fertility potential is currently assessed, but for which intraindividual variability is fairly large. Enrollment in the two trials was lower than expected because many couples had to be excluded from both groups when they failed to meet just one of the strict inclusion criteria related to semen quality. This led to a reassessment of the literature on which the semen cut points are based and, ultimately, to the conclusion that they are not well supported and that the attempt to diagnose male factor infertility should be abandoned.

On June 15, 1992, the study design was revised in favor of a single trial which would include all infertile couples where the female partner is "normal" and the male has at least some motile sperm. The primary study question to be tested in this single trial is whether Metrodin and/or intrauterine insemination are efficacious in the treatment of the group of infertility patients fitting this broader definition. A secondary analysis will search for points along the continuum of male semen parameters that appear to influence the efficacy of treatment. Yet another set of analyses will utilize the data collected in the course of the trial, together with ancillary data on sperm parameters in fertile males, to try to identify boundaries that define male-factor infertility with more precision and accuracy than has heretofore been possible.

NICHD NATIONAL REPRODUCTIVE MEDICINE NETWORK

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Section 1. INTRODUCTION AND BACKGROUND

Fecundity per cycle among normally fertile couples is approximately 25 percent. However, an estimated 10-15 percent of couples fail to conceive during a 12 month period of unprotected intercourse (Mosher, 1985). Among the conditions that relate to infertility are reduced sperm quantity and quality, endometriosis, tubal damage, ovulatory dysfunction, and cervical factors. Couples who are infertile without identifiable cause are said to have unexplained infertility. It is unclear whether these couples have some heretofore unknown cause of infertility or are simply reflecting the lower end of a Gaussian distribution of natural cyclic fecundity, determined by factors such as increasing age. Male factor infertility, typically diagnosed on the basis of decreased sperm concentration, poor sperm motility and abnormal sperm morphology, may also represent the extreme of a normal distribution of sperm quality parameters.

Of the many diagnoses given to infertile couples, unexplained infertility and male factor infertility are among the most difficult for which to advise therapy, partly because they involve areas of reproduction about which little is known. Nevertheless, intrauterine insemination (IUI) and ovarian stimulation with human menopausal gonadotropins (hMG) have been used, both singly and in combination, to treat couples with these diagnoses. Such treatments are expensive, time consuming and not without risk (although perhaps less so than GIFT), but it remains unclear to what extent they actually increase fecundity in cases of unexplained or male factor infertility. This is because studies to date have involved small numbers of subjects drawn from selected populations; have either been uncontrolled or have used different types of controls (coitus, intracervical insemination, untreated cycles in the same individuals); have followed different treatment protocols; and have, in some instances, reported fecundity rates for treatment groups involving a mixture of diagnoses.

To provide a rigorous evaluation of the efficacy of ovarian stimulation and intrauterine insemination, as well as the combined treatment, we propose to conduct a multicenter randomized controlled trial. Infertile couples in whom the female appears to be normal will be randomly assigned to one of four treatment arms: intracervical insemination (ICI, the control group), intrauterine insemination (IUI), hMG with intracervical insemination (hMG with ICI), and hMG with intrauterine insemination (hMG with IUI). The particular hMG to be used in the trial is Metrodin. Randomized couples will be followed for up to four treatment cycles and the per couple fecundity rate determined for each arm. Potential confounding variables such as age, duration of infertility and type of infertility (primary or secondary) will be controlled in the analysis of treatment efficacy. In addition to comparing each of the three treatments to ICI alone, we will also investigate the relative efficacy of the treatments by comparing hMG with IUI to IUI alone, and hMG with IUI to hMG with ICI. The trial will have a sample size adequate to detect 2.5-fold differences between experimental and control groups.

Following is a brief review of the published literature concerning the treatments we propose to evaluate.

Ovulation Induction

It is not difficult to postulate that ovulation induction in anovulatory women will increase fecundity. The mechanism by which this therapy might increase fecundity in women who already ovulate is less certain, but is presumed to relate to the increase in the numbers of oocytes available for fertilization.

Welner et al. (1988) studied couples enrolled in the infertility clinic at Yale University between 1982 and 1985 with a diagnosis of unexplained infertility. Ninety-seven couples received up to four cycles of hMG while awaiting *in vitro* fertilization. Sixty percent of these

women had previous surgery to correct tubal disease or endometriosis. Forty-eight couples with unexplained infertility who chose not to receive hMG treatment served as a control group. The fecundity rate per couple in the treated group (0.12) was significantly higher than their spontaneous fecundity rate (0.01), and was higher than the fecundity rate in the control group (0.04). Serhal et al. (1988) also reported fecundity rates of 0.12 per couple and 0.06 per cycle among 25 couples with unexplained infertility who were treated with hMG.

Dodson et al. (1989) conducted a prospective clinical trial at Duke University Medical Center involving 27 women with polycystic ovary syndrome. Each cycle of the subjects in the trial was randomly assigned to treatment with hMG alone or hMG plus a gonadotropin releasing-hormone agonist (leuprolide). Four pregnancies occurred in 25 cycles initiated by hMG alone (per cycle fecundity [f] = 0.16) and nine pregnancies occurred in 33 cycles initiated with hMG plus leuprolide (f = 0.27). The difference in per cycle fecundity rates for the groups was not statistically significant.

Intrauterine Insemination

Intrauterine insemination using the first portion of the ejaculate was introduced in the mid 1800s as a method of treating male factor infertility (Nachtigall 1979). *In vitro* fertilization procedures have necessitated the development of techniques to concentrate sperm without seminal plasma. As a result, motile sperm can be injected into the uterus after washing, free of seminal plasma and its consequent risk of infection, cramping and anaphylaxis (Allen, 1985). A comprehensive review of 18 studies of patients treated with IUI (Allen et al., 1985) indicated that among 714 patients with various factors contributing to their infertility, IUI treatment was associated with an overall fecundity rate per couple of 0.28, on average, with a range of zero to 0.62. Studies of the efficacy of IUI alone for couples with a diagnosis of male factor infertility, however, report somewhat inconsistent results. DiMarzo

et al. (1986) observed a fecundity rate of 0.22 among nine couples diagnosed with male factor infertility who were treated with IUI alone for up to eight cycles, but no pregnancies among three couples with unexplained infertility. Emperaire (1989) reported a fecundity rate of 0.11 among 82 couples with male factor infertility after six cycles with IUI. Kerin and Quinn (1987) reported a pilot study of IUI in couples with male factor infertility and concluded that it had therapeutic benefits if the treatment was carefully timed with ovulation. On the other hand, 47 couples with long-term male factor infertility (mean 5.3 years) were enrolled in a prospective study at the University of Hong Kong (Ho et al., 1989). One anovulatory woman and 14 women who had long cycles also were treated with clomiphene citrate. Up to three cycles per couple were randomized to LH-timed IUI and up to three cycles to LH-timed vaginal intercourse. Only one couple conceived during 124 vaginal intercourse cycles and none of the couples conceived during 114 IUI cycles. These couples may represent a select group with very low probability of conception. Serhal et al (1988) reported fecundity rates of 0.07 per couple and 0.03 per cycle among 15 couples with unexplained infertility treated with IUI alone. Corson et al. (1989) reported a fecundity rate per cycle of 0.10 among couples with unexplained infertility treated with IUI alone.

Ovulation Induction with Intrauterine Insemination

Several studies have addressed the efficacy of IUI in combination with hMG ovarian stimulation. Two involved random assignment of couples to treatment (Cruz et al., 1986 and Nulsen et al., 1990); the remainder of the studies considered the records of selected patients and calculated fecundity per cycle based on whatever treatment had been used. The results are summarized below for couples with male factor infertility or unexplained infertility, although the studies generally included small numbers of subjects with these diagnoses and most made no comparison to an untreated control group.

Couples seen at the University of Medicine and Dentistry - Rutgers Medical School with a diagnosis of oligoasthenospermia were treated with ovarian stimulation with hMG alone or with clomiphene citrate (Cruz et al., 1986). The first insemination was randomized to IUI or ICI, and subsequent treatments were alternated; vaginal intercourse was not restricted. For 96 IUI cycles among these 49 couples, f was 0.07, and for 86 ICI cycles, f was 0.01 ($p < 0.001$); the fecundity rate per couple during IUI was 0.14 and during ICI was 0.02 ($p < 0.05$). The majority of conceptions occurred within three treatment cycles.

Serhal et al. (1988) studied 62 couples with unexplained infertility at University College and Middlesex School of Medicine, London. One group of 15 women was inseminated using IUI alone; 25 women were treated with hMG alone; and an additional 22 women were treated with hMG followed by IUI. It is not clear how the treatment groups were formed, but only two of 25 women receiving hMG alone and one of 22 woman receiving hMG plus IUI had a diagnosis of secondary infertility, while half the women receiving IUI alone (8 of 15) had secondary infertility; the duration of infertility was substantially shorter in the IUI alone group. The rates of fecundity per couple and per cycle, respectively, were most impressive for the hMG plus IUI group (0.41 and 0.26), and were significantly different from the group with hMG alone (0.12 and 0.06) and IUI alone (0.07 and 0.03).

Yovich and Matson (1988) reported on 345 couples with a single detectable fertility problem treated with IUI and stimulated with hMG, clomiphene citrate, or both at a referral center in Western Australia from 1982 to 1986. No pregnancies occurred among 13 couples with asthenozoospermia. For 42 couples with oligozoospermia, the fecundity rate was 0.21 per couple and 0.10 per cycle. The rates were only slightly lower for 68 couples with unexplained infertility (0.18 per couple and 0.09 per cycle).

Records were reviewed for all women treated with ovulation stimulation at the University of Texas Health Science Center at San Antonio and Humana Women's Hospital

from 1985 to 1987 (Kaplan et al., 1989). Fecundity rate per cycle using IUI and stimulation by hMG or clomiphene citrate plus hMG was compared to GIFT. For patients with male factor infertility, similar rates were observed for superovulation plus IUI (0.15) and for GIFT (0.19). No couples with unexplained infertility conceived using superovulation plus IUI, while the cyclic fecundity rate for GIFT in such couples was 0.37. The pregnancy rate for all diagnoses combined was significantly better for GIFT, with an odds ratio of 3.25 ($p=0.001$) after adjustment for endometriosis, duration of infertility, and total motile sperm count.

A review by Dodson et al. (1987) of the records of all couples treated with IUI and ovulation stimulation with hMG at Duke between 1983 and 1986 found the fecundity rate per cycle in those with a diagnosis of unexplained infertility (0.19) to be similar to the normal rate of about 25 percent. Corson et al. (1989) reviewed the records of all couples having at least one cycle of IUI from 1984 to 1986 at the Philadelphia Fertility Institute. Among couples with unexplained infertility, f was 0.10 for IUI alone (ten cycles studied), 0.17 for hMG plus IUI (12 cycles studied), and 0.33 for clomiphene citrate plus IUI (three cycles studied). Among couples with male factor infertility, neither IUI alone nor ovulation stimulation plus IUI increased the per cycle fecundity rate. In 40 couples diagnosed with male factor infertility and 11 couples with unexplained infertility treated at the University Hospital of Trondheim, Norway with clomiphene citrate, hMG, and IUI (Sunde et al. 1988), this combined therapy achieved f of 0.05 for oligozoospermia, 0.20 for oligoasthenozoospermia, 0.18 for asthenozoospermia, and 0.07 for unexplained infertility. Fecundity rates were not reported separately by diagnosis, and no control group was studied. Patients seen at the University of Massachusetts Reproductive Endocrinology Clinic (Daly, 1989) for unexplained infertility elected to receive no aggressive therapy ($n=47$) or alternating cycles of hMG and hMG with IUI ($n=20$). The fecundity rate per cycle was 0.04 for the control group; the rate was 0.11 for the study group during 55 treatment cycles and was 0.02 during nontreatment cycles; no

data were presented differentiating effects of hMG from hMG with IUI.

