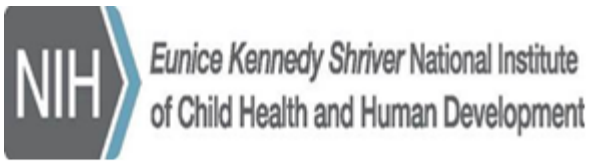

Reproductive Medicine Network
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Optimal treatment for women with a Persisting Pregnancy of Unknown Location - a Randomized Clinical Trial of women at risk for an ectopic pregnancy: Active Treatment versus Expectant Management (No Treatment) The "ACTorNOT TRIAL"

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1 Acronyms

AE	Adverse Event
CFR	Code of Federal Regulations
CBC	complete blood count
CMP	comprehensive metabolic panel
CI	Confidence Interval
DSMB	Data and Safety Monitoring Board
EP	Ectopic Pregnancy
FDA	Food and Drug Administration
hCG	human Chorionic Gonadotropin
HIPAA	Health Information Portability and Accountability Act
IRB	Institutional Review Board
IUFD	Intrauterine Fetal Demise
IUP	Intrauterine Pregnancy
LMP	Last Menstrual Period
MTX	Methotrexate
PHI	Personal Health Information
POC	Products of Conception
PPUL	Persisting Pregnancy of Unknown Location
PUL	Pregnancy of Unknown Location
SAE	Serious Adverse Event

2 Study Summary

Title	***Optimal Treatment for Women with a Persisting Pregnancy of Unknown Location (PPUL) - A Randomized Clinical Trial of Women at Risk for an Ectopic Pregnancy: Active Treatment versus No Treatment*** ***The "ACTorNOT TRIAL"***
Short Title	*ACTorNOT*
Test Article	*Methotrexate*
Phase	*N/A (comparative efficacy)*
Methodology	*This is a randomized clinical trial for women identified to have a persisting pregnancy of unknown location (PPUL) (a nonviable gestation). Randomization will be into active versus expectant management. Additionally, women randomized to active management will be equally randomized between two active management strategies.* *Randomization will be 1:2 between expectant management and active management, and 1:1 between active management A and active management B (thus randomization will be 1:1:1 into the three management arms).* *The arms will be:* *1) Expectant management* *2) Active management A)* *Determine the location of the pregnancy and only treat those with an EP: (Uterine evacuation followed by methotrexate (50 mg/m2) given as an intramuscular injection) for those that have evidence of a non-visualized ectopic pregnancy)* *3) Active management B)* *Empiric treatment of all women with a PPUL without determination of the location of the gestation (Treatment with methotrexate).* *After randomization to initial management plan, all patients will be followed by their clinicians until resolution of the PPUL. The clinician will determine subsequent management based on clinical course, further evaluation of serial human Chorionic Gonadotropin (hCG) and symptoms.*
Study Duration	*Recruitment Period: 3 years* *Subject Follow-up: 2 years* *Total Duration: 5 years (2014-2019)*
ClinicalTrial.gov Registration Number	*NCT01800162*

Objectives	*The primary outcome measure in each of each 3 treatment arm is the uneventful clinical resolution of a PPUL without change from the initial management strategy.* *Secondary outcome measures are: number of ruptured ectopic pregnancies, number and type of re-interventions (additional methotrexate injections or surgical procedures), treatment complications, adverse events, number of visits and time to resolution, patient satisfaction, and future fertility.*
Number of Subjects	*276 subjects with a PPUL*
Diagnosis and Main Inclusion Criteria	*Inclusion criteria will include pregnant women who are hemodynamically stable, ≥ 18 years of age, diagnosed with a persisting pregnancy of unknown location (defined as: no definitive ultrasound evidence of intrauterine or extra uterine gestation and a plateau in at least two serial hCG values (defined as less than an 15% rise per day or less than a 50% decline over 2-14 days,)*
Statistical Methodology	*The percent success of initial management course will be compared for each study arm. The two hypotheses to be tested will be that 1) active management is superior to expectant management and 2) the two active management strategies are non-inferior to each other.* *If active management is not superior to expectant management (or if the two active management strategies are non-inferior), the determination of which management strategy is optimal will be based on secondary outcomes. Secondary outcome measures and cost will be modeled in a cost effectiveness analysis using average cost and charge per procedure.*

3 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), 45 CFR 46, applicable government regulations and institutional research policies and procedures.

3.1 Background

A woman with pain and bleeding in the first trimester of pregnancy is at risk for ectopic pregnancy (EP) and should be distinguished from a woman with an ongoing potential viable intrauterine pregnancy (IUP) and from a woman with a miscarriage. Ectopic pregnancy (EP) is defined as the implantation of an embryo outside the uterus. EP is a major cause of maternal morbidity and responsible for 6% of pregnancy-related deaths (1, 2). However if diagnosed and treated early and before rupture, morbidity is limited and conservative management is preferred (3). Early diagnosis permits early treatment and allows for procedures that preserve fallopian tube function and fertility (4).

There is worldwide consensus regarding the utility of trans-vaginal ultrasound and serial quantitative serum human chorionic gonadotropin (hCG) concentrations in the diagnosis of women at risk for EP. Diagnosis can be straightforward when ultrasound definitively identifies an IUP or EP (6). However, ultrasound can be inconclusive in up to 40% of women with a symptomatic first trimester pregnancy (7). This clinical quandary is termed a 'pregnancy of unknown location' (PUL). A PUL is not a diagnosis but a transient state in the diagnostic process of a woman at risk for EP (8). The management of a woman with a PUL necessitates further surveillance and/or diagnostic tests to achieve a final diagnosis, including (but not limited to) serial hCG concentrations to determine if a pregnancy is growing or resolving (non-viable). Ultimately, a woman is usually diagnosed with one of three outcomes: an ongoing growing IUP, a miscarriage, or an EP. If the pregnancy resolves without any intervention, the location is never known and is termed a resolved PUL (8).

During the course of evaluation of a woman with a PUL, up to one third of women will be found to have serial hCG values that neither rise nor decline. This is diagnostic of a nonviable gestation (either a miscarriage or an EP) and is termed - a persisting PUL (PPUL). The hCG is produced by the trophoblast tissue that is either in the uterus or the tube (and is not visible on ultrasound). Surgical exploration in the form of uterine evacuation (dilation and curettage) is often performed to confirm the location of the persistent trophoblast tissue. If trophoblast tissue is found at the time of uterine evacuation, a miscarriage has been diagnosed (and treated). If the hCG concentration does not decline after uterine evacuation, the trophoblast is presumed to be in the fallopian tube and an ectopic gestation is confirmed (5). An ectopic gestation can then be treated medically with methotrexate, to hasten the resolution of the extra-uterine trophoblast tissue (9, 10).

Of note, methotrexate will act on the trophoblast tissue if it is in the uterus or in the tube. Some have advocated that it is unnecessary to identify the location of the gestation. Thus, some have advocated treating a woman with a PPUL with methotrexate without first determining the location of the gestation (11).

Finally, both early miscarriage and early ectopic pregnancy can be managed expectantly (12-18). A recent study in the Netherlands demonstrated no difference in primary treatment success rate of single-dose methotrexate versus expectant management, 31/41 (76%) and 19/32 (59%), respectively [relative risk (RR) 1.3 95% confidence interval (CI) 0.9–1.8]. The absolute difference in failure rate found between active and expectant management was 18%. Expectant management of an EP or a PPUL is uncommon in the United States (16).

Thus, there are currently three commonly used strategies to manage a woman with a PPUL with true equipoise as to which is more effective and optimal: Expectant management would avoid the morbidity associated with a surgical intervention needed to determine location and/or the morbidity of methotrexate. However during the time of expectant management, women are at risk for rupture of an EP with its inherent morbidity and mortality or at risk for complication from retained products of conceptions from an incomplete miscarriage. Moreover, resolution of a PPUL can take up to 6 weeks. We plan to test if active management is superior to expectant management with sufficient power to identify an absolute difference of only 18%. Thus, if expectant management has similar efficacy to active management it can become an evidence-based treatment option for this population of women.

If active management is superior to expectant management, or even if similar in efficacy, it will likely still be desired by some and will likely continue to be a common treatment strategy. Thus, determination of which active management strategy is optimal is also an important clinical question. Active management can be divided into two strategies A) Determine the location of the pregnancy and only treat those with an EP: (Uterine evacuation followed by methotrexate (MTX) for only those who have evidence of a non-visualized EP) and (B) Empiric treatment of all women with a PPUL without determination of the location of the gestation: (MTX administered to all women with a PPUL). MTX is currently a standard of care to medially manage an un-ruptured EP (9, 11), but is not a standard of care to treat a miscarriage because methotrexate has inherent morbidity.

We have demonstrated that up to 50% of women with a PPUL have an EP and 50% have a miscarriage (5). However, surgical intervention in the form of a uterine evacuation (dilation and curettage) to identify if there were products of conception (trophoblast tissue) in the uterus was necessary to make this distinction. Thus, empiric treatment of a woman with a PPUL with MTX may result in overtreatment of 50% of women. Conversely, the morbidity and cost of a uterine evacuation may outweigh the cost and morbidity of "overtreatment" with MTX. Lack of objective data to inform clinicians as to the optimal strategy is an identified and universally accepted knowledge gap and a research priority and is therefore the focus of this protocol (8).

Of note, all women with a PPUL, regardless of the initial strategy adopted by a clinician (or allocated to in this protocol), will be followed until clinical resolution of the gestation. In some cases resolution is complete and uneventful, even if the location of the pregnancy is never ascertained. Complete uneventful resolution of the PPUL is the primary outcome of this trial. In other cases the clinical course and symptoms dictate intervention and abandonment of the initial management strategy. Until the gestation is completely resolved (i.e. all trophoblast tissue has been resorbed, as evidenced by absence of hCG in the serum) a women may become clinically symptomatic from an EP or miscarriage. Based on the clinical course after initial intended management, some receive additional intervention and/or treatment. Intervention may be needed to diagnose and/or treat an EP that becomes symptomatic (rupturing or ruptured) or to treat a woman with a miscarriage that becomes symptomatic because of retained products of conception. Thus, women may require surgical or medical intervention to diagnose or treat an EP, or require surgical or medical intervention for an unresolved miscarriage. A clinically important example is that approximately 10-20% of women with an EP treated with MTX fail medical management and require surgical management (16, 19). Quantification of these interventions, including side effects, time to resolution and cost are the secondary outcomes of this study. These outcomes will determine which management strategies are optimal if the efficacy is similar.

3.2 Preclinical Data

This type of study is not applicable in animals.

3.3 Clinical Data to Date

The medical management of ectopic pregnancy is the use of intramuscular MTX. This is a common medical procedure with widely published recommendation (9, 10). MTX treatment has been used as single dose or multi-dose (19). We have demonstrated the efficacy and safety with the use of a 2 dose regimen (20). This two-dose regimen was developed under IND 65407. One dose of MTX was used in the recent trial in Amsterdam (6). We expect that two doses of MTX will be more effective than one dose and thus our success rate will be higher (20).

3.4 Risk/Benefits

All three management strategies in this randomized clinical trial are used as part of clinical standard of care, and therefore, we believe that the patient is not exposed to any 'experimental' risks. This study is a comparison of the efficacy and safety of three currently available and commonly used strategies. Randomization to one of these strategies therefore poses minimal risk to a subject. There is risk associated with the clinical condition, including the possibility of rupture of an ectopic pregnancy. Each strategy has mildly different risks associated with the treatment plan.

Subjects randomized to 'Expectant Management' may be at a higher risk for rupture of an ectopic pregnancy or retained products of conception, but avoid the morbidity associated with surgical and medical intervention.
Subjects randomized to Active management A) ‘Uterine evacuation followed by MTX for some’ will be exposed to the risks of surgical intervention of uterine evacuation (risk of bleeding, infection and uterine perforation), but may be spared the exposure, and morbidity associated with MTX (risk of nausea, abdominal pain, mouth sores).
Subjects randomized to Active management B) ‘Empiric MTX for all’ may avoid the risk of uterine evacuation but are exposed to the side effects of MTX (see 2. above).
All subjects will have the risk of all therapeutic options explained to them as is the current practice for the clinical evaluation and management of a PPUL. Of note, during this treatment course, all subjects are inherently at risk for rupture from their potential ectopic pregnancy.

Additional risks include loss of confidentiality. Loss of confidentiality is prevented through omitting all personal identifiers in the research database.

In summary, the risks of participation in the research are mild (above that of their clinical condition) and are balanced by the potential benefits of the research to society.

4 Study Objectives

The goal of this study is to:
1) Determine if active management of women with a PPUL is superior to expectant management.

2) Determine if two common active management strategies of a women with a PPUL are non-inferior to each other.

3) Determine which management strategies are optimal based on secondary outcomes of cost, number of procedures, side effect, and time to resolution.

4.1 Primary Objective

The primary outcome measure is the frequency of clinical resolution for each management strategy for a PPUL. Clinical resolution is defined as an uneventful decline of serum hCG to an undetectable level (less than 5 mIU/mL) by the initial intervention strategy. This outcome is accepted and commonly used to assess efficacy of medical and expectant management of miscarriage and EP (16, 20, 21).

4.2 Secondary Objective: Assessment of

- Number of ruptured ectopic pregnancies in each group
- Quantification of re-interventions needed to manage a woman with a PPUL
    - Outcomes include:
        - number of interventions beyond that of intended initial strategy in each group
            - additional number of MTX injections
            - additional surgical procedures
                - uterine evacuation (or dilation and curettage)
                - laparoscopy
                - laparotomy
- Treatment complications and adverse events
- Number of procedures (lab tests, ultrasounds)
- Number of visits
- Time to resolution
- Patients' preferences
- Acceptability
- Future fertility

5 Study Design

5.1 General Design

This is a multi-site randomized comparative efficacy trial of strategies to manage a woman with a PPUL.

Randomization will be 1:2 between expectant management and active management, and 1:1 between active management A and active management B. (Thus randomization will be 1:1:1 into the three management arms.)

The arms will be:
1) Expectant management

2) Active management A)
Determine the location of the pregnancy by a uterine evacuation, followed by a pathologic evaluation. If no evidence of a uterine pregnancy is determined (i.e. non-visualized ectopic pregnancy), begin methotrexate dosage (50 mg/m2 given as an intramuscular injection).

3) Active management B)
Empiric treatment of all women with a PPUL without determination of the location of the gestation *(Treatment with methotrexate)*

For specifics of how MTX will be administered, please see below.

All patients will be followed by their clinicians who will determine subsequent management based on changes in clinical course, further evaluation of serial hCGs, repeat ultrasound, and symptoms. It is anticipated that in most cases the failed pregnancy will resolve (or be treated) successfully. Some women will fail or elect to stop initial management strategy and will be offered surgical or medical management. For example, the failed initial medical management of an ectopic pregnancy or miscarriage necessitates surgical intervention.

5.2 Subject Selection and Withdrawal

5.2.1 Inclusion Criteria

1. Female with a persisting pregnancy of unknown location:
   a. A pregnancy of unknown location is defined as a pregnancy in a woman with a positive pregnancy test but no definitive signs of pregnancy in the uterus or adnexa on ultrasound imaging. A definitive sign of gestation includes ultrasound visualization of a gestational sac with a yolk sac (with or without an embryo) in the uterus or in the adnexa (8). Ultrasound must be performed within 7 days prior to randomization.
   b. Persistence of hCG is defined as at least 2 serial hCG values (over 2-14 days), showing < 15% rise/day*, or < 50% fall between the first and last value. (This abnormal pattern of serial hCG confirms that the gestation is nonviable.)

   *Calculated by day X/ baseline X 100 and then compare to table for the number of days between values as below:

   2 days 30% or less
   3 days 50% or less
   4 days 75% or less
   5 days 100% or less
   6 days 130% or less

7 days 166% or less

These numbers are rounded (conservatively) to accommodate ease of determination eligibility
The actuals % rise for 15%/ per day is: 1 day 15%, 2 days 32.3%, 3 days 52.1%, 4 days 74.9%, 5 days 101.1%, 6 days 131.3%, 7 days 166%

A minimal rise for a viable intrauterine pregnancy is 23% per day or 53% for two days. (4)

2. Patient is hemodynamically stable
3. Greater than or 18 years of age

5.2.2 Exclusion Criteria

1. Hemodynamically unstable in need of acute treatment
2. Most recent hCG > 5000 mIU/mL
3. Patient obtaining care in relation to a recently completed pregnancy (delivery, spontaneous or elective abortion)
4. Diagnosis of gestational trophoblastic disease
5. Subject unwilling or unable to comply with study procedures
6. Known hypersensitivity to MTX
7. Presence of clinical contraindications for treatment with MTX (ACOG guidelines, **Appendix B**)
8. Prior medical or surgical management of this gestation
9. Subject unwilling to accept a blood transfusion
10. Patient ≤ 6.0 weeks gestation with known conception date with slow but continuous rise in hCG values (even if these values meet the inclusion definition above).

5.3 Subject Recruitment and Screening

Subjects will be recruited for participation in this study from the clinical practices at the participating institutions. The subjects will be patients who are currently undergoing clinical care at these approved sites. The site staff will be responsible for identifying eligible patients who meet the inclusion criteria, and have none of the exclusion criteria. All subjects will be counseled and sign the informed consent form before undergoing any study procedures.

5.4 Informed Consent

The informed consent form will adequately address the risks and the benefits for the study, and will be approved by the IRB before any patients are enrolled in the study. No study procedures will be conducted before the patient signs the informed consent form.

The informed consent regarding clinical procedures (surgical intervention, administration of MTX, or expectant management, including side effect of each and chance of rupture of an EP) will be given in the context of normal clinical care by the treating clinicians, following local clinical standards.

6 Study Procedures

6.1 Allocation of Randomization and Treatment

After a woman is identified to have a persisting pregnancy of unknown location by her clinical team (or clinician), eligibility will be determined. In the event that a clinical patient of the investigator (or study staff) meets the eligibility criteria for study participation, the investigator (or study staff) is required to document a second opinion related to the determination of viability of the pregnancy. If eligible, the subject will be offered enrollment into the study. The subject will be randomized by a computerized randomization tool.