The empirical evidence suggests that hMG with IUI does increase fecundity in couples diagnosed with male factor infertility; the success of this therapy compared to IUI alone, to ICI with or without hMG, or to vaginal intercourse may depend on the underlying cause, e.g., oligozoospermia versus asthenozoospermia. In couples with unexplained infertility, insemination alone may be ineffective (Table 1), and the value of ovulation induction and its interaction with insemination remains to be established (Table 2). Treatment with hMG plus IUI is expensive, poses some risk of hyperstimulation syndrome and is associated with a 25-30 percent incidence of multiple pregnancy (Hurst and Wallach, 1990). As the use of these treatments is increasing, there is an urgent need to determine their true efficacy in well controlled trials involving couples with clearcut diagnoses of unexplained or male factor infertility. Referral centers for infertility, such as the Network's Reproductive Medicine Units (RMUs), are a reasonable locus for testing efficacy since this is the setting in which these therapies are usually being applied. The trial we propose may also recruit some subjects directly from community physicians known to the RMUs. Sample size has been calculated to allow for a comparison of efficacy between treatments as well as for comparison of each treatment against the control group.

TABLE 1.

Fecundity Rate Per Cycle and Per Couple with Unexplained Infertility Treated by IUI Alone

First Author Year	Number of Pregnancies	Total Number of Cycles	Fecundity Rate Per Cycle	Number of Couples	Fecundity Rate Per Couple
Serhal, 1988	1	30	0.03	15	0.07
Corson, 1989	1	10	0.10	---	---
Nulsen, 1990	0	25	0.00	---	---

TABLE 2.

Fecundity Rate Per Cycle and Per Couple with Unexplained Infertility
Treated by IUI with hMG Ovulation Induction

First Author Year	Number of Pregnancies	Total Number of Cycles	Fecundity Rate Per Cycle	Number of Couples	Fecundity Rate Per Couple
Cruz, 1986	7	96	0.07	49	0.14
Dodson, 1987	6	31	0.19	19	0.32
Emperaire, 1988	5	---	---	32	0.16
Yovich, 1988	12	134	0.09	68	0.18
Serhal, 1988	9	34	0.26	22	0.41
Sunde, 1989	1	15	0.07	---	---
Daly, 1989	6	55	0.11	20	0.30
Corson, 1989	2	12	0.17	---	---
Kaplan, 1989	0	---	---	7	0.00
Nulsen, 1990	9	32	0.28	---	---
Dodson, 1990	17	116	0.15	---	---
Hurst, 1990	4	17	0.24	---	---

Section 2. OVERVIEW OF THE STUDY

The NICHD National Reproductive Medicine Network will conduct a multicenter randomized controlled trial to evaluate the efficacy of ovulation induction with human menopausal gonadotropin (hMG) and intrauterine insemination (IUI) -- compared to intracervical insemination (ICI), a surrogate for timed vaginal intercourse -- in the treatment of infertile couples when the female partner appears to be normal and the male partner has at least some motile sperm. The particular hMG to be used in the trial is Metrodin, a drug similar to Pergonal. In order to avoid selection by socioeconomic status, patients will not be required to pay out-of-pocket for tests or treatments related to the trial. Couples enrolled will receive up to four cycles of treatment. Insofar as possible, these will be consecutive cycles; however, rest cycles may be required for clinical indications and, in addition, subjects will be allowed up to two rest cycles for personal reasons.

The trial will enroll a total of 932 couples who have failed to conceive after a year of trying and have received no previous treatment with hMG or intrauterine insemination. Couples who meet the eligibility requirements after completing a full evaluation (described below in Section 4) will be randomly assigned to one of four treatment groups:

1) Intracervical insemination (control group)
2) Intrauterine insemination
3) hMG with intracervical insemination
4) hMG with intrauterine insemination

Randomization will occur within a Reproductive Medicine Unit (RMU), to ensure a balance of treatments at each site. Only couples who agree to be randomized can be enrolled in the study.

Each couple will undergo up to four cycles of therapy. Rates of conception, complications, and treatment failures will be determined for the four groups at each RMU.

Five statistical comparisons will be made: rates of outcomes in each of the treatment groups will be compared to the rates in the control group. In addition, in order to evaluate the relative efficacy of IUI and hMG, the group receiving IUI with hMG will be compared to the group receiving ICI with hMG and to the group receiving IUI without hMG. The Bonferroni adjustment for multiple comparisons will be made, so each test will be performed at the $0.05/5 = 0.01$ significance level.

All couples who are randomized will be included in the statistical analyses, regardless of treatment outcome or completion of all four study cycles. Differences across RMUs and confounding variables such as age and duration or degree of infertility (primary or secondary) will be considered in the analysis. A detailed description of the protocol for the trial is given in Section 3 below.

Section 3. DETAILED DESCRIPTION OF THE STUDY

A. Study Objectives

This study addresses the question of whether superovulation with hMG, IUI, or the combination of hMG/IUI increases the likelihood of conception in infertile couples when the female partner appears to be normal. Because of the arbitary nature of cutpoints for differentiating normal from abnormal semen quality, the protocol has been revised to allow all males with any motile sperm to be entered into the trial.

B. Study Design

A 2-factor design will be used as diagrammed below:

	IUI	ICI
hMG		
No hMG		

Infertile couples will be recruited from patients with a well-documented diagnosis of unexplained infertility in the female, regardless of the values for semen quality in the male, according to criteria described below in Section 3E. Eligible couples will be randomized to one of the four treatment arms represented by the cells in the above fourfold table using a random number scheme described below in Section 4C. Treatment will continue until pregnancy is achieved or until four treatment cycles are completed without pregnancy. Women who do not demonstrate adequate ovarian response to increasing levels of hMG stimulation during the first two treatment cycles will be included in the analysis as treatment failures, but will not undergo additional treatment in the study.

C. Procedures

1. hMG protocol

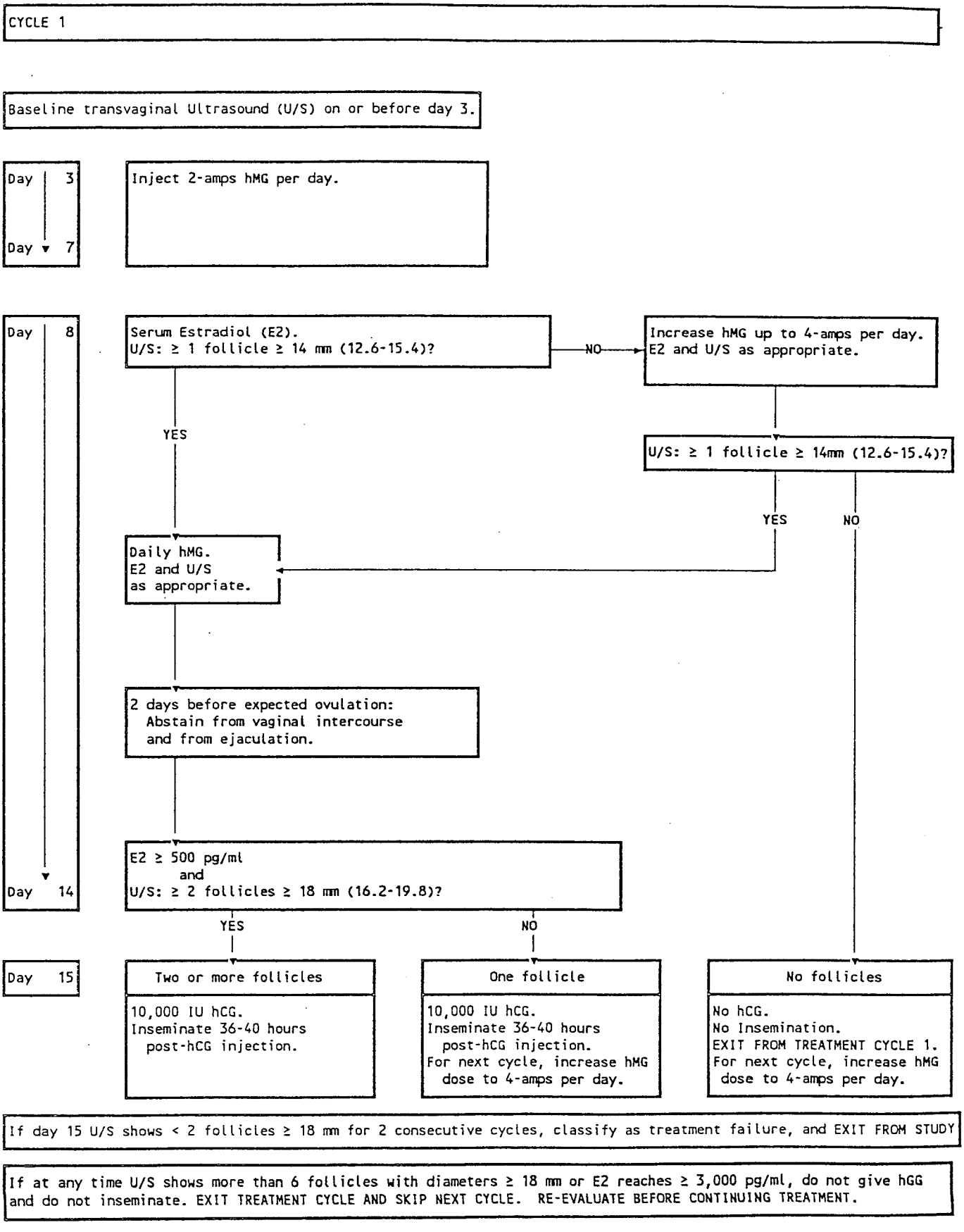
As outlined in Figure 1 below, women randomized to one of the two hMG treatment arms will have a baseline transvaginal ultrasound (U/S) examination on or before day 3 of the menstrual cycle. In carrying out the hMG protocol, the criteria for estradiol level and follicle size can be adjusted within a $\pm$ 10% range to allow for measurement error and clinical judgement. All other instructions are to be followed to the letter and the $\pm$ 10% margin should be adhered to strictly.

Starting on the morning of cycle day 2 or 3, hMG will be administered at a dosage of 2 amps per day. On cycle day 8 (range: cycle days 7-9), serum estradiol (E_2) will be measured and a transvaginal U/S will be performed. If there is at least one follicle having a mean diameter in two dimensions of $\geq$ 14 mm (range: 12.6-15.4 mm), daily hMG will be continued and E_2 and U/S will be obtained as appropriate until there are at least 2 follicles $\geq$ 18 mm (range: 16.2 -19.8 mm) and E_2 is greater than 500 pg/ml (range: 450-550 pg/ml).

If there are no follicles measuring $\geq$14 mm by cycle day 8, daily hMG administration will be continued but the hMG dose can be increased by the principal investigator up to a maximum of 4 amps per day. E_2 and U/S monitoring will continue as appropriate until there are at least 2 follicles $\geq$18 mm (range: 16.2-19.8 mm) and E_2 is greater than 500 pg/ml (range: 450-550 pg/ml). If no follicles measuring 14 mm are seen by day 15, the couple exits this treatment cycle.

Beginning two days prior to expected ovulation (approximately cycle day 12), each couple will be instructed to abstain from vaginal intercourse and the male partner will be instructed not to ejaculate until the insemination sample is obtained. When at least two follicles measuring $\geq$ 18 mm are seen and E_2 is greater than 500 pg/ml, hMG will be discontinued and hCG (10,000 IUI) will be administered. A single insemination (IUI or ICI) will

Figure 1. hMG Treatment Protocol Decision Tree



be performed 36-40 hours after hCG administration. Couples will be advised to abstain from intercourse for 72 hours following the insemination in order to insure that any conceptions occurring in that cycle are actually the result of the treatment.

Women who develop only one follicle measuring $\geq$ 18 mm by cycle day 15 (i.e., after 12 days of hMG stimulation) will receive hCG on day 15 and undergo insemination as above, but will commence the next cycle (unless pregnancy occurs) with 4 amps per day of hMG. In all other respects they will follow the above protocol for hMG administration and monitoring.

Women who show no follicle development by cycle day 15 will not receive hCG or insemination, but will commence the next cycle with 4 amps per day of hMG. If criteria for hCG administration are not reached on this high-dose hMG regimen, no further attempts at ovarian stimulation will be provided as part of the study.

> ***At any time, if more than 6 follicles measuring $\geq$ 18 mm (range 16.2-19.8 mm) are seen by U/S or if E_2 reaches $\geq$ 3,000 pg/ml (range 2700-3300 pg/ml), no hCG will be given and no insemination will be done. No treatment will be given during the <u>following</u> menstrual cycle but the woman will be monitored. If conception occurs, the pregnancy will be followed in the same way as all other study pregnancies. If menses occurs, the woman may re-enter the trial during the subsequent cycle provided that the transvaginal U/S on cycle day 3 indicates both ovaries are < 10 cm (range 9-11 cm) on all diameters [or the absence of ovarian follicular cysts > 3 cm (range 2.7-3.3 cm)]. To prevent a repeat occurrence of hyperstimulation, subsequent treatment cycles should be conducted using a "step-down" administration of hMG, as follows: 3 amps of hMG for 2 days, then 1 amp daily.***

After a rest cycle taken for personal reasons rather than a clinical indication, a woman may re-enter treatment only if menses occurs.

2. Spontaneous ovulation monitoring protocol

Women who are not randomized to hMG stimulation will undergo insemination (IUI or ICI) timed to their spontaneous ovulation. The day of expected ovulation will be determined by averaging the length of previous menstrual cycles and/or by charts of basal body temperature. Beginning four days prior to expected ovulation, a woman will test for an LH surge using an OvuQuick (Quidel Inc) urinary dipstick. This urinary LH test will be performed daily, using the second void of the morning, until an LH surge is detected. Beginning two days prior to expected ovulation, couples will be instructed to abstain from vaginal intercourse and the male will be instructed not to ejaculate until the insemination sample is obtained. Insemination (IUI or ICI) will be performed on the day after the LH surge, between 9:00 a.m. and 3:00 p.m. If an LH surge is not detected, the woman should stop testing after 9 days. On cycle day 24 (range: days 22-26), a serum progesterone level should be obtained to determine whether she has ovulated. A women must exit the study if she has 2 documented anovulatory cycles.

3. IUI protocol

Washed sperm will be prepared using the following procedures. Semen specimens will be collected at the clinical site by masturbation after at least 48 hours of abstinence, and will be allowed to liquify at room temperature. Evaluation and preparation of the semen will begin within one hour of collection. A 0.07 ml aliquot of the semen will be analyzed for sperm concentration, percent motility and progression; slides will be made for sperm morphology assessment and video recordings will be made for subsequent CASA. Viscous samples will be mechanically dispensed by repeating passage through a sterile 15 gauge hypodermic needle attached to a sterile hypodermic syringe. The remaining semen will be transferred to a 15 ml Falcon conical tube. If the semen volume is greater than 5 ml, the sample will be divided equally between two 15 ml tubes. The semen will be diluted 1:2 (V/V) with medium. The

medium will be Hams F10 buffered with HEPES and supplemented with 1.5% Albuminar, which is equivalent in protein concentration to 7.5% serum. If debris or gelatinous substances are present, the semen-medium mixture will be allowed to settle for one to two minutes. The diluted semen will then be carefully removed from the settled debris and aliquoted into 15 ml tubes, using 5 ml per tube. Tubes will be centrifuged at 250 x g for 10 minutes, the supernatants aspirated and the pellets resuspended in 0.5 ml of medium. All suspensions will be combined into 1 tube and medium will be added until the total volume is 3 ml. The tube will be centrifuged for 10 minutes, after which the supernatant will be aspirated. The final pellet will be resuspended by adding in 0.35 ml of medium. An aliquot of 0.05 ml of the sperm suspension will be removed for analysis of sperm concentration, percent motility and progression; slides will be made for sperm morphology assessment and video recordings will be made for subsequent CASA. The remaining 0.3 ml of sperm suspension will be drawn into a Shepard catheter which is attached to a 1 cc syringe.

IUI will be performed within 2 1/2 hours of the time of semen collection. Patients will be placed in the dorsal lithotomy position and a speculum will be used to expose the cervix. A sample of cervical mucus will be collected and evaluated for spinnbarkheit, ferning and cellularity. The presence of sperm in the mucus will be recorded. The Shepard catheter containing the inseminate will be passed through the cervical canal into the uterine cavity and a 1 cc syringe will be used to inject the sperm into the uterus. Patients will remain supine for 10 minutes.

4. ICI protocol

The semen specimen will be collected at the clinical site by masturbation after at least 48 hours of abstinence, and will be allowed to liquify at room temperature. Evaluation of the semen will begin within one hour of collection. A 0.07 ml aliquot will be removed from the

specimen for analysis of sperm concentration, motility and morphology. (If necessary, an aliquot of up to 0.3 ml can be removed for analysis, provided that no more than 30% of the total volume is taken.) A videotape of this sample will be recorded for later analysis by CASA.

ICI will be carried out within 1 1/2 hours of the time of semen collection. Patients will be placed in the dorsal lithotomy position and a speculum will be used to expose the cervix. A sample of cervical mucus will be collected and evaluated for spinnbarkheit, ferning and cellularity. The presence of sperm in the mucus will be recorded. The entire remaining semen specimen will be delivered to the cervix using a sterile 18 gauge angiocatheter. Patients will remain supine for 10 minutes.

Insofar as is possible, all the inseminations at an RMU should be performed by the same person, with one other person covering on weekends. Quality control of the IUI and ICI procedures is discussed in Section 8 below, under Responsibilities of the Reproductive Medicine Units.

D. Sample Size

We hypothesize that the pregnancy rate in the control group (no hMG/ICI) for this revised study will be a weighted average of the hypothesized control pregnancy rates in the two earlier populations --- 10% for the couples with unexplained infertility and 5% for couples with male factor infertility. Based on the enrollment experience of the RMUs, and on a desire to be conservative, we project that 50% of the combined population will be from the unexplained infertility group and that 50% will be from the male factor infertility group. The overall control pregnancy rate is therefore hypothesized to be $0.50 \times 0.10 + 0.50 \times 0.05 = 0.075$.

There will be three statistical comparisons in which each of the experimental groups (no hMG/IUI, hMG/IUI and hMG/ICI) is compared to the control group (no hMG/ICI). In

addition, two other pairwise comparisons will be made (hMG/IUI versus no hMG/IUI and hMG/IUI versus hMG/ICI). In order to correct for the increased chances of finding statistical significance solely because of the multiplicity of comparisons being performed, the Bonferroni test criterion will be employed: each of the primary comparisons will be tested at the significance level of 0.05/5 = 0.01 using a two-tailed test. That is, a critical ratio must exceed 2.576 instead of 1.96 in order for the corresponding comparison to be declared statistically significant with an overall error rate of 0.05.

The cumulative per-couple fecundity rate in at least one of the experimental groups is hypothesized to be 0.1875, a 2.5-fold increase over the hypothesized rate of 0.075 in the control group. With the parameters of the study as given above, and with a power of 80% to find statistical significance, the required total size is 840 couples, 210 couples per regimen (Fleiss 1981). We further hypothesize success rates of 0.10 and 0.20 in some pair of experimental regimens. The power to find significance with a sample of 210 couples per treatment group is 62%. Power is therefore moderate to detect as significant a difference between a slightly effective and highly effective test regimen.

We may wish to be conservative and assume that there is a loss of information in 10% of the couples. A total of 932 couples should therefore be randomized, 233 to each treatment group.

An issue that has to be considered is the likely inadequacy of our projected sample size for the secondary analyses of semen characteristics. Given the principle that such analyses should be performed in the study's control group, it is ironic that the pregnancy rate in the control group will likely be the lowest of all.

E. Inclusion and Exclusion Criteria

Couples of all races and ethnic origins will be eligible to enter the trials. Because of geographic location and patient demographics, the five participating RMUs will be able to provide subjects from minority groups. In addition, by adhering to the principle that patients should not have to pay out-of-pocket for tests or treatments related to the trial, there should be no selection by income.

Eligibility criteria for entrance into the trial are intentionally conservative or "strict" so that the findings will stand up to criticism. The aim is to exclude any couple with a possible "explanation" for reduced fertility in the female partner. The minimum criteria for inclusion in the study based on a standard diagnostic workup are outlined on the next page; exclusion criteria based on medical history are immediately following. In addition, Appendix C. (p. 64) is a compilation of decisions by the Clinical Subcommittee that further clarifies the inclusion and exclusion criteria.

Inclusion Criteria For Females*

1. Age 40 years or younger.

2. Pregnancy test negative.

3. Evidence of a normal pelvis and uterine cavity based on results of a laparoscopy and hysterosalpingogram (or hysteroscopy) anytime in the past.

   a. Patients with minimal or mild endometriosis (AFS Stage I or II) are eligible after a 6-month interval post-treatment.
   b. Patients with potentially significant defects seen on hysterosalpingogram (HSG) must be evaluated by repeat HSG and/or hysteroscopy. They are eligible if repeat HSG or hysteroscopy fails to confirm clinically significant abnormalities.
   c. Patients with a bicornuate, arcuate, didelphic or T-shaped uterus are eligible.
   d. Patients who have minor intra-abdominal adhesions that would not compromise fertility, and those who have had previous cervical conization or excision of uterine polyps, are eligible.

4. Late luteal phase biopsy normal (i.e. ± 3 days of expected dating based on next menses). Outside biopsy results acceptable if RMU confirms diagnosis on review of slides.

5. Serum antisperm antibody test negative (< 50% of antibodies directed at the head and/or entire sperm by immunobead test on serum at 1:10 dilution); borderline results can be sent to U.C. Davis for review.

6. The following serum hormone concentrations are within the normal range of the RMU laboratory:

   a. prolactin
   b. thyroid stimulating hormone
   c. follicle stimulating hormone (cycle day 1-5) [N.B. An extra tube of blood is to be drawn at the same time and sent to the DCC for quality control analyses.]

7. Two of the last 3 menstrual cycles between 24 and 40 days.

8. 1 year of unprotected intercourse in a stable monogamous relationship without a pregnancy.

Inclusion Criteria For Males

1. Age 55 years or younger.

2. Semen antisperm antibody test negative (< 20% of antibodies directed at the head and/or entire sperm by immunobead test on seminal sperm); borderline results can be sent to U.C. Davis for review.

3. Any motile sperm in the screening semen sample. (If < 2 million sperm/ml or < 10% motile sperm, special protocols will be used for semen evaluation.)

4. 1 year of unprotected intercourse in a stable monogamous relationship without a pregnancy.

Exclusion Criteria For Females

1. Previous IVF, GIFT, ZIFT or TET (ovulation induction).

2. Previous treatment with hMG.

3. Previous intrauterine insemination with the current partner.

4. History of chronic disease:
   a. thyroid disease
   b. diabetes
   c. collagen vascular disease
   d. chronic renal disease
   e. chronic adrenal disease
   f. any current chronic medication (previous 6 months or longer) for psychiatric indication
   g. any current chronic medication (previous 6 months or longer) for asthma
   h. any current chronic medication (previous 6 months or longer) for hypertension

5. History of chemotherapy; history of radiotherapy to the abdomen or pelvic area.

6. History of tubal surgery or significant tubal adhesions.

7. Endometriosis $\geq$ AFS Stage III.

8. History of myomectomy (abdominal), ovarian cystectomy, or unilateral oophorectomy, unless subsequent laparoscopy indicates the absence of significant pelvic adhesions.

Exclusion Criteria For Males

1. Previous IVF, GIFT, ZIFT or TET (ovulation induction) with the current partner.

2. Previous intrauterine insemination.

3. Vasovasostomy ever.

4. Varicocelectomy within previous 6 months.

5. History of pelvic node dissection.

All recommendations by the RMUs about eligibility will be reviewed by the DCC, which will meet weekly to make the final determination. Questions about eligibility that arise early on in the course of screening a particular couple can be referred to the DCC for an early decision.