Once the subject is randomized to initial management strategy, her clinical care will be continued with her clinical team (or clinician). Standard of care is to follow the subject until complete resolution of the persisting pregnancy of unknown location (defined by resolution of hCG from the serum to a value of less than 5 mIU/mL) or treatment of an ectopic pregnancy (if identified). Follow up includes serial outpatient monitoring of hCG values, monitoring patient signs and symptoms, as well as ultrasound as needed. Based on these findings the treating physician may judge that surgical or medical intervention is required to diagnose or treat an ectopic pregnancy or miscarriage. Subjects will be screened for eligibility for MTX only after it is determined that they will receive it (i.e. via randomization or clinical discretion). Those who are randomized to receive MTX, but then are not able to receive it due to safety laboratory values, will be managed per the judgment of her treating physician.

Randomization will be performed when the patient is identified to have a persisting pregnancy of unknown location by a central randomization office utilizing an internet-based program. Randomization will be stratified by site. A 1:1:1 randomization scheme for Arms 1, 2 and 3, respectively, will be followed.

Below the three arms of the trial are described:

6.1.1 Expectant management

In this management arm the allocated plan is to expectantly manage the persisting pregnancy of unknown location without surgical or medical intervention, but with close clinical surveillance using serum hCG monitoring.

Success

Success of this management arm will be complete resolution of hCG from the serum, without medical or surgical intervention.

Failure

I) Failure is defined as the need for surgical or medical intervention to treat a persistent or ruptured ectopic pregnancy.

II) The need to perform a uterine evacuation to complete a miscarriage or to treat heavy bleeding also will be considered failure of this management arm.

6.1.2 Active management A: Uterine evacuation followed by MTX for those that have evidence of a non-visualized EP

In this management arm, a uterine evacuation or dilation and curettage will be scheduled. At the clinician's discretion, this can be performed using local anesthesia, sedation or general anesthesia and can use a manual or electrical vacuum evacuation. The procedure should be performed within three days of randomization.

A repeat serum hCG value will be obtained within 12–36 hours of completion of the procedure. Based on this value one of two courses will be followed:

a) If the value has decreased by greater than (or equal to) 15%:
The uterine evacuation is considered compete and successful. No further treatment is indicated and the subject is followed as an outpatient until complete resolution of hCG from the serum.

b) If the value has decreased less than 15% (or increased):
The uterine evacuation is considered not to have removed the products of conception and the trophoblastic tissue is presumed to be ectopically located. In this case the diagnosis of a non-visualized ectopic pregnancy has been confirmed (5, 8). Treatment of the non-visualized ectopic pregnancy will be with intramuscular MTX using the 2-dose protocol (18). The administration of the first MTX injection should be within 48 hours of making the diagnosis of a non-visualized EP. For specifics regarding administration of MTX utilizing the 2 dose protocol, see **Appendix B**.

After administration of MTX, no further treatment is indicated and the subject is followed as an outpatient until complete resolution of hCG from the serum.

If a woman is randomized to receive MTX but is ineligible after screening with safety laboratory abnormalities, she will not receive MTX, but will remain in the allocated treatment arm for statistical purposes. She will be treated at the discretion of her treating physician and success and failure will be determined based on treatment course as described below.

Success
Success of this management arm will be complete resolution of hCG from the serum after either uterine evacuation only (situation "a") or after uterine evacuation and MTX administration (situation "b"), without further surgical intervention.

Failure
I) Failure of MTX management is defined as the need for surgical intervention to treat a persistent or ruptured ectopic pregnancy. The need to administer additional doses of MTX to treat a persistent ectopic pregnancy will be collected as a secondary outcome, but will not be defined as failure of this management arm because additional doses of methotrexate as necessary are part of the protocol for medical management of EP.

II) The need to perform a second uterine evacuation to complete a miscarriage or to treat heavy bleeding will be considered failure of this management arm.

6.1.3 Active management B: Empiric treatment with MTX

In this management arm, treatment will proceed directly to intramuscular MTX. The MTX should be administered within two days of randomization. For specifics regarding administration of MTX utilizing the 2 dose protocol, see **Appendix B**.

If a woman is randomized to receive MTX but is ineligible due to screening with safety laboratory abnormalities, she will not receive MTX, but will remain in the allocated treatment arm for statistical purposes.

She will be treated at the discretion of her treating physician and success and failure will be determined based on treatment course as described below.

Success
Success of this management arm will be complete resolution of hCG from the serum after MTX administration, without surgical intervention.

Failure
I) Failure of MTX management is defined as the need for surgical intervention to treat a persistent or ruptured ectopic pregnancy. The need to administer additional doses of MTX to treat a persistent ectopic pregnancy will be collected as a secondary outcome, but will not be defined as failure of this management arm because additional doses of methotrexate as necessary are part of the protocol for medical management of EP.

II) The need to perform a uterine evacuation to complete a miscarriage or to treat heavy bleeding will be considered failure of this management arm.

6.2 Data Collection

Information collected includes baseline information, treatment allocation, and the clinical course of each subject.

6.2.1 Serum and Plasma samples

Serum and plasma samples will be obtained to assess for potential molecular markers of success at randomization (before treatment) and at approximately weekly intervals until resolution, as available. These samples will be obtained at the time of a clinical blood draw and will be banked. Residual serum from clinical tests will also be collected (if available) and banked for future assessment of serum predictive markers. Serum samples will be collected at all sites. Plasma samples will be collected at the University of Pennsylvania only.

Testing on these blood samples may include a proteomic screen and assessment of a panel of exploratory proteins potentially including but not limited to: ADAM 12, Inhibin A, Progesterone, Activin A, Vascular Endothelial Growth Factor (VEGF), Pregnancy-specific beta 1-glycoprotein, Pregnancy-associated plasma protein-A (PAPA), Glycodelin, Placental growth factor 1 (PIGF).

These blood samples may be used for genetic testing in the future. An example of potential genetic testing would be polymorphisms in genes involved in implantation, messenger RNA of proteins associated with early pregnancy or micro RNA.

6.2.2 Baseline information

Baseline information will include:

- Demographics: age, race, ethnicity, site of treatment
- Past gynecologic, obstetric and medical history
- Characterization of the presenting signs and symptoms:
  a) chief complaint
  b) amount of pain (scale of 1–10)
  c) bleeding (none, scant, light, heavy)
- Results of laboratory tests: including hCG and relevant chemistry, hematology, blood type, and transvaginal pelvic ultrasound

6.2.3 Follow up visits

Data collected at all follow up visits will include:

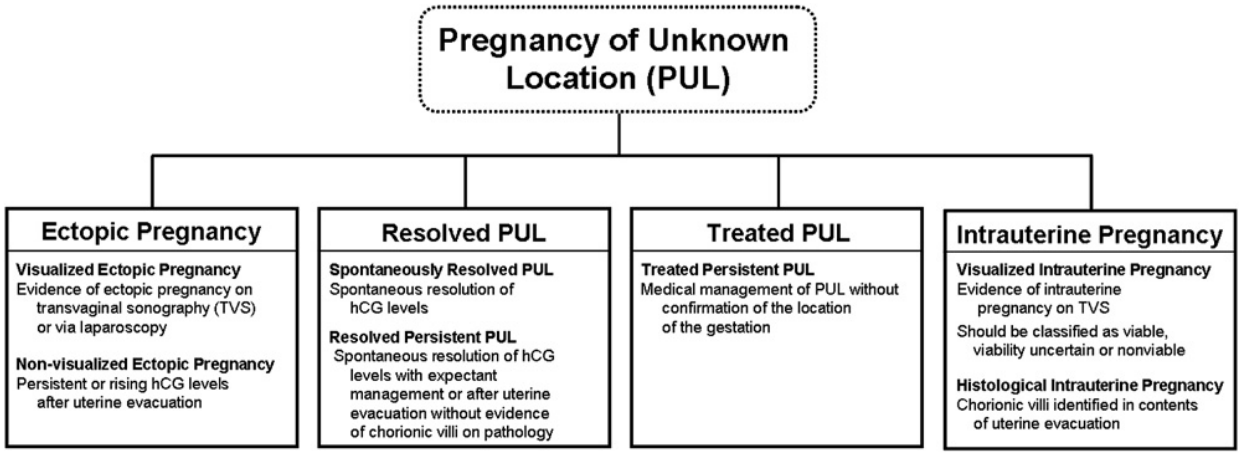
- Date
- Location (outpatient, emergency room, inpatient)
- Change in symptoms (increase or decrease in pain and or bleeding)
- Serum hCG value and other relevant laboratory values (hematology, chemistry, if ordered)
- Results of ultrasound (if performed)
- Adverse events
- Procedures performed (i.e. dilation and evacuation, injection with MTX, laparoscopy)

This process will be continued until the persistent pregnancy of unknown location has resolved (hCG <5 mIU/mL) or a diagnosis of ectopic pregnancy has been made and treated.

6.2.4 Final Diagnosis Categorizations

Final diagnosis will be categorized as: resolved persistent PUL, histological non-viable IUP, and non-visualized EP (8). (See Figure 1 below.)

Figure 1: Pregnancy of Unknown Location (PUL)



If an EP is diagnosed, information on initial treatment (medical vs. surgical) and success of initial treatment will be collected.