Section 4. METHODS OF RECRUITMENT AND RANDOMIZATION

A. Methods of Recruitment

Each of the participating centers in the National Reproductive Medicine Network operates a large, multifaceted clinical service and serves as a referral center for couples with a variety of reproductive disorders. In about ten percent of couples completing a thorough infertility investigation, no apparent explanation is found for their failure to conceive (unexplained infertility). In 40-50 percent of infertile couples, male factors are found to be abnormal; in about half of these (20-25 percent) the female partner appears to be normal and an abnormal male factor is the only apparent problem (pure male factor infertility). While these two diagnoses are reasonably common, many of those diagnosed will already have received treatment. Such treatment failures represent a group with lower fertility potential. To minimize potential selection bias, only couples who have received no prior treatment with hMG or intrauterine insemination will be eligible for randomization. In addition, efforts will be made to recruit subjects through physicians in the medical community surrounding each center. Participating community physicians would bill for the diagnostic workup in the usual fashion but must agree to follow a standardized protocol for tests and diagnoses.

Attempts to establish a network of community physicians (ideally, sufficient to refer 60 couples per year in whom the female appears to be normal) have been made by several RMUs using the following approaches:

1) Personal contact between the research center and community physicians, by letter (on either center or network letterhead), describing the protocol, its benefits and risks.

2) Presentations at hospital departmental meetings, Grand Rounds, or other educational meetings focusing on treatment options for infertile couples.

3) News releases (print, radio, television media) describing the Network in general

and perhaps the study in particular, including its purpose, selection criteria, and potential benefits to eligible couples.

4) Satellite clinics contracted by the RMU where patients will be recruited, evaluated and treated, with the understanding that all semen evaluations and inseminations must be performed at the RMU.

Recruitment of subjects from the community at large must be done carefully, both to insure standardization and to avoid any appearance of shunting patients away from the physicians' private practices. At the same time, the establishment and funding of the National Reproductive Medicine Network is a newsworthy event. A news release focusing on the Network in general, its makeup, and the types of problems it intends to study, should be designed to introduce the Network in a non-threatening way. (The Office of Public Information at each medical center may be able to help with this.) The release should conclude with a brief "for example" look at this study, the Network's first. No overt recruitment appeal should be made, but a telephone number should be provided at the end of the release for couples or physicians desiring further information. Local infertility support groups may be able to help with dissemination of information. All inquiries will be answered by the local center's Research Nurse. An "information sheet" describing the National Reproductive Medicine Network will be developed for distribution. As specific research protocols are developed, suitable information sheets for each will be developed.

Emphasis will be placed on the potential benefits of participation to eligible couples, including:

a) Access to "state of the art" therapy, i.e., the latest standardized techniques for assessing the etiology of infertility, for performance of IUI and ICI, for timing insemination, or for stimulating the recruitment and ovulation of multiple oocytes.

b) Contribution to medical knowledge.

B. Phase of Infertility Workup at Recruitment

The diagnostic workup will be completed before a couple becomes eligible to enter the study. For this reason it is clearly essential to define the testing protocols and diagnostic criteria clearly and explicitly. We will insure agreement and adherence to these standards by conducting quality control studies on portions of the infertility workup following initial recruitment. Appendix B contains a description of quality control protocols related to enrollment, treatment procedures, data forms and laboratory tests. As mentioned previously, community physicians and satellite clinics providing patients will be asked to use the same definitions, testing protocols, and diagnostic criteria that will be used at the RMUs. If there is documentation in the medical record of the post-coital testing, hysterosalpingogram, laparoscopy and endocrine evaluations, these results will be used for diagnosis. The endometrial biopsy may be performed elsewhere but slides should be available for review at the RMU. On-site semen collection is encouraged but not required. Semen evaluations and antisperm antibody immunobead tests will be performed at the RMUs and quality control procedures will be established to insure the uniformity of laboratory assessments across sites. The University of California, Davis has agreed to review any borderline results on the antisperm antibody tests.

C. Randomization

From the scientific and ethical standpoints, infertile couples in whom the female partner appears to be normal may be randomly assigned to any of the four treatment blocks of this study; i.e., there are no convincing data from existing controlled studies that any of the proposed regimens is superior for treating these couples. Couples will be counseled by the Research Nurse at the RMU regarding risks and benefits of all treatment blocks. At the time of counseling, it will be emphasized that those randomized to "no hMG" will be offered up to four cycles of hMG treatment at the end of the trial if they have not already conceived.

All subjects will be asked to sign an informed consent to participate in the study (see Appendix A). Only those eligible couples who are willing to accept randomization can be enrolled in the trial.

The randomization procedure will stratify on RMU, i.e., each RMU will have its own independent randomization schedule. Permuted blocks of size four or eight will be employed within each RMU.

The DCC will review the relevant enrollment forms and will respond to the RMU with a decision on eligibility and, where appropriate, a randomization assignment. If the forms are incomplete or the documentation inadequate, the RMU will be notified; members of the DCC will meet weekly to review and resolve all such questionable cases. As part of quality assurance, the DCC will double check, in detail, on eligibility information for a randomly selected 4% of subjects, by requesting the entire medical record for review.

Section 5. MEASURES OF EFFICACY AND ADVERSE EFFECTS

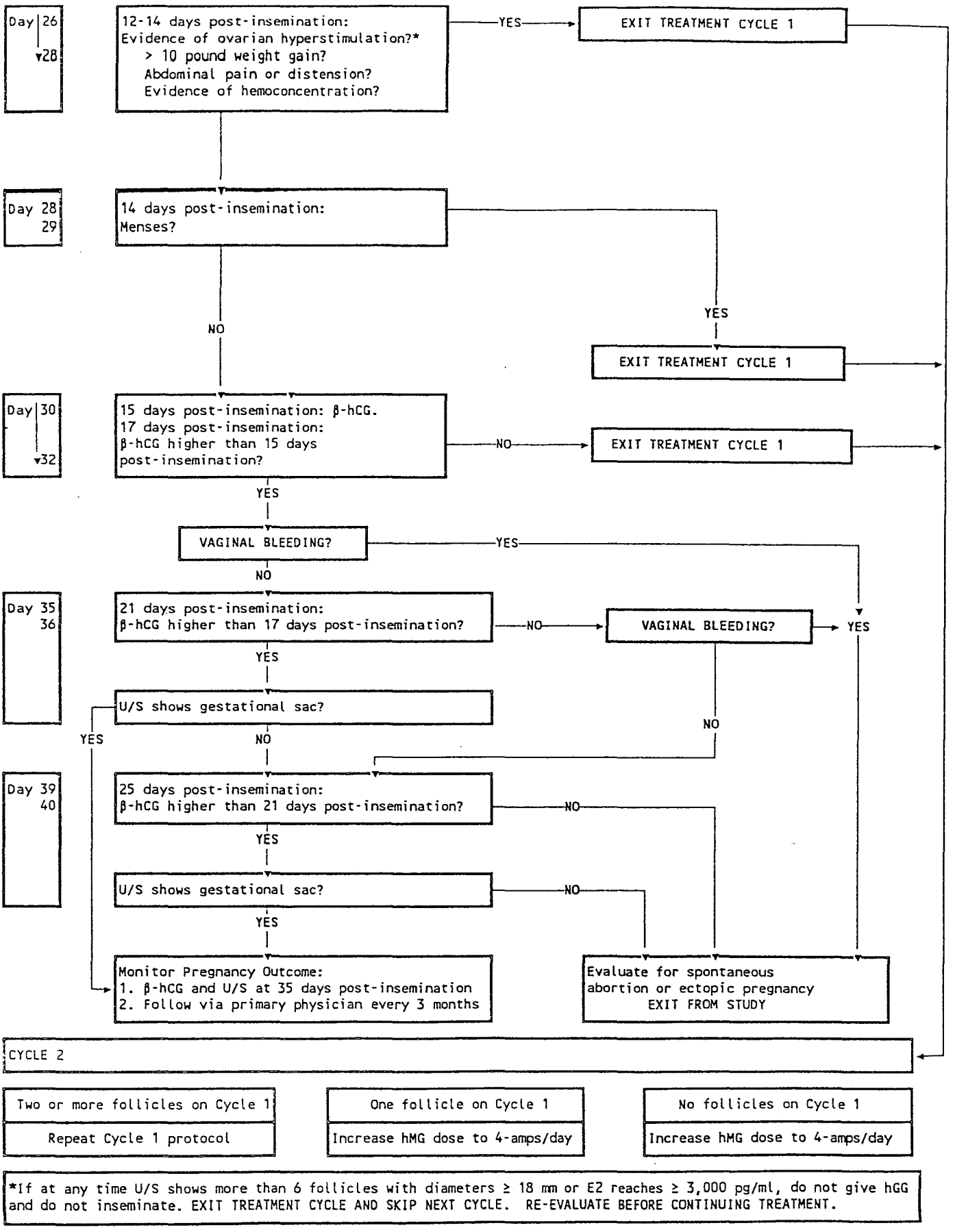
A. Specific Measures of Efficacy

The relevant measure of treatment efficacy for this study is pregnancy, which will be determined by a standard protocol as outlined in Figure 2 below.

Ovulation will be taken to be the day of insemination, i.e., the day after a morning LH surge for women in the spontaneous ovulation groups, and the day corresponding to 36 hours after administration of hCG in the hMG-stimulated groups.

If menses does not occur by luteal day 14 (around cycle day 28-29), a blood sample will be drawn on luteal day 15 for serum β-hCG and the test will be repeated in two days (irrespective of whether menses begins in the interim) to evaluate whether β-hCG is rising (Romero et al., 1986). If the β-hCG is rising and if menses have not occurred, β-hCG will be repeated on luteal day 21 and a transvaginal ultrasound will be performed. This corresponds to the day that a gestational sac can usually first be seen by transvaginal ultrasound (Fossum et al., 1988). If no sac is seen, the β-hCG and ultrasound will be repeated four days later. Vaginal bleeding that occurs between the second β-hCG assay and the scheduled ultrasound will be evaluated by RMU physicians for possible miscarriage or ectopic pregnancy according to standard clinical practice.

Figure 2. Evaluation of Efficacy and Adverse Effects of Treatment



Using the above protocol to monitor early pregnancy, a continuum is seen with different pregnancy outcomes defined as follows:

1) **Preclinical abortion:** serum β-hCG > 10 mIU/ml on luteal day 15 (cycle day 29-30) and a higher serum β-hCG on luteal day 17, but no gestational sac seen subsequently by ultrasound.

2) **Clinical abortion:** Occurrence of a spontaneous abortion after a gestational sac is seen, but before 20 completed weeks gestation estimated from LMP (i.e., less than 18 weeks post-insemination).

3) **Preterm delivery:** Delivery between 20 and 37 weeks gestation estimated from LMP (i.e., 18 to 35 weeks post-insemination).

4) **Term delivery:** Delivery after 37 completed weeks of gestation estimated from LMP (i.e., after 35 weeks post-insemination).

Other pregnancy outcomes will be determined, e.g., presence of multiple pregnancy at the time of early ultrasound exam (five weeks after insemination, seven weeks after last menstrual period, or when the serum β-hCG reaches 2,000 mIU/ml by IRP) and at delivery; ectopic pregnancy; and presence of congenital anomalies at delivery.

B. Specific Measures of Adverse Effects

Adverse effects may be considered for 1) method of insemination, and 2) method of ovulation induction. For each, adverse effects may be assessed a) subjectively, and b) objectively.

1. Method of Insemination (IUI or ICI)

a) Subjective Evaluation

A structured questionnaire has been developed to evaluate the patient's overall level of satisfaction/dissatisfaction with the assigned method of insemination, as well as the presence or absence of specific symptoms during/following insemination. More specifically, it measures that patient's feelings regarding the time required to perform the insemination and the degree of pain or cramping associated with the procedure.

Patients who drop out will be asked to complete a separate questionnaire asking them to indicate which of a list of potential factors played a role in their decision to drop out, and to rank those factors from most to least influential. The factors include: cost, time/inconvenience, and side effects.

b) Objective Evaluation

Few, if any, measurable adverse effects are expected from either ICI or IUI. Patients will be asked to call the Research Nurse for temperature elevations > 100°F. In general, patients will be evaluated clinically to ascertain subclinical pelvic inflammatory disease (PID). Patients will be counseled regarding the possibility of PID in an insemination cycle, and will be given a specific set of guidelines concerning when to call the Research Nurse.

2. Method of Ovulation Induction

a) Subjective Evaluation

Each questionnaire will evaluate the level of satisfaction with the time required for monitoring treatment with hMG/hCG, and the degree of discomfort experienced with parenteral injections, with venipunctures, and with ultrasound exams. Each patient will be asked to indicate the presence or absence (and degree) of symptoms such as abdominal pain

or discomfort, abdominal distension, bloating, weight gain, nausea, vomiting, diarrhea, headache, pain at injection sites, etc.

Patients who drop out of treatment will be asked to complete a questionnaire asking them to indicate and rank those factors that played a role in their decision. The list of factors include cost, time/inconvenience, requirement for parenteral medication, requirement for repeated venipuncture, requirement for ultrasounds, and concern regarding side effects (multiple gestation, hyperstimulation syndrome).

b) Objective Evaluation

1) All patients

Within 12 to 14 days after insemination, clinical criteria will be used to ascertain those patients with greater than mild hyperstimulation. Each woman will be asked whether she has experienced a weight gain of more than 10 pounds. Those reporting weight gain will be evaluated for evidence of severe hyperstimulation. The following laboratory measures and clinical criteria will be considered:

a) Ovaries > 10 cm in maximum diameter

b) Evidence of marked hemoconcentration:

1. Significant rise in hemoglobin or hematocrit > 15%
2. Evidence of electrolyte imbalance
3. Evidence of ascites or pleural effusion
4. Evidence of hypervolemic shock
5. Evidence of hypercoagulable state
6. Decreased urine output

The number of patients (cycles) requiring such workups, and the number meeting criteria for severe hyperstimulation, will be recorded. Most patients will not require such testing; in asymptomatic subjects no special effort will be made to evaluate ovarian size or to measure hematologic parameters following the hCG injection.

2) Patients Who Conceive

Data will include the rates of multiple gestation, preclinical abortion, clinical abortion, preterm delivery and term delivery, and eventual pregnancy outcome (including the incidence of congenital anomalies). A sonogram will be obtained five weeks after insemination or seven weeks after the last menstrual period, or when the serum β-hCG reaches 2,000 mIU/ml by IRP. Thereafter, the Research Nurse will contact the patient's obstetrician every three months to gather information on the course of the pregnancy. Obstetrical and newborn records will also be obtained after delivery.

Section 6. DATA TO BE COLLECTED AND FORMS TO BE COMPLETED

Data collection forms have been developed in two broad categories: pre-randomization forms and post-randomization forms. An initial questionnaire is provided to screen out couples who are ineligible on the basis of age, prior treatment, or relevant surgery. Those who pass the screen complete recruitment questionnaires and other pre-randomization forms (some of which will involve abstracting information from medical records) to determine a couple's eligibility for the trial and willingness to participate. In addition, they provide baselines against which change can be assessed. Once a couple is disqualified, there is no need to complete any of the subsequent pre-randomization forms. We have also included a form for recording data on ineligibles as well as on couples who refuse to participate.

Each week, the DCC will upload all completed recruitment questionnaires, diagnostic test abstracts and enrollment summaries from each RMU. The DCC will review the data and send an eligibility determination form back to the RMU for each couple. If the information is complete and the couple is eligible, this form will also include the randomization assignment.

The post-randomization forms include: forms for documenting treatment administration and for monitoring treatment response; forms for documenting outcomes of treatment; forms for subjective and objective evaluations of treatment, including adverse reactions and side effects; and a form for documenting any drop-outs/ withdrawals. The treatment forms are arranged as a set, with one set covering one cycle. They have been designed in the hope that they may serve as case notes in the RMU medical charts in order to reduce the amount of record-keeping required of clinical personnel. In addition, we have included a first cycle questionnaire for each partner that can be completed while waiting for the insemination procedure. While all of the other forms have been limited to items that are needed to accomplish the research goals of the trial, these "waiting room" questionnaires include

variables that are not strictly needed but are certainly of interest and would be useful for ancillary studies.

Table 3 lists the forms by category and name and indicates those that are to be completed by clinical staff at the RMU, by the study subjects (*) or by DCC personnel (**).

TABLE OF DATA COLLECTION FORMS

FORM #	LABEL	DESCRIPTION
FORMS FOR INITIAL RECRUITMENT OF POTENTIAL PARTICIPANTS		
1.	None	LOG BOOK: LIST OF POTENTIAL PARTICIPANTS
2.	SC	INITIAL SCREENING FOR ELIGIBILITY
PRE-RANDOMIZATION FORMS: ELIGIBILITY DETERMINATION		
		QUESTIONNAIRES:
3.		WOMAN'S RECRUITMENT QUESTIONNAIRE:
	WR1	1. DEMOGRAPHIC, REPRODUCTIVE/CONTRACEPTIVE HISTORY, OTHER INFERTILITY TREATMENTS
	WR2	2. PREGNANCY HISTORY
4.		MAN'S RECRUITMENT QUESTIONNAIRE:
	MR	1. DEMOGRAPHIC, REPRODUCTIVE HISTORY, SURGICAL AND MEDICAL HISTORY
5.	*NP	NONPARTICIPANT QUESTIONNAIRE
		ABSTRACT FORMS FOR MEDICAL/LABORATORY RECORDS OF DIAGNOSTIC TESTS:
6.	SE	SEMEN EVALUATION
7.	BX	LATE LUTEAL PHASE ENDOMETRIAL BIOPSY
8.	HO	BASELINE SERUM HORMONE LEVELS
9.	PC	POST-COITAL TEST AND CERVICAL MUCUS PROFILE (OPTIONAL)

ABSTRACT FORMS FOR MEDICAL/LABORATORY RECORDS OF DIAGNOSTIC TESTS (continued):

10.	ASABW	ANTISPERM ANTIBODY PROFILE: WOMAN
11.	ASABM	ANTISPERM ANTIBODY PROFILE: MAN
12.	HY	HYSTEROSALPINGOGRAM
13.	LA1	LAPAROSCOPY
14.	LA2	HYSTEROSCOPY (OPTIONAL)

FORMS FOR FINAL ELIGIBILITY AND RANDOMIZATION DECISIONS:

15.	RMU version	INFORMED CONSENT FORM
16.	EN	ENROLLMENT SUMMARY SENT TO DCC BY RMU
17.	**EL Report	SUMMARY OF INCLUSION/EXCLUSION CRITERIA, ELIGIBILITY DETERMINATION
18.	**ER	ELIGIBILITY NOTICE AND RANDOMIZATION SUMMARY RETURNED TO RMU BY DCC

POST-RANDOMIZATION FORMS: TREATMENT PROTOCOLS AND STUDY OUTCOMES

SELF-ADMINISTERED QUESTIONNAIRES FOR COUPLES STARTING TREATMENT:

19.	*WQ	WOMAN'S TREATMENT CYCLE QUESTIONNAIRE
20.	*MQ	MAN'S TREATMENT CYCLE QUESTIONNAIRE

FORMS FOR MONITORING TREATMENT (PACKET OF FORMS DIFFERS FOR EACH OF THE FOUR TREATMENT GROUPS):

21.	TX	TREATMENT ADMINISTRATION AND RESPONSE SUMMARY: INCLUDES METRODIN INJECTION SUMMARY, ESTRADIOL LEVELS, TRANSVAGINAL ULTRASOUND MONITORING hCG INJECTION SUMMARY, INSEMINATION SUMMARY
22.	OV	SPONTANEOUS OVULATION MONITORING (FOR GROUPS NOT RECEIVING METRODIN/hCG)

FORM #	LABEL	DESCRIPTION
		FORMS FOR MONITORING TREATMENT (continued):
23.	CM1	CERVICAL MUCUS CHARACTERISTICS: LUTEAL DAY 1 OF TREATMENT CYCLE
24.	IN	INSEMINATION SUMMARY
25.	SE	SEMEN EVALUATION
26.	SPW	POST-WASH EVALUATION
27.	RC	REST CYCLE SUMMARY
		FORMS FOR WOMAN'S EVALUATION OF TREATMENT:
28.	*WEO	METRODIN/hCG OVULATION INDUCTION
32.	*WES	SPONTANEOUS OVULATION MONITORING
30.	*WEI	INSEMINATION
		FORMS FOR CLINICIAN'S (OBJECTIVE) EVALUATION OF TREATMENT:
31.	EI	INSEMINATION
32.	EHS	SEVERE OVARIAN HYPERSTIMULATION
33.	AD	ADVERSE REACTION REPORT
		FORMS FOR MONITORING OUTCOMES OF TREATMENT:
34.	PM	EARLY CLINICAL PREGNANCY MONITORING: INCLUDES β-hCG LEVELS, ULTRASOUND (# GESTATIONAL SACS), AND VAGINAL BLEEDING
35.	US	35 DAYS POST-INSEMINATION EVALUATION
36.	PO1	PREGNANCY OUTCOMES (COMPLICATIONS, DELIVERY)
37.	PO2	NEONATAL CHARACTERISTICS
		FORMS FOR TERMINATING PARTICIPATION IN THE STUDY:
38.	*WD	WITHDRAWAL QUESTIONNAIRE (DROP-OUTS)
39.	FD	FINAL DISPOSITION (ALL PARTICIPANTS)
40.	F4	4 MONTH FOLLOW-UP
41.	F12	12 MONTH FOLLOW-UP

Section 7. DATA MANAGEMENT

A. Overview

Paper case report forms and parallel computerized data entry screens will be designed and produced by the Data Coordinating Center (DCC) and distributed to each Reproductive Medicine Unit. Training of RMU nursing staff in data recording guidelines will be performed prior to subject enrollment. A data management manual will be given to each RMU and will serve as the specification and reference in matters of data management. RMU staff designated to perform data entry operations will be responsible for weekly transmission of data to the Data Management Center (DMC) at the DCC. RMU staff will be responsible for acting on DMC-initiated error correction and data validation requests in a timely manner.

The DMC will serve as the sole resource for RMU technical and procedural questions regarding materials and concerns of data management. DMC personnel will be available from 9:00 a.m. to 5:00 p.m. (E.S.T.) each business day to address RMU queries and problems. Each week each RMU will transmit data to the DMC by uploading data to the local BITNET host computer and sending files to the DMC host computer. Uploaded data will be filtered through programs that validate data integrity and report suspected discrepancies and omissions to DMC staff. DMC staff will work with the RMU staff to resolve data problems and will conduct quality control studies on incoming data. DMC staff will load and maintain the study master files at the DMC and maintain master files at the clinical sites.

DMC staff will work closely with biostatistical staff to write programs for statistical analysis for reporting study progress, and for interim analyses. Information pertinent to the conduct and operation of the study will be provided by the DMC on a per-request basis.

B. Basic Data Entry System

Responses recorded on printed questionnaires will be entered into local personal computers for electronic storage. SAS/FSP data entry screens and SAS/AF menuing application will be created at the DMC and sent to the RMUs on magnetic media to accommodate this task. Each data entry screen will contain items for couple ID, data enterer ID, date of clinical event being recorded, and data elements collected during the clinical event (eg. intake, blood sample, insemination, etc.). Additional forms-tracking and quality control checks will be completed by the software system and permanently attached to the user-entered data (e.g., entry date, whether this form has been edited or modified, whether this form has been reviewed for quality control, etc). Computed values of derived items are calculated and displayed at entry time. Item level error checking will assess each item and provide the user with messages regarding acceptability of entered values. The details of data flow are as follows. Each week the RMU will exercise a SAS/AF menu option to transmit newly entered data to the DMC. This option will gather all files to be sent to the DMC into a separate hard drive directory as raw ASCII files and "lock" the records on the PC so that they may not be modified subsequent to transmission. The RMU will dial into their local BITNET or INTERNET host computer and upload the entire contents of their PC's "transfer" directory using KERMIT script files provided by the DMC. At the completion of the KERMIT data upload to the local host, the KERMIT script file will send the files to the DMC host.