The groups will also be compared as to the percentage of women diagnosed with each outcome. For example, women randomized to uterine evacuation will limit the diagnosis of resolved PUL or treated PUL as the procedure will more likely result in the diagnosis of EP (when uterine evacuation demonstrates no chorionic villi but the hCG value rises post-op) or nonviable IUP (when uterine evacuation demonstrates chorionic villi and thus the diagnosis of nonviable IUP is made).

6.2.5 Quality of Life, Acceptability, and Cost

A questionnaire assessing side effects and satisfaction and time away from work will be administered 3 weeks after management plan is initiated (range can be 2-4 weeks) (See **Appendix C**).

6.2.6 Long term follow up

To assess fertility after the operation of the index persisting pregnancy of unknown location, the patient will be contacted by means of a questionnaire, every six months for a period of 24 months (See **Appendix D**). Questions will focus on the desire for pregnancy, contraceptive use, infertility treatment, and the occurrence of any pregnancies and their outcome (including live birth, miscarriage or ectopic pregnancy). If a hysterosalpingogram or a diagnostic laparoscopy with chromopertubation is performed to assess the status of the tubes, the results will be recorded in the Case Record Form. However, assessment of tubal patency by means of a hysterosalpingogram or a diagnostic laparoscopy is not part of the protocol.

Standardized definitions of outcomes of a pregnancy of unknown location are provided in **Appendix A.**

7 Statistical Plan

7.1 Sample Size Determination

The assumptions for sample size for this aim include allocation to expectant vs. active management (Table 1) AND when allocated to active treatment, equal allocation to one of two active treatment arms (Table 2). Thus the overall allocation is 1:1:1 to the three arms. All sites will have balanced randomization so that each site will contribute equal ratios for the 3 treatment arms.

Data suggest a 25% "failure" rate for expectant management: (3, 12, 13, 14). A recent randomized trial demonstrated that the failure rate for expectant management was approximately 40% for women with EP (13/32 (40.6%) (16). We anticipate that the failure rate in this trial will be approximately one half of that value because it is estimated that one half of the woman will have EP (and the other half miscarriage). Thus, failure rate of 25% for expectant management will be compared to an estimated failure rate for active management.

This failure of medical management for a PPUL is based on a modification of the failure rate for MTX to treat an EP. The failure of MTX to treat EP in the literature ranges from 8–25% (14, 15, 16, 17) with a population based estimate of 14.7 % (2). Specifically, we have demonstrated a failure rate of 13% for the 2 dose study protocol (20). The failure rate of MTX for a PPUL or non-visualized EP in this protocol is purposely lower than other estimates in the literature because not all women will have an EP. Also, women who do have a non-visualized EP are good candidates for successful medical management, with lower than average failure rates (21, 22). Thus, we estimated the failure rate in 'Uterine evacuation followed by MTX for some' to be 6%. The failure rate in 'Empiric MTX for all' is estimated to be 8% to account for a number of women who actually have a miscarriage (not an EP) that are not successfully treated with MTX. Medical management of a miscarriage with MTX is not the optimal treatment and some women will ultimately need a uterine evacuation. A failure rate of 7% (the average of 6% for 'Uterine evacuation followed by MTX for some' and 8% for 'Empiric MTX for all') will be used as the expected failure rate of active management.

The primary hypothesis will test the superiority of active management (both active management arms combined) to expectant management with 90% power. The sample size requirement for the comparison of 25% failure vs. 7% failure requires 160 women allocated to active and 80 women allocated to expectant management (Table 1). With this sample size we will conclude that if the difference between active and expectant management is greater than 18%, active treatment is superior. This is a clinically relevant difference.

The sample size is determined to achieve 90% of power if the absolute difference is at least 18%. This difference will be lower when the active treatment is less successful and/or the expectant management is more successful. An absolute difference of less than 18% (or an hypothesized absolute failure rate for expectant management of less than 25%) would be considered clinically acceptable and would provide evidence to support its use.

Table 1: The sample size requirement comparisons of active expectant management

Sample Size Comparisons	Expectant Management	Active Management
Expected success rate	75%	93%
Expected failure rate	25%	7%
Number of subjects	80	160
Number of subjects with 15% inflation	92	184

Our secondary hypothesis is to determine which active management strategy is optimal. To address this question we proposed using a non-inferiority approach to the two active management arms (Table 2). With 1:1 randomization within the active treatment arm (80 in each active management strategy), assuming failure rates of 6% vs. 8%, with 80% power, we can test a non-inferior margin of 12%. Therefore, if one arm has an absolute failure rate above the upper limit for the CI (13%) it will be considered non-inferior. If the two failure rates are similar, and within the bounds of the CI, secondary outcomes will be considered to assess which is optimal.

Table 2: Non-inferiority approach to the two active management arms

Non-inferiority approach to the two active management arms	Active management strategy A 'Uterine evacuation followed by MTX for some'	Active management B 'Empiric treatment with MTX for all"
Expected success rate	94%	92%
Expected failure rate	6%	8%
Number of subjects	80	80
Number of subjects with 15% inflation	92	92

We have inflated the sample size by 15% to 276 women (92, 92, 92) to account for loss to follow-up. Based on anticipated recruitment of 175 cases of persistent PUL a year, we project that recruitment will take 2-3 years.

7.2 Statistical Methods

The percent failed of initial treatment course will be compared for each study arm, using logistic regression models which will include adjustment for site and any covariates determined to be imbalanced among the treatment arms. The primary analysis will assume 'Intent to Treat' (ITT) principles, whereby every participant randomized will be included for analysis. An "as treated" participant analysis will also be conducted, but considered secondary.

For our primary hypothesis, we hypothesize that there will be a higher failure rate for expectant management, compared to active management (both active management arms combined). For our secondary hypothesis we anticipate that the lowest failure of assigned active treatment will be uterine evacuation followed by medical management for some (active management strategy A) because this strategy will treat women with a miscarriage (with uterine evacuation) and will treat women with EP with MTX. The "failure" rate of empiric medical MTX management for all (active management strategy B) will be higher, as MTX is not always effective for women with a miscarriage (as they may need uterine evacuation later). If efficacy of active and expectant management is similar (or if the two active management strategies are similar) we will evaluate secondary outcomes and a cost effective analysis (see below).

Secondary outcome measures will be compared among the treatment arms. These outcomes include:

- Number of ruptured ectopic pregnancies in each group
- Quantification of re-interventions needed to manage a woman with a PPUL

  - Outcomes include:
    - number of interventions beyond that of intended initial strategy in each group
      - additional number of MTX injections
      - additional surgical procedures
        - uterine evacuation (or dilation and curettage)
        - laparoscopy
        - laparotomy
- Treatment complications
- Adverse events
- Number of procedures (lab tests, ultrasounds)
- Number of visits
- Time to resolution
- Patients' preferences
- Acceptability
- Future fertility (if desired)

Above and beyond the success or failure of the initial treatment method, the clinical consequences of the morbidity of the intervention and the percentage of failed treatment is also of great importance. Taking into account these factors, as well as cost, it is hypothesized that expectant management may be less slightly effective, but preferable. Alternatively in the comparison of active strategies, empiric treatment with MTX may be slightly less effective but preferable.

A cost effectiveness analysis is planned based on the cost and frequency of secondary outcomes (including medical tests, procedures and office visits). Financial costs and charge per procedure will be ascertained for this analysis using national averages. The cost effective analysis will be conducted from the perspective of the payer.

8 Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Loss of confidentiality is prevented through omitting personal identifiers in the research database. The dataset available to the researchers will identify patients by a unique ID number unrelated to any personal identifiers, and will be stripped of identifying information such as medical record number, name, contact information including address and phone number. A single web-based database will be used for all sites, but clinicians will only be able to view patients from their own hospital/practice site.

8.2 Records Retention

Per 21 CRF 312.62, it is the investigator's responsibility to retain study essential documents for at least 2 years after the investigation is discontinued and the FDA is notified. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

9 Study Monitoring, Auditing, and Inspecting (Technical Aspects)

9.1 Study Monitoring

A monitoring plan that satisfies the Guideline for Monitoring of Clinical Investigations of the National Cancer Institute will be used. A Project Manager from the DCC will lead this effort, and report findings to the DCC PI. The Project Manager will have full knowledge of the study protocol, Manuals of Procedures, and is familiar with the database system and is trained to review patient charts. The Project Manager will be responsible for training and supervising other personnel.

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

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

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

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

9.2 Safety Monitoring

Safety of this study will be closely monitored. A Data and Safety Monitoring Board (DSMB) will evaluate the data at midpoint of recruitment and at the reporting of each serious adverse event (SAE). An interim analysis will be scheduled for safety after one half (138) of the subjects complete the trial. If safety or efficacy is an issue, one arm will be dropped or the study stopped. A two-arm study would still have clinical value.

9.3 Adverse Events

Adverse Events

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Not all events that would traditionally be defined as AEs will be collected for this trial. Intercurrent illnesses or injuries should not be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

There are a number of expected side effects related to women at risk for ectopic pregnancy including mild abdominal pain, vaginal bleeding, and nausea. There are also a number of expected side effects related to medical management (nausea and vomiting, abdominal pain, diarrhea, headaches, fatigue, loss of appetite) and surgical management (nausea and vomiting, abdominal pain, diarrhea, headaches, fatigue, loss of appetite, vaginal bleeding, surgical site incision pain). Some of these symptoms will be collected as part of patient satisfaction and quality of life (patient self reports). The only non-serious events that will be otherwise specifically collected and classified as AEs for this study are those that are both unexpected and considered to be related to study procedures or study drug.

Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that results in any of the following outcomes:

• Death
• Life-threatening (see Note A)
• Inpatient hospitalization or prolongation of existing hospitalization
• Persistent or significant disability/incapacity (see Note B)
• A congenital anomaly/birth defect

http://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm.

Note A: the term “life-threatening” in the definition of “serious adverse event” refers to any serious adverse event that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form might have caused death.

Note B: the term “disability” in the definition of “serious adverse event” refers to a substantial disruption of a person’s ability to conduct normal life functions.

Note C: There are two serious adverse events that are expected and related to the condition of ectopic pregnancy: life threatening event due to rupture, and hospitalization for observation or recovery from surgery. In addition, salpingectomy for treatment of ectopic pregnancy may render a woman permanently infertile if her other tube had been previously removed.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring

intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All SAEs, regardless of relatedness, will be collected for this trial.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 42 days following the last administration of study treatment.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

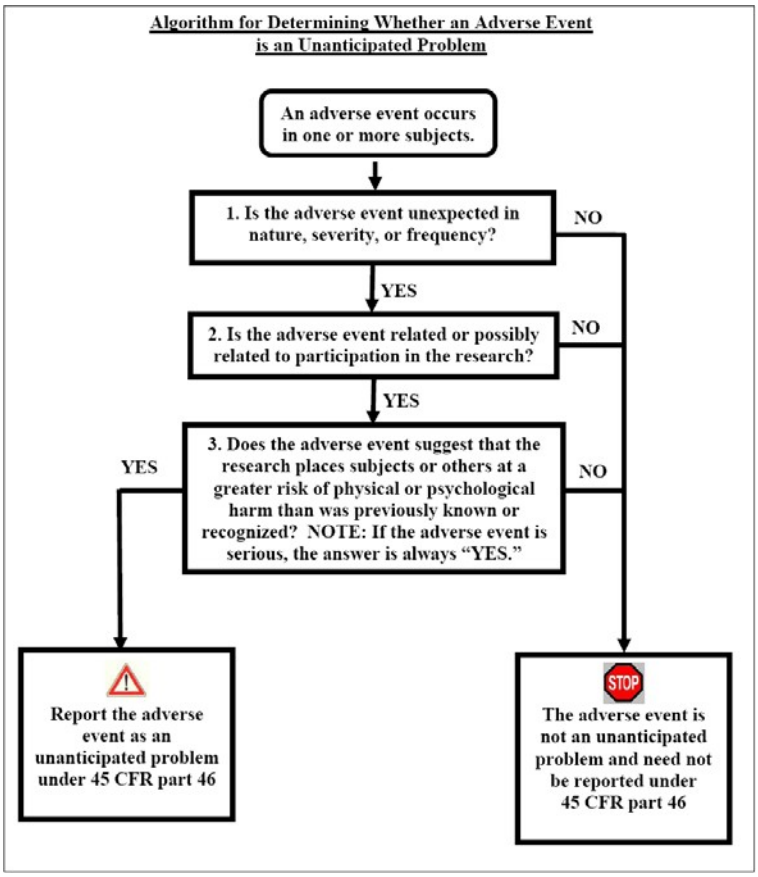
The trial will be discontinued if a death or life-threatening adverse event related to the use of MTX, and not related to the underlying condition, occurs.

9.4 Reporting Adverse Events

All serious adverse events (SAEs) that occur from the start of study drug through 42 days after the last dose of study medication must be reported. A serious adverse event is defined as: fatal or immediately life-threatening; severely or permanently disabling; requiring or prolonging inpatient hospitalization; overdose (intentional or accidental); congenital anomaly; pregnancy loss after 20 weeks gestation; neonatal death up to 6 weeks after delivery; or, any event adversely affecting the study's risk/benefit ratio. Additionally, any event that, based on appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above is considered an SAE.

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

DCC staff will enter the SAE information in the central database and the Safety Surveillance team, consisting of the DCC, NICHD research scientist and lead PI of the protocol, will analyze the SAE to determine if it meets the criteria listed in the OHRP 45CFR46 and/or FDA 21CFR312.32 & 3.14.80.



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

TYPE	SITE	DCC
Unanticipated and related/possibly related SAE, fatal or life-threatening	Report to DCC within 1 business day of discovery	Notify DSMB by end of next business day of receiving site report
Other unanticipated and related/possibly related SAE	Report to DCC within 1 business day of discovery	Notify DSMB within 5 business days of receiving site report
Anticipated and related/possibly related SAE	Report to DCC within 5 business days of discovery	Notify DSMB within 5 business days of receiving site report
Unrelated SAE (anticipated or unanticipated)	Report to DCC within 10 business days (no more than 3 weeks) of discovery	Notify DSMB within 10 business days (no more than 3 weeks) of receiving site report

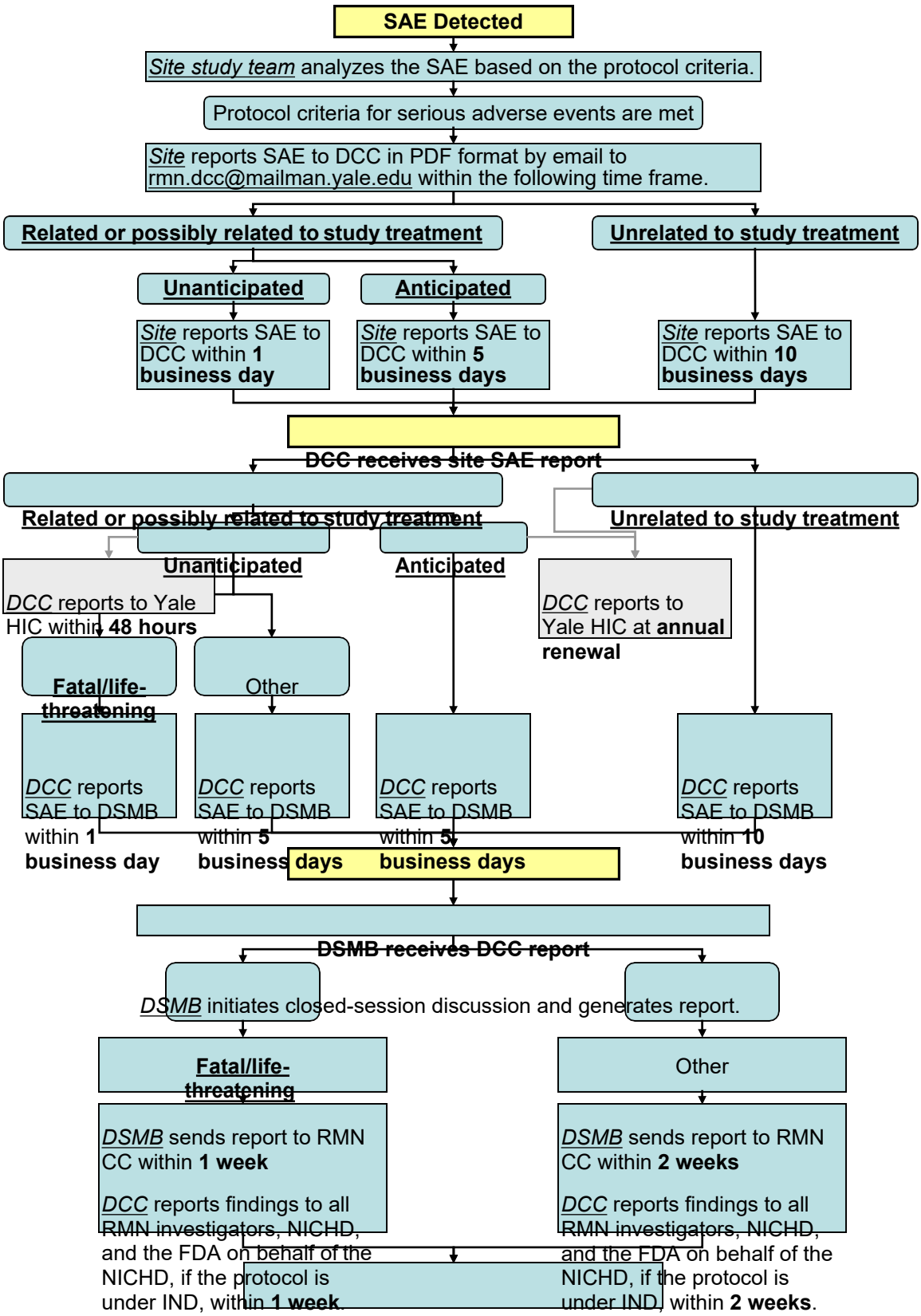
Upon receiving notification of an SAE, the DSMB will review it via a closed-session email or conference-call discussion arranged by the NICHD RMN Committee Coordinator (RMN CC). The DSMB will send a report to the RMN CC within two weeks; reports for life-threatening SAEs will be submitted in one week. The DSMB

report will include: statement indicating what related information the DSMB reviewed; the review date; the DSMB's assessment of the information reviewed; and the DSMB's recommendation, if any, for the DCC.