Error detection and the DMC methods for handling errors deserves special mention. Datasets received at the DMC will be processed by programs specific to each dataset. Such programs perform various levels of error checking. Detected errors will be described in a report returned to RMU staff for appropriate action and correction, and the record in question will be "unlocked" for modification. The name of the error-checking program, the date it was

run at the DMC, and a code indicating the success or failure of the error-checking algorithms are encoded within the dataset when the error-checking program is run. The only mechanism for clearing a record with outstanding errors is to have the same program reanalyze the record marked as free of errors codes to signify acceptance. Only records marked as free of errors can be merged into the master study data files at the DMC.

A slightly different edit process occurs when an error is detected after the data have been merged into the master data files. Regardless of whether the error is detected at the DMC or the RMU, a set sequence of actions is to take place. A copy of the incorrect record is made with internal error flags set to indicate the presence of a problem, and the record is given the same status as a newly entered record. At the same time the existing record in the master data files of both the RMU and the DMC is flagged as outstanding for correction. Essentially, the record in error becomes a version 1 record, and the record sent to the RMU for editing and correction becomes the version 2 record. The editing process to correct the record is the same as that described above with one exception: when this record is corrected, it will be merged into the master data files as version 2. Only the highest version of a record will ever be reported or analyzed, however, previous versions could be recovered if necessary. Thus a chronological history for each record could be produced in the event of an audit.

C. Quality Control and Monitoring

Standard quality control procedures will be implemented to assess the reproducibility and accuracy of many data elements and procedures within the project. The DMC will issue requests to the RMU to perform a task again. The data associated with these quality control studies will be stored in the master data files with an indication that a record is being recoded for quality control purposes. Such requests typically target 2-5 percent of data for collection

a second time, where feasible and ethical. Quality control records never appear in primary analyses.

The details of this process need the cooperative advice of all parties involved: RMU principal investigators, research nurse clinicians, laboratory personnel and coordinating center data management staff.

The following procedures will be considered for quality control experiments:

1. **Subject Enrollment**
2. **Data Collection**
3. **Data Entry**
4. **Treatment Protocols**
5. **Specimen Handling and Laboratory Procedures**
6. **Data Checking**
7. **Quality Control**

Quality control protocols are described in Appendix B of this document.

D. Personnel Training and Certification

A Data Management Manual has been created to instruct both RMU staff and coordinating center staff in the elements, tasks, procedures and documentation standards of the data management system and in quality control procedures. These materials serve as reference for description and policy concerning responsibilities for data.

Since the computerized data management system requires codes for who collected data, who recorded data, who entered data, who transmitted data, who edited data, who merged data, etc., we plan to conduct reevaluation of the certification testing via the quality control procedures noted in Appendix B. Therefore, individuals can be periodically assessed

for accuracy, consistency, and compliance.

E. Data Management Center Staff Responsibilities

DMC staff will create data entry screens, create the menu system, gather recommendations for error checking and implement these on each screen, implement the quality control experimental designs, build the coordinating center master data files and the master files at each RMU. Data input programs will be created for each laboratory system that provides magnetic data files.

Before the study begins, pilot tests of all the forms and computer programs will be conducted. Requests for updates and additions from the RMUs or the DMC will be integrated as unanticipated needs arise. As the study starts, it is anticipated that each center will upload data to the coordinating center on one specific day each week. Each incoming dataset will be run through programs that produce reports for the RMU or that produce files ready to be merged with the DMC and RMU master data files. The RMU will initiate the transfer of data to the DMC, but the DMC will have responsibility for file management at the RMU site. This latter responsibility will be accomplished either through direct dial-in to the RMU computer or by programs downloaded from the DMC and run on the RMU computer. In either case, DMC staff will directly manage and supervise the master data files and the resolution of data errors or quality control checks.

All errors detected by programs and quality control checks will be reviewed by DMC staff for determination of appropriate action and followed through to completion. Quality control requests to the RMU staff, and the collection, storage and analysis of the quality control data, will be the responsibility of the DMC staff.

All reports will be produced by programs written and executed by the DMC staff. It is anticipated that monthly project status reports will be required for internal DCC review and that quarterly reports will be produced for DCC Steering Committee review. All statistical analyses will be conducted by programs written by DMC staff working in cooperation with biostatistics and epidemiology staff.

Section 8. RESPONSIBILITIES OF REPRODUCTIVE MEDICINE UNITS, DATA COORDINATING CENTER AND STEERING COMMITTEE

A. Reproductive Medicine Units

The RMUs will recruit, evaluate and treat the participants in the clinical studies. Recruiting will be individualized to the local community, but entry of couples into the trials and conduct of the protocol will be standard at all the sites. Each RMU will have physician staff representing multiple disciplines, including Obstetrics and Gynecology, Reproductive Endocrinology, and Andrology, either in the participating department or as collaborators. Staffing will include an experienced research nurse and a data entry clerk, and such other personnel as may be required by the study. Each RMU will conduct its own semen analyses, laboratory testing and ultrasound examinations. Blood samples for quality control monitoring of the estradiol assay in particular will be sent from the DCC for analysis at the RMUs; samples will also be exchanged among RMUs periodically. Video recordings of semen samples will be made using identical microscopes and cameras at all the RMUs, and tapes sent to the RMU at University of California, Davis (UCD). The RMUs will furnish the DCC with information required to generate standard forms and manuals, and will comply with its reporting requirements. The RMUs will collect the data with attention to fidelity of records and transcription, and provide information in uniform data format to the DCC for analysis. Each data form will be scanned at the RMU, and the files will be sent to the DCC to create an archive of visual images of the hard-copy forms as a backup to the computer database.

The RMU at UCD will manage a quality control program for andrology laboratory procedures related to the clinical studies. Guidelines will be provided in three general areas: personnel training, equipment calibration, and compliance. Detailed protocols will be written and provided to all RMUs for semen evaluation, antisperm antibody immunobead testing and

video recording for CASA. The laboratory technicians from each site have received group and individual instruction at UCD. Baseline performance and variation for each technician has been established using standardized slides and videotapes. UCD will coordinate the exchange of standardized slides and videotapes among the RMUs on a regular basis, and the results of these analyses will be used by UCD for laboratory quality assurance. UCD will coordinate the exchanges of standard sera which will be analyzed for antisperm antibodies at the RMUs for quality control of immunobead testing. Supplies and equipment will be identical at each site, and standard protocols for calibration and operation of equipment will be followed. Videotapes and duplicate sperm morphology slides from all semen evaluations will be sent to UCD for further analyses. The performance of each RMU will be monitored by comparing the results of manual semen evaluations with CASA data, and sperm morphology data obtained on the same specimen at UCD. CASA data for all semen evaluations will be uploaded from UCD to the DMC on a regular basis. In addition, 2-5 percent of the sperm morphology slides will be reevaluated at UCD, and these data will also be sent to the DMC for quality control purposes. Personnel from UCD will visit each RMU at least once a year for problem solving, review or change of procedures, modification of equipment, etc.

B. Data Coordinating Center

The DCC has primary responsibility for data collection, management and analysis. The Principal Investigator and other key personnel provide expertise in epidemiology, statistics, data management, quality control, study coordination, and administrative aspects of multicenter clinical studies. The DCC helps in the development of the study protocol and produces standard data entry forms, a Procedures Manual and a Data Management Manual. It makes recommendations to the Steering Committee regarding statistical methods, sample size, and data collection and handling. Data will be collected and entered at the RMUs locally,

and transmitted to the DCC for management and analysis. The DCC is responsible for training the Research Nurses at the RMUs and for auditing performance at each of the sites. The DCC will report to the Steering Committee every six months regarding data accumulation, quality control, and the performance of the RMUs.

C. Steering Committee

Overall management and supervision of the study protocol will be carried out by a Steering Committee consisting of the Principal Investigators of each Unit and of the DCC, and the NICHD staff member serving as Research Coordinator. In addition to review and approval of the Protocol, the Steering Committee will review the reports from the DCC on the aggregated data, and decide on the format and content of published reports.

D. Data and Safety Monitoring Board (DSMB)

A Data and Safety Monitoring Board will be created, consisting of 3-4 individuals with expertise in reproductive endocrinology, biostatistics, and epidemiology and/or experience with clinical trials. These individuals should be independent of the study and of companies providing drug or other materials for the trials. The Board will be responsible for recommending early termination or a major revision of the study either because of concern for safety, because of strong evidence for efficacy of one of the treatments, or because of compelling evidence that the study is unlikely to produce definitive results. The final decision on such a recommendation rests with the Steering Committee. Only the DSMB, together with Dr. Fleiss for the DCC, will have access to interim data broken down by treatment group.

Section 9. STATISTICAL METHODS

A. Randomization

Randomization will stratify on Reproductive Medicine Unit (RMU), with randomly permuted blocks of size four or eight being used. Within each block, equal numbers of couples will be assigned to the control group and each treatment group.

The Data Coordinating Center (DCC) will be responsible for carrying out the random assignment of couples to treatment groups. As described previously, on a weekly basis the DCC will upload relevant data from each RMU for determining eligibility or ineligibility of enrolled couples. For couples deemed eligible, the DCC will randomize using a computer algorithm written by the staff of the DCC, or will notify the RMU in the event that the documentation has raised questions. Questionable cases will be resolved at weekly meetings of the DCC. The RMUs may request an expedited review if the timing of the regular weekly review would force a couple to delay entrance into treatment for another menstrual cycle.

B. Quality control

In order to check quality control, and to suggest remediation if necessary, the DCC will request that each RMU reevaluate a sample of records or reprocess a sample of forms. During the first half of the trial a 10 percent sample of forms will be selected for repeat processing; if reliability is found to be lacking, steps will be taken to improve the quality of data recording and entry. During the second half of the trial, a 2 percent sample will be selected in order to confirm that high quality data recording and entry are maintained. To evaluate reliability, standard errors of measurement and intraclass correlation coefficients will be calculated for continuous variables, and kappa statistics will be calculated for categorical variables.

C. Some issues associated with multicenter studies

The greatest challenge to the DCC with respect to the multicenter aspect of the study is the development of quality control and monitoring procedures to assure that the data from the RMUs are precise, accurate and complete, and that there is uniform adherence to all aspects of the study's protocol: inclusion and exclusion criteria, treatment schedules, criteria for response, etc. The analysis of data from a multicenter study is straightforward provided there is no treatment-by-center interaction, i.e., provided the differences between treatment and control groups are the same in all centers. The analysis begins by estimating the treatment-control differences separately within each of the centers, and proceeds by computing a weighted average of these differences, where the weights are proportional to the precisions of the differences (Fleiss, 1986a).

When treatment-by-center interaction exists, the analysis and the conclusions both become more complicated (Fleiss, 1986b). While planning to examine the data for evidence of interaction, we shall attempt to prevent it by relying on quality control procedures to assure comparability across centers.

If an RMU is found to be enrolling patients at a rate that is much lower than expected, consideration may have to be given to dropping that center from further participation in the trial (data on patients already enrolled would be included in the final analyses, but no new patients would be enrolled). On the other hand, if an RMU is found to be enrolling patients at a rate that is much higher than expected, consideration might be given to having that center enroll more than its intended quota of patients.

D. Interim analyses

Every six months, the DCC will provide the Steering Committee with aggregate summaries of the data collected to date. On the recommendation of the DSMB, which will

have access to data broken down by treatment group, the Steering Committee will decide whether to continue the study or to terminate it. These decisions will seriously affect the operating characteristics of the study (significance level and power), and should therefore be made according to rules developed for performing interim analyses of accumulating data (Friedman et al., 1985: Chapter 15; Pocock, 1983: Chapter 10).

The possibility must be entertained that one of the experimental treatments is less effective than the control. If this seems to be the case based on the interim data, and if harm to the patient is possible, the Steering Committee should be encouraged to decide on early termination of that treatment arm with less persuasive evidence than required for early termination with a positive conclusion (Lan and Friedman, 1986). That is, the Steering Committee might decide to drop an investigational regimen with the conclusion that it may be poorer than the control if the p-value for the test comparing the two is 0.15 or less.