The RMN CC will then forward the DSMB report to the DCC for the record and appropriate disbursal. The DCC will forward reportable events to all RMN investigators, NICHD, and the FDA on behalf of the NICHD if the protocol is under IND. The NICHD Project Scientist will review, sign, and return the IND safety report to the DCC within 2 business days, and will follow up with the site PI and DCC on the SAE until it is resolved. The Protocol PI will evaluate the frequency and severity of the SAEs and determine if modifications to the protocol and consent form are required. Site PIs will report the SAE to their site IRB according to local IRB requirements. Further information is found in the RMN DSMB Communication Procedure.

Adverse events deemed non-serious will also be recorded throughout study participation from the start of study drug through day 42 after the last dose of study medication, and reported to the DCC. If an anticipated serious adverse event occurs at a frequency greater than expected, the DCC will notify the DSMB by the end of the next business day of discovery and follow the procedures for reporting serious and unanticipated and related adverse events. The DCC will forward relevant safety information to the DSMB. If an adverse event not initially determined to be reportable to the FDA under 21CFR312.32 is so reportable, the DCC will report the adverse event to the FDA within 15 calendar days after the determination is made.

A flowchart for SAEs follows:


SAE Detected
Site study team analyzes the SAE based on the protocol criteria.
Protocol criteria for serious adverse events are met
Site reports SAE to DCC in PDF format by email to rmn.dcc@mailman.yale.edu within the following time frame.
Related or possibly related to study treatment
Unrelated to study treatment
Unanticipated
Anticipated
Site reports SAE to DCC within 1 business day
Site reports SAE to DCC within 5 business days
Site reports SAE to DCC within 10 business days
DCC receives site SAE report
Related or possibly related to study treatment
Unrelated to study treatment
Unanticipated
Anticipated
DCC reports to Yale HIC within 48 hours
DCC reports to Yale HIC at annual renewal
Fatal/life-threatening
Other
DCC reports SAE to DSMB within 1 business day
DCC reports SAE to DSMB within 5 business days
DCC reports SAE to DSMB within 5 business days
DCC reports SAE to DSMB within 10 business days
DSMB receives DCC report
DSMB initiates closed-session discussion and generates report.
Fatal/life-threatening
Other
DSMB sends report to RMN CC within 1 week
DCC reports findings to all RMN investigators, NICHD, and the FDA on behalf of the NICHD, if the protocol is under IND, within 1 week.
DSMB sends report to RMN CC within 2 weeks
DCC reports findings to all RMN investigators, NICHD, and the FDA on behalf of the NICHD, if the protocol is under IND, within 2 weeks.

Site investigators report to their local IRB

CFR= Code of Federal Regulations

9.5 Auditing and Inspecting

The Investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and any applicable compliance and quality assurance groups (e.g. local Hospital or University entities) of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an Investigator in this study implies acceptance of potential inspection by these entities.

9.6 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and local Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

9.7 Study Finances

9.7.1 Conflict of Interest

None of the investigators have a conflict of interest associated with this study.

10 Publication Policy

10.1 Overall Policy

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

10.2 Main Study

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

10.2.1 Major Publications

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

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

The Steering Committee Chair and NIH Project Scientist will be authors. Occasionally, additional authors, both within and outside the RMN may be appropriate. In these cases, the final decision will be by Network consensus (majority vote of the steering committee required).

2. *First Author:* The lead investigator initiating the protocol, chairing the Protocol Subcommittee will be the first author. The first author would always be expected to prepare the initial draft of the manuscript, after receiving approval from the Network to proceed. The author will prepare the first draft of the manuscript in a timely fashion after receiving all the relevant data analyses from the DCC. The primary author will circulate the final draft to all authors prior to submission, with a timely turnaround of comments from other authors expected. Final decision of the manuscript content will be determined by the Protocol Subcommittee. In the event that the initiating protocol investigator declines first authorship or fails to meet the timeline determined by

the Steering Committee (as determined by majority vote) and monitored monthly, the next RMU investigator in the rank order of authors (described below) will be the first author.

3. *Authorship Order:* All authorships are expected to meet reasonable criteria as set forth by (International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. http://www.icmje.org. Updated February 2006. Accessed April 4, 2007.) The overall authorship order will be 1) the primary author, 2) RMU investigators, additional outside investigators with a limit of one author per site (e.g. SCCPIR investigators if applicable), followed by the Steering Committee Chair, NIH Project Scientist, and then the authors of the DCC.

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

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

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

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

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

10.2.2 Minor Publications

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

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

10.3 Ancillary Study

An Ancillary Study is an observational study, conducted as a supplement to a Main Study, and will have a separate written protocol. By definition, an Ancillary Study involves all or a subset of patients enrolled in a Main Study. An Ancillary Study does not involve any additional participants. To be defined as an Ancillary Study, there must be a need for collection of additional data not already collected in the Main Study. An Ancillary Study may also be designed by another Network investigator, who would serve as the lead investigator and primary author of the paper. Ancillary Studies may be a "single-center" or "multi-center".
A "single-center" Ancillary Study is a study in which all data are collected, stored and analyzed at a single center. The center bears the additional cost of such a study. The study requires approval of the Main Study Protocol Subcommittee and the Steering Committee. The center conducting the study is responsible for the analysis and reporting of the results. Abstracts and manuscripts resulting from data from the single-center Ancillary Study are not subject to the RMN Publications Policies.
A "multi-center" Ancillary Study is defined as one for which data or material (such as specimens) are collected at more than one center, or additional funds for conduct of the study are provided by the NICHD RMN and the DCC provides data analysis. Multi-center Ancillary Studies require the approval of the Main Study Protocol Subcommittee and the Steering Committee.
Authorship will be as per Major publications above with the exception that the individual leading the ancillary study and writing the paper would be the first author, followed by ranked RMN primary investigators, etc. A center not participating in the ancillary study would not receive authorship unless by majority vote of the steering committee.

10.4 Pilot Study

A Pilot Study is a preliminary study that generates data to help in the design of a Main Study and is the responsibility of the Main Study Protocol Subcommittee. The DCC collaborates with the Protocol Committee

to complete the analysis, which may or may not generate an abstract for presentation and/or a manuscript for publication. The DCC writes a Final Report if there is sufficient data to justify one. It is not expected there will be any secondary analyses resulting from a Pilot Study.

10.5 Related Publications

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

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

10.6 Outside Studies

Outside studies will result from the sharing of intellectual property, data and/or specimens with investigators whose protocols have been approved by the steering committee, and who comply with all components of those policies. All publications will acknowledge the assistance of NICHD, the RMN, and the Protocol Subcommittee in making the database available on behalf of the project. In addition, however, a disclaimer will need to be included stating, "The contents of this report represent the views of the authors and do not represent the views of the NICHD Reproductive Medicine Network." The authors will be requested to cc the submitted manuscript to the NICHD program official to ensure compliance. These policies apply to both Network centers and outside centers.

10.7 Presentations

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

However, investigators should avoid citing specific numbers in review articles and chapters, for this could jeopardize peer review publication. Authorship, First Author, and Author Order are as described for Major Publications, and if there is an authorship limit to the abstract we will follow the plan above under Major Publications. Oral and poster presentations, including those resulting from secondary analyses at professional societies, must list all authors and participating institutions. In addition, they must include both the NICHD RMN logo and NIH Department of Health and Human Services logos that can be found on the Network web site.