The most widely used procedure for performing several interim statistical analyses while holding the overall significance level at the usual value (0.05 or 0.01) is the one due to O'Brien and Fleming (1979). This procedure will be adopted for interim analyses aimed at testing for efficacy.

E. Methods of analysis

The unit of analysis will be the couple, and the primary response variable will be a binary one: success if the woman conceives while in the study versus failure if not. The most important principle underlying the statistical analysis will be the intention-to-treat principle. It is characterized by the aphorism "If randomized, analyzed": a couple who has been randomized to a treatment group is analyzed along with all other couples so randomized, even if they were minimally compliant. This principle leads to a likely underestimation of a

treatment's effect, but the alternative of removing minimally compliant or noncompliant couples could lead to the worse bias of overestimating its effect. For example, a couple's decision to discontinue complying with the assigned treatment regimen might be due to a perceived lack of efficacy. The withdrawal of such a couple from analysis could result in an overestimation of that treatment's effectiveness.

The primary statistical analysis will consist of separate comparisons of each experimental treatment's success rate versus the control's after stratifying on RMU using the Mantel-Haenszel chi-square procedure (1959). If other variables measured at baseline are found to be distributed very differently in different treatment groups (the criterion for "very different" might be statistical significance at the 0.10 or 0.20 level), they would be adjusted for statistically, either by post-stratification (using the Mantel-Haenszel procedure) or by regression control (using logistic regression modeling) in a secondary, confirmatory analysis. Given the likelihood that these variables will be only slightly correlated with response, the results of the secondary analysis will almost surely confirm the results of the primary one, with respect both to the direction of the difference between the treatments and to its statistical significance or nonsignificance. In the extremely unlikely event that the results of the primary and secondary analyses are contradictory, there would be little if any credibility to any attempted definitive inference from the study.

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Appendix A.

Example of Research Consent Form

Names of Participants: _____ / _____
(woman) (man)

I. Description of the Study:

You are being asked to participate in a study which evaluates the success rate of four standard procedures used to treat infertility. Couples such as yourself are commonly treated with drugs to stimulate the ovaries to develop eggs and/or inseminated with the man's sperm. However, the actual success rate of this type of treatment is unknown.

This study will ask couples with infertility such as yourselves to accept a random assignment to one of four types of treatment for the duration of four menstrual cycles. Hopefully, during one of these cycles you will become pregnant. The number of pregnancies in each treatment group will be compared to see which treatment results in the highest number of pregnancies.

The four types of treatment are described below:

1. Intracervical Insemination (ICI) is the placement of sperm in your cervix. If you are selected for ICI, you will be asked to test your urine to detect the day that you ovulate. On that day your partner will be asked to provide a semen sample at our office. We will prepare the semen for insemination in your cervix. The insemination is not painful and feels like a Pap smear. Hormone levels in your blood may be measured to test for pregnancy. About 1½ teaspoons (7.5 cc) of blood will be drawn for each sample, but the total volume of blood will not be more than ¼ cup (60 cc) per month. Up to 4 blood samples may be drawn each month. If pregnancy is indicated by a positive blood test, your uterus will be examined by ultrasound.

Patients' Initials ____ / ____

2. Intrauterine Insemination (IUI) is the placement of sperm in your uterus. If you are selected for IUI, you will be asked to test your urine to detect the day that you ovulate. On that day your partner will be asked to provide a semen sample at our office. We will prepare the semen for insemination into your uterus. A small tube will be passed through your cervix and the semen will be injected into your uterus. In addition, up to 4 blood samples may be drawn each month. About 1½ teaspoons (7.5 cc) of blood will be drawn for each sample, but the total volume of blood will not be more than ¼ cup (60 cc) per month. Hormone levels in your blood and urine may be measured to test for pregnancy. If pregnancy is indicated by a positive test, your uterus will be examined by ultrasound.

3. Human Menopausal Gonadotropins (hMG) and Intracervical Insemination (ICI) is stimulation of your ovaries with drugs and placement of sperm in your cervix. If you are selected for hMG and ICI, you will be given daily injections of a drug (hMG) in order to stimulate more than one ovulation at one time. This requires daily injections of hMG by your partner for approximately 7 to 10 days. The response to the treatment will be monitored by taking blood samples to measure hormones in your blood. About 1½ teaspoons (7.5 cc) of blood will be drawn for each sample, but the total volume of blood will not be more than 1 cup (240 cc) per month. In addition, your ovaries will be examined by ultrasound to show the number and size of follicles (containing eggs) that are developing. When the eggs are ready to ovulate, another drug, human chorionic gonadotropin (hCG) will be given to you to stimulate the release of your eggs.

Two days later, your partner will be asked to provide a semen sample at our office. We will prepare the semen for insemination in your cervix. This is not painful and feels like having a Pap smear taken.

Patients' Initials ____ / ____

About 8 to 11 blood samples and ultrasound tests of your ovaries will be performed during each month. Up to 4 blood samples may be drawn to measure hormone levels in your blood to test for pregnancy. If pregnancy is indicated by a positive blood test, your uterus will be examined by ultrasound.

4. Human Menopausal Gonadotropins (hMG,) and Intrauterine Insemination (IUI) is stimulation of your ovaries with drugs and placement of sperm in your uterus. If you are selected for hMG and IUI, you will be given daily injections of a drug (hMG) in order to stimulate more than one ovulation at one time. This requires daily injections of hMG by your partner for approximately 7 to 10 days. The response to the treatment will be monitored by taking blood samples to measure hormones in your blood. About 1½ teaspoons (7.5 cc) of blood will be drawn for each sample, but the total volume of blood will not be more than 1 cup (240 cc) per month. In addition, your ovaries will be examined by ultrasound to show the number and size of follicles (containing eggs) that are developing. When the eggs are ready to ovulate, another drug, human chorionic gonadotropin (hCG) will be given to you to stimulate the release of your eggs.

Two days later, your partner will be asked to provide a semen sample at our office. We will prepare the semen for insemination in your uterus.

About 8 to 11 blood samples and ultrasound tests of your ovaries will be performed during each month. Up to 4 blood samples may be drawn to measure hormone levels in your blood to test for pregnancy. If pregnancy is indicated by a positive blood test, your uterus will be examined by ultrasound.

II. Possible Risks and Discomforts:

As a participant in this study, you undertake possible risks from drawing blood samples, insemination, ovarian examination by ultrasound, and hMG and hCG injections.

1. Risks of Drawing Blood Samples

a) **Discomfort, bruise, leaking of blood into adjacent tissue, bleeding from or about the punctured site.** These risks are the result of skin and vein puncture by the needle used to draw blood. These occur with moderate frequency but are usually not serious and have no long-term effect. These discomforts may be treated by direct pressure and by applying moist heat.

b) **Infection.** Bacterial infection may occur following puncture of the skin by the needle. The chance that this will occur is very low and no serious harm will result. Treatment is with antibiotics and moist heat.

c) **Anemia.** Anemia, a reduction in the number of red blood cells or hemoglobin, may result from the drawing of large amounts of blood. Because so little blood is drawn for this study, no more than 1 cup (240 cc) per month, the chance that anemia will occur is very low, and correction of any blood loss should be easily accomplished by the iron in the food you eat.

2. Risks of Insemination

a) **Uterine cramping.** You may experience mild cramps in your uterus after insemination. This occurs with moderate frequency but is of short duration and causes no long-term problems. The cramps will go away without treatment.

b) **Infection.** Bacteria in the semen or in the vagina may be passed into the uterus with insemination. The chance of infection is believed to be very small. The treatment for any infection that develops is antibiotics. Although unlikely, a severe infection may require hospitalization and intravenous antibiotics.

3. Risks of Repeated Ovarian Examination by Ultrasound

Up to the present time, there is no known risk of damage to genetic material from examination of the ovaries by ultrasound at the doses used in this study. Some women experience discomfort during the examination, as it is necessary to place the ultrasound sensor in the vagina.

4. Risks of hMG and hCG Injections

a) **Ovarian Hyperstimulation:** If overstimulated by hMG, your ovaries may become too large, and may bleed or rupture. Fluid may collect in your abdomen and lungs and your blood may become concentrated. If not treated, such blood concentration may lead to blood clots and heart failure. Ovarian hyperstimulation symptoms are rare in patients monitored as closely as this study requires. Hyperstimulation is treated with intravenous fluid therapy, salt restriction, and albumin.

b) **Allergic reactions:** These are rare and are treated with an antihistamine.

c) **Local irritation:** Drug injections may cause local irritation around the injection site. This is usually relieved by moist heat.

d) **Injury from injection:** Your partner or another individual may be trained to give you the drug injections. There is some risk that a nerve could be damaged with the needle. This may cause you to have pain and some numbness. There is no treatment and symptoms from the nerve injury will go away without treatment.

e) **Mood swings:** You may feel nervousness and irritation for a few days prior to ovulation. These feelings will go away without treatment.

f) **More than one baby:** Because hMG stimulates the release of more than one egg, it is possible to become pregnant with two or more babies. Pregnancies involving two or more babies are at a higher risk of miscarriage and premature

labor. There is also a slightly higher risk the pregnancy may occur in the tubes, outside the uterus. A tubal pregnancy might require removal by surgery.

g) Miscarriage: Pregnancy after hMG injections is associated with a higher risk of miscarriage. Up to 25 percent of patients who become pregnant after hMG injections have a miscarriage.

5. Other complications

The risks and discomforts listed above are the most commonly expected complications of the treatments used in this study. You may develop a complication that we did not know could occur with these treatments.

III. Compensation

You will not be paid for participation in the study and will not be reimbursed for time lost from work. However, you will have access to the latest techniques for diagnosing and treating infertility. All semen processing, insemination and physician fees during the four cycles of study participation will be free of charge to you. In addition, you will receive enough hMG for up to four cycles of ovulation induction. You may be assigned to a study group that gets hMG treatments during the study period. If you are assigned to one of the other groups, and do not become pregnant during the study, hMG will be provided for up to four months after the study is over. If you become pregnant during the study period or during one of the cycles after the study, no further hMG will be provided.

IV. Determination of Pregnancy Outcome

If you become pregnant, the physician responsible for your care will be contacted every three months in order to determine the status of your pregnancy. The medical records of your delivery will also be obtained with your permission.

Patients' Initials ____ / ____

V. Continuation in the Program

You are volunteering for this study and if you refuse to participate you will have no penalty or loss of benefits. Once you begin the study, you are under no obligation to continue and you are free to withdraw at any time during the course of the study.

VI. Notice of New Scientific Information.

You will be given notice of any important new scientific findings related to the treatment of infertility that are made during your participation in the study, which may affect your willingness to continue in the study.

VII. Further Information.

If at any time you have any questions or want additional information concerning any part of the study, or if you feel you have been injured as a result of this study, please contact:

Sandra Ann Carson M.D.
University of Tennessee Medical Group
66 North Pauline
Memphis, TN 38105
901-528-5859 or 528-6634

PARTICIPANTS' AGREEMENT AND CONSENT

Understanding Risks. The risks of participation in this study have been fully explained to me and I understand all of the information given. I have been given a full opportunity to ask questions regarding participation in the study and all my questions have been answered.

I understand that I will be assigned to one of the four treatment groups, at random, and that I will continue in that group for as long as I participate in the study.

I understand that I will not be compensated for participation in the study and will not be reimbursed for time lost from work.

Content of Consent Form. I have fully reviewed and understand the contents of this Consent Form. I have been given a full opportunity to ask questions about the contents of this Consent Form and all my questions have been answered.

Limitation of Release. By signing this Consent Form, I do not release the Reproductive Medicine Network, National Institutes of Health, University of Tennessee, Memphis, University of Tennessee Medical Group or any of their employees, agents or physicians from liability for their own negligence. In the event of physical injury, I understand that none of these institutions, agents or individuals have funds budgeted for compensation either for lost wages or for medical treatment, and that neither treatment nor reimbursement will be available from the Reproductive Medicine Network, National Institutes of Health, University of Tennessee, Memphis, University of Tennessee Medical Group or any of their respective employees, agents or physicians.

Acceptance of Terms and Conditions. I understand that my acceptance into the study is conditional upon my agreement to the terms and conditions of the Consent Form, and I agree

to at all times abide by its terms and conditions. In the event that I withdraw from the study, I will remain bound by the terms and conditions of the Consent Form with regard to all events occurring either before or after withdrawal. I intend that the terms and conditions of the Consent Form will be binding on me, my heirs, executors, administrators, representatives, and assigns.

Consent. With full knowledge and understanding of the risks and consequences of my participation, I consent to the medical procedures described in this Consent Form and agree to participate in this study. I consent and agree to enter the study of my own free will.

Confidentiality Clause. All the information I provide to the study will be kept confidential. My name will not be used and all information collected will be presented as group statistics.

_____ _____

Signature of Participant (woman) Date

_____ _____

Signature of Participant (man) Date

_____ _____

Physician Date

Consent acknowledged and signature of Participants witnessed by:

_____ _____

Witness Date

Appendix B.

Quality Control Procedures

Quality Assurance

While the protocol sets out the research plan for proposed trials, a manual of procedures gives detailed guidelines for day-to-day conduct and a description of methods and procedures for DCC logistic support and management. The Procedures Manual will document the quality assurance (QA) evaluation procedures, authority and responsibility for QA functions, and courses of action resulting from QA findings. In this appendix, we provide an overview of the areas and methods of quality assurance that will be implemented in the Network.

1. Pre-implementation Certification

Prior to the start of the trial, the following materials and systems will be tested at each RMU to assess ease of use, reliability, ease of maintenance and level of security:

data forms
BITnet communication system
protocol handbook
procedures manual
RMU computer system
RMU paper filing system
RMU electronic data entry system
central database
central data monitoring programs
central data editing programs
central performance monitoring report generation programs
data archiving and security programs
protocol management system

1.1 Site Certification

Each RMU will be required to pass site certification prior to patient enrollment. This certification will involve implementing the protocol for one cycle on each of 1-2 couples to demonstrate preparedness, understanding, and adherence to protocol requirements. The following areas will be assessed:

subject enrollment
data recording and computer entry
local project management methods
clinical procedures
specimen handling and laboratory procedures
problem notification and resolution procedures

1.2 Laboratory Certification

The laboratories at each RMU and the DCC are required to establish comparability of methods and results prior to patient randomization. The following areas will be assessed:

specimen tracking procedures
delay between specimen collection and assay
standards of inter- and intra-assay quality control
results reporting
specimen inventory and storage

1.3 Coordinating Center Certification

The DCC must establish mechanisms and procedures for monitoring the trial, dealing with unexpected events, and reporting trial progress, as follows:

a regular schedule of staff meetings with good attendance
a system for production and distribution of communications
procedures for problem adjudication and resolution
scenarios for adverse reactions, trial stopping rules, etc.
production of a report summarizing pre-implementation progress

2. Ongoing Quality Assurance

During the course of the study, all components of the trial are subject to some level of monitoring and review in order to detect difficulties as early as possible, to insure data integrity, and to identify both internal and external sources of potential bias.

2.1 Eligibility Data

Since accuracy and thoroughness of eligibility information prior to randomization are crucial, eligibility data will be audited against source documents in 4% of couples evaluated. Additionally, the starred items can be revalidated from repeat testing or contemporaneous

record keeping prior to randomization.

age
pregnancy test*
hysterosalpingogram
endometrial biopsy*
laparoscopy
late luteal phase biopsy
serum antisperm antibody test*
semen antisperm antibody test*
post-coital mucus characteristics*
prolactin*
TSH*
FSH*
menstrual cycle length*
one year unprotected intercourse
semen analysis*
previous IVF, GIFT, ZIFT, TET, hMG
history of: thyroid disease
diabetes
collagen vascular disease
chronic renal disease
chronic adrenal disease
chronic medication
chemo- or radio-therapy
tubal surgery
vasovasostomy
varicocelectomy within previous six months
pelvic node dissection
signed informed consent

2.2 Laboratory Tests

Laboratory assays and tests should undergo three levels of quality assurance: [i] central lab standards sent to all RMU labs for inter-lab reliability; [ii] random request for RMU labs to re-assay a specific sample for intra-lab reliability; and [iii] exchange of samples among RMU labs for inter-lab reliability. The following tests and assays will be evaluated:

estradiol
progesterone
prolactin
TSH
FSH
semen antisperm antibody test
serum antisperm antibody test
ß-hCG

2.3 Treatment Protocol

Since there is agreement to limit the scope of data collection, we will not be able to rely on redundant or indirectly cross-validating items to insure data quality. It is therefore essential that collection of the remaining data be closely monitored. RMUs will be asked to reacquire a small random sample of each data item. Where this is impossible or unreasonable, we will attempt to evaluate data accuracy by having multiple observers make independent assessments and measuring interobserver agreement. A third method is to collect objective evidence to substantiate a value. Following is a cursory list of data elements and suggested methods of assuring quality:

transvaginal U/S follicle number and size: interobserver
transvaginal ultrasound ovary size: interobserver
estradiol levels: repeat sample
abstinence from vaginal intercourse pretreatment: objective evidence
recording of menses: objective evidence
OvuQuick (LH): repeat sample
locus of insemination: interobserver
ß-hCG: repeat sample
temperature elevations: repeat sample
weight changes: repeat sample
abdominal distention: interobserver
hemoglobin/hematocrit: repeat sample
electrolyte imbalances: repeat sample
ovarian hyperstimulation: interobserver
subjective evaluation of insemination method: repeat sample
subjective evaluation of ovulation induction method: repeat sample
dropout questionnaire: repeat sample

2.4 Forms and Data Entry

Insuring accuracy and replicability of data involves detecting data errors and providing mechanisms to correct such errors before they enter the database to be used in the statistical analyses. We proposed to use a hierarchial scheme of data checking. On-line error checking at time of data entry will correct for item level errors, within-form consistency between items, within-visit consistency between forms, and cross-visit consistency. Each data entry form is also checked by computer to evaluate whether collection of the data meets the timing prescriptions of the protocol. We will ask the RMUs to double-enter approximately 5% of all forms to assess keying error rates. Finally, the DCC will generate reports summarizing cycle

data for individual couples for review and signoff by the RMU staff. The following forms are to be produced and will be subject to quality assurance evaluation:

Recruitment Forms

subject recruitment form
request for randomization
informed consent
detailed eligibility forms (for quality assurance audit of eligibility only)
demographics
occupational/lifestyle exposures
female reproductive history
male reproductive history
medical history
hysterosalpingogram
endometrial biopsy
laparoscopy
post-coital mucus
semen analysis
laboratory tests

Treatment Timing/Treatment/Follow-up Forms

OvuQuick
cervical mucus analysis
ultrasound
estradiol
semen analysis
CASA analysis
treatment given : hMG, hCG, ICI, IUI
pregnancy outcomes

Protocol Support Forms

adverse reactions/side effects
subjective evaluation of insemination method
objective evaluation of insemination method
subjective evaluation of ovulation induction method
objective evaluation of ovulation induction method
dropout questionnaire

2.5 Data Management Processes

The process of data transmission and handling from local data entry systems to the central database can introduce data errors and result in lost forms. For quality control, the

data associated with each couple are to be recorded in a casebook, with each form identified by couple number, RMU number, and a unique page number. Casebook forms are referred to when entering data into the computer. The computer files at the RMU to be used for data entry are downloaded from the DCC with these unique identifiers on the computer entry screens. At the conclusion of each cycle, an electronic copy of the data is transmitted to the DCC for review and assessment. When a patient goes off protocol at the conclusion of the four cycles or because of a pregnancy, scanned images of the original pages of the casebook will be sent to the DCC for archiving. With identical unique page numbering of both paper and computerized forms, forms tracking is a simpler task. A small, random proportion of electronic data transmissions from RMUs to the DCC will be replicated to assess the error rate associated with transmissions.

2.6 Data Edits

The most complicated aspect of data management to review for quality assurance is the data edit process (i.e., where a previously entered value is found to be in error and must be corrected by the clinical staff). We propose the following:

1. the RMU transmits a cycle of data to the DCC and the RMU copy of the data is locked against further modification

2. the DCC runs quality assurance programs against data and performs detailed audit of 4% of forms

3. if no error is detected, the data are merged with study data files

4. if an error is detected, an edit message is sent to the RMU requesting correction along with a new copy of the data (eg. version 2). Both are to be returned to the DCC: the returned edit message records who made the change, for what reason, from what value, to what value, and the date the change was made

5. resubmitted data are treated the same as an initial submission so that this process may repeat

6. RMU performance is described in terms of the number of error-free cycles merged with the study data files and in terms of the number of outstanding edit messages

2.7 Data Security

Measures must be taken to insure the safety and integrity of the study data base as it accumulates prior to analysis. For the most part this is accomplished by following conventional standards of practice for data processing; however, the implementation of these standards needs to be independently assessed on a random, periodic basis. These standards are:

daily backup of files created or modified
weekly backup of files created or modified in the past week
monthly backup of all files
two copies of all weekly and monthly backup tapes kept in different locations
log files of all merges to the study files sufficient to reconstruct the sequence in which data entered the study data files
log files of user name, date, time, and terminal location of every access to the study data files
severely limited write access to the study data files by user name and terminal location
periodic data recovery drills

2.8 The Quality Assurance Process

We propose that the Data and Safety Monitoring Board act as an external quality assurance panel to review the implementation of the quality assurance tasks described above. The DSMB traditionally consists of consultants external to the project with expertise in clinical trials and the areas of data processing, project administration and quality assurance. A member of NICHD staff might also serve in this capacity.

Appendix C.

Protocol Amendments

Decisions of the Clinical Subcommittee of the Reproductive Medicine Network

1. "A woman with external fibroid should not be excluded from the study if her uterus is no more than 8 weeks in size and she has a normal cavity on HSG".

2. A woman treated for Stage I or II endometriosis by laser, drug therapy or "excised with scissors and cauterized" must wait 6 months to be randomized even if the excised lesions show no endometriosis.

3. Inclusion of a woman with 1 fallopian tube. If the tube is removed because of evidence of "intrinsic tubal disease", 1 tube is still an exclusion. However, if the tube was removed "incidentally", and the remaining tube and ovary on the other side are completely normal, she can be enrolled if a subsequent laparoscopy shows no significant adhesions and an otherwise normal pelvis.

4. Tubal surgery for an ectopic pregnancy is an exclusion.

5. Uterine surgery for lesions not known to be associated with infertility (e.g., myoma, septum) is not grounds for exclusion. However, to be eligible for randomization, a post-operative laparoscopy and/or HSG/hysteroscopy, as appropriate, must show no significant post-operative adhesions.

6. If menses has not occurred following a treatment cycle or rest cycle, it is acceptable to allow Provera to bring on menses and the woman can be treated during the next cycle.

7. A woman had an endometrial biopsy following a negative urinary pregnancy test. The pathology report stated that "a small villous fragment was seen" suggesting an "occult" pregnancy. Does the woman have to wait 12 months to be randomized? No. She should be randomized. This was a pregnancy nobody would have detected.

8. All cycles that are initiated as study cycles should be counted toward the four on-study cycles. If the cycle is not completed as planned (e.g., inadequate follicle stimulation, premature ovulation, inability to produce a specimen), it still counts as an "attempt."

9. Where a need exists, a Mylex nonspermicidal condom may be used to obtain specimens for insemination.

10. If a woman has been on Clomid, documentation of regular menstrual periods before the Clomid is sufficient to prove menstrual cyclicity. However, the endometrial biopsy must have been done in a non-Clomiphene cycle.

11. A woman who is on Tenormin because of Mitral Value Prolapse is not eligible because chronic medication is an exclusion. She can be randomized if she is off medication for 6 months.