11 References

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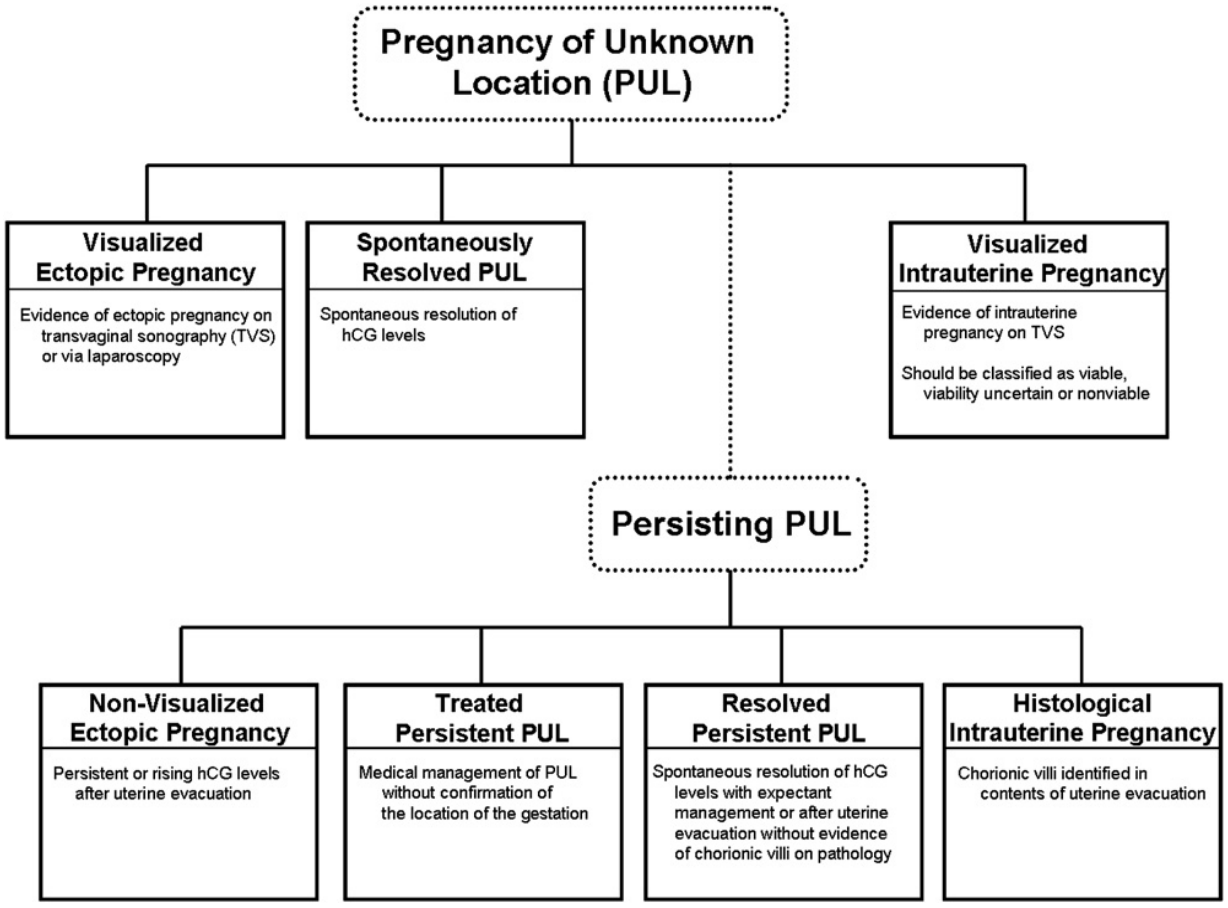
12 Appendix A: Definition of Risk Factors and Variables

Definition of pregnancy outcome will include:



13 Appendix B: Two-Dose Methotrexate Protocol

Baseline hematologic, hepatic (ALT AST, GGT) and renal function testing (serum creatinine) will be established via serum complete blood count (CBC), comprehensive metabolic panel (CMP), and hCG level. Baseline laboratories must be performed within 5 days of administration of MTX with the exception of the hCG value, which must be obtained within 24 hours of MTX administration.

Specific exclusionary parameters include elevation of liver function testing greater than or equal to 1.5 times of the upper limit of normal, white blood cell count less than 3000/uL, platelet count less than 100,000/uL, and clinical significant renal dysfunction (at the discretion of the clinician). Women will also be excluded from beginning MTX therapy if any hematologic, liver, or renal laboratory values are below the lower limit of normal. If any of these parameters are met, MTX administration is contraindicated.

The patient will be counseled that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is prohibited during treatment with Methotrexate.

The patient will receive the first dose of MTX 50mg/m^2 on treatment day 0.

She will receive a second dose of MTX 50mg/m^2 on treatment day 4 **and** a serum hCG level will be drawn.

The patient will have a serum hCG evaluated on treatment day 7.

If the decline in serum hCG level is greater than or equal to a 15% decline from day 4 to day 7, the patient will then receive weekly serum hCG levels until they are <5mIU/mL, at which point treatment will be successfully completed.

If the serum hCG levels from day 4 to day 7 fails to decline by at least 15%, the patient remains clinically stable, and screening laboratory values (hematologic, hepatic and renal function testing will be established via serum complete blood count (CBC), comprehensive metabolic panel (CMP) will be repeated and if not exclusionary, the patient will receive a third dose of MTX 50mg/m^2.

Specific exclusionary parameters include elevation of liver function testing greater than or equal to 1.5 times of the upper limit of normal, white blood cell count less than 3000/uL, platelet count less than 100,000/uL, and clinically significant renal dysfunction (at the discretion of the clinician). If any of these parameters are met, MTX administration is contraindicated and it will be held until values return to the normal range (if subsequent dose is desired).

If MTX is administered on treatment day 7, the patient will return for a treatment day 11 visit.

On treatment day 11, the patient will obtain a serum hCG level.

If the decline in serum hCG level is greater than or equal to a 15% decline from day 7 to day 11, the patient will then receive weekly serum hCG levels until they are <5mIU/mL, at which point treatment will be successfully completed.

If the serum hCG levels from day 7 to day 11 fail to decline by at least 15%, the patient remains clinically stable, and screening laboratory values (hematologic, hepatic and renal function testing will be established via

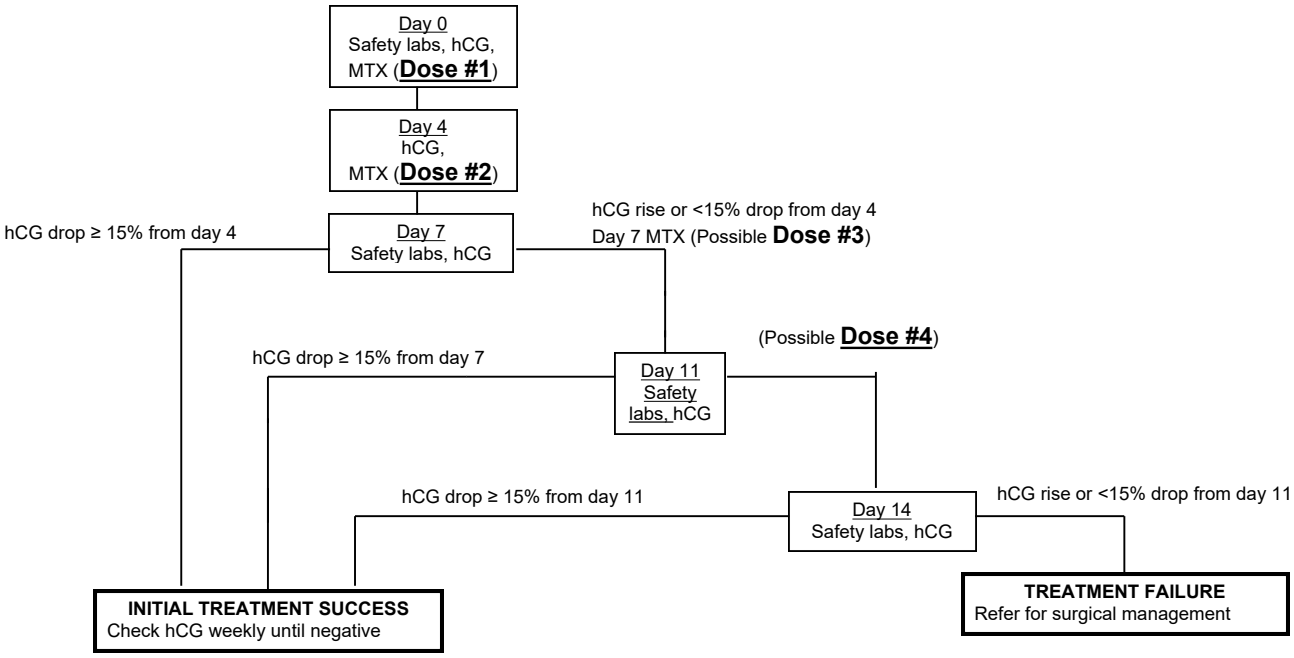
serum complete blood count (CBC), comprehensive metabolic panel (CMP) will be repeated and if not exclusionary, the patient will receive a fourth dose of MTX 50mg/m^2.

Specific exclusionary parameters include elevation of liver function testing greater than or equal to 1.5 times of the upper limit of normal, white blood cell count less than 3000/uL, platelet count less than 100,000/uL, and clinically significant renal dysfunction (at the discretion of the clinician). If any of these parameters are met, MTX administration is contraindicated and it will be held until values return to the normal range (if subsequent dose is desired).

If MTX is administered on treatment day 11, the patient will return for a treatment day 14 visit.

On treatment day 14, the patient will obtain a serum hCG level. If the decline in serum hCG level is greater than or equal to a 15% decline from day 11 to day 14, the patient will then receive weekly serum hCG levels until they are <5mIU/mL, at which point treatment will be successfully completed.

If the serum hCG levels from day 11 to day 14 fails to decline by at least 15%, medical management will be considered a failure and the patient will be referred for surgical treatment.



Exclusion criteria for administration of Methotrexate (ACOG Guidelines)

Absolute contraindications

1. Breastfeeding
2. Overt or laboratory evidence of immunodeficiency
3. Alcoholism, alcoholic liver disease, or other chronic disease/condition
4. Liver disease
5. Preexisting blood dyscrasias, such as bone marrow

hypoplasia, leukopenia, thrombocytopenia
6. Significant Anemia
7. Known sensitivity to methotrexate
8. Active pulmonary disease
9. Peptic ulcer disease
10. Hepatic, renal, or hematologic dysfunction

Relative contraindications

1. Gestational sac larger than 3.5 cm
2. Embryonic cardiac motion

14 Appendix C: Patient Satisfaction Questionnaire

Patient Satisfaction Questionnaire
Source Document
Reproductive Medicine Network

Optimal treatment for women with a Persisting Pregnancy of Unknown Location - a Randomized Clinical Trial of women at risk for an ectopic pregnancy: Active Treatment versus Expectant Management (No Treatment) The "ACT or NOT TRIAL"

A. QUALITY OF LIFE

1. Visit date ___ ___ ___- ___ _ - 2 0 1 ___
Month Day Year

1A. Questionnaire done ☐ Yes ☐ No

2. Since you enrolled in the study, how much of the time have you had the following problems with your work or other regular daily activities as a result of your physical health?

IF NO, SKIP TO SECTION D ITEM 3.

		None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
A.	Cut down on the amount of time you spent on work or other activities	☐	☐	☐	☐	☐	☐
B.	Accomplished less than you would like	☐	☐	☐	☐	☐	☐
C.	Were limited in the kind of work or other activities	☐	☐	☐	☐	☐	☐
D.	Had difficulty performing the work or other activities	☐	☐	☐	☐	☐	☐

3. *Since you enrolled in the study, how much of the time have you had the following problems with your work or other regular daily* activities as a result of any emotional problems (such as feeling depressed or anxious)?

		None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
A.	Cut down on the amount of time you spent on work or other activities	☐	☐	☐	☐	☐	☐
B.	Accomplished less than you would like	☐	☐	☐	☐	☐	☐
C.	Didn't do work or other activities as carefully as usual	☐	☐	☐	☐	☐	☐

4. The next questions ask about your social activities from the time you enrolled in the study until now.

A. To what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors or groups?

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

B. Compared to your usual level of social activity, has your social activity decreased, stayed the same or increased because of a change in your physical or emotional condition?

- ☐ Much less socially active than before
- ☐ Somewhat less socially active than before
- ☐ About as socially active as before
- ☐ Somewhat more socially active than before
- ☐ Much more socially active than before

C. How often has your health limited your social activities (like visiting friends or close relatives?)

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

D. Compared to others your age, are your social activities more or less limited because of physical health or emotional problems?

- ☐ Much more limited than others
- ☐ Somewhat more limited than others
- ☐ About the same as others
- ☐ Somewhat less limited than others
- ☐ Much less limited than others

5. The next questions are about any physical pain you may have experienced.

A. How much bodily pain have you had since you enrolled in the study?

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

B. Since you enrolled in the study, how much of the time has pain interfered with the following things?

		None of the Time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
B.	Your normal work (including the work both outside the home and housework)	☐	☐	☐	☐	☐	☐
C.	Your mood	☐	☐	☐	☐	☐	☐
D.	Your ability to work or move about	☐	☐	☐	☐	☐	☐

E.	Your sleep	☐	☐	☐	☐	☐	☐
F.	Your recreational activities	☐	☐	☐	☐	☐	☐
G.	Your enjoyment of life	☐	☐	☐	☐	☐	☐

6. From the time you enrolled in the study until now, how much of the time:

		None of the Time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
A.	Did you feel full of life?						
B.	Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
C.	Did you feel worn out?						
D.	Did you feel tired?	☐	☐	☐	☐	☐	☐
E.	Did you have enough energy to do the things you wanted to do?		☐	☐	☐	☐	☐

B. ACCEPTABILITY

The next questions are about the medical treatment you had for your pregnancy.

	Totally Unacceptable	Somewhat Unacceptable	Neutral	Somewhat Acceptable	Totally Acceptable
1. How acceptable was the treatment?	☐	☐	☐	☐	☐
2. How acceptable was the cramping pain?	☐	☐	☐	☐	☐
3. How acceptable was the bleeding?	☐	☐	☐	☐	☐
4. How acceptable were the side effects of the treatment?	☐	☐	☐	☐	☐
5. How acceptable was the duration of the symptoms?	☐	☐	☐	☐	☐
6. How acceptable was the time spent on treatment?	☐	☐	☐	☐	☐

7. Overall, do you think the side effects of your treatment are:

Better than what you expected ☐
About the same as expected ☐
Worse than what you expected ☐

8. If someone you know has a condition similar to yours, would you recommend this treatment to her?

Absolutely not ☐
Probably not ☐
Not sure ☐
Probably yes ☐
Absolutely yes ☐

9. If you ever had a condition similar to yours in the future, would you want the same type of treatment?

Absolutely not ☐
Probably not ☐
Not sure ☐
Probably yes ☐
Absolutely yes ☐

C. COST INFORMATION (FOR PERIOD AFTER YOU ENROLLED INTO THE STUDY)

1. Did you miss any days of school or work due to your pregnancy? ☐ Yes ☐ No

IF YES, ANSWER A AND B.

	Work	School
How many days?	__	__

2. Has your illness required any members of your family or friends to help you out (either by taking care of you or by managing your household)? ☐ Yes ☐ No

IF YES, ANSWER A AND B.

A. About how many hours total have family or friends spent in helping with your care?
_____hours

B. How many hours total did they spend helping by caring for your children?
_____ _____hours ☐ Not Applicable

3. Were they required to take off time from work to assist you? ☐ Yes ☐ No

IF YES, ANSWER A.

A. How much money total was lost to them for staying home? $_____

4. Did you pay for someone to take care of you, your household or your children? ☐ Yes ☐ No

IF YES, ANSWER A.

A. How much overall have you paid for the care? $_____

5. How much of your time was spent at each doctor's visit for your pregnancy after you enrolled in the study? Please include transit time, the amount of time that you may have had to wait, and all time associated with the doctor's visit.

A. Initial Visit _____Minutes Visit Date: ____/_____/20__ _
Month Day Year

B. 2nd Visit _____Minutes Visit Date: ____/_____/20__ _
Month Day Year

C. 3rd Visit _____ Minutes Visit Date: ____/_____/20__ _
Month Day Year

D. 4th Visit _____Minutes Visit Date: ____/_____/20__ _

Month Day Year

E. 5th Visit _____Minutes Visit Date: ____/_____/20__ _
Month Day Year

F. 6th Visit _____Minutes Visit Date: ____/_____/20__ _
Month Day Year

G. 7th Visit _____Minutes Visit Date: ____/_____/20__ _
Month Day Year

E. 8th Visit _____Minutes Visit Date: ____/_____/20__ _
Month Day Year

H. 9th Visit _____Minutes Visit Date: ____/_____/20__ _
Month Day Year

I. 10th Visit _____Minutes Visit Date: ____/_____/20__ _
Month Day Year

J. 11th Visit _____Minutes Visit Date: ____/_____/20__ _
Month Day Year

K. 12th Visit _____Minutes Visit Date: ____/_____/20__ _
Month Day Year

L. 13th Visit _____Minutes Visit Date: ____/_____/20__ _
Month Day Year

M. 14th Visit _____Minutes Visit Date: ____/_____/20__ _
Month Day Year

N. 15th Visit _____Minutes Visit Date: ____/_____/20__ _
Month Day Year

O. 16th Visit _____Minutes Visit Date: ____/_____/20__ _
Month Day Year

6. How much does it cost you every time you come to the clinic, including transportation and parking? $___ __

7. How much did you pay for medicines you bought from the drug store? $ _ _____

8. Can you think of any other costs associated with your pregnancy after you enrolled in the study? ☐ Yes ☐ No

If Yes, Specify:

_____ $ _____

_____ $ _____

_____ $ _____

_____ $ _____

9. Below is a list of possible side effects. Please select the most appropriate response for each of the following symptoms:

Symptom	None	Mild	Moderate	Severe	Duration in Days (0.5 increments)	Not Applicable
1. Nausea						
2. Vomiting						
3. Belly or Pelvic Pain						
4. Loss of Appetite						
5. Mouth Sores						
6. Diarrhea						
7. Blood in Stools						
8. Heart Burn/Indigestion						
9. Hair Loss						
10. Headaches						
11. Fatigue						
12. Vaginal bleeding						
13. Sharp Abdominal Pain						
14. Dizziness or weakness						
15. Shoulder or back pain						
16. Persistent dry, non-productive cough						
17. Skin rash or reaction						
18. Surgical site incision pain Infection						
19. Infection						
20. Uterine Perforation						
21. Uterine Infection						
22. Other (Specify) _____						

10. How would you rate your overall Satisfaction with this treatment?

☐ **Very Dissatisfied** ☐ **Dissatisfied** ☐ **Neither Dissatisfied or Satisfied** ☐ **Satisfied** ☐ **Very Satisfied**

Signatures

To the best of your knowledge the above information is correct.

Subject's Signature:_____Date:_____/_____/2 0 __
Month Day Year

The above information has been verified with the subject and is complete.

Coordinator's Signature:_____ Date:__/__/2 0 _____
Month Day Year

15 Appendix D: Patient Fertility Questionnaire

Fertility Questionnaire
Source Document
Reproductive Medicine Network

Optimal treatment for women with a Persisting Pregnancy of Unknown Location - a Randomized Clinical Trial of women at risk for an ectopic pregnancy: Active Treatment versus Expectant Management (No Treatment) The "ACT or NOT TRIAL"

Was this visit completed? ☐ Yes ☐ No

Menstrual Cycle Information

1. How many days is your menstrual cycle ON AVERAGE? *(calculated from the first day of your period to the first day of your next period)* __ Days
2. What is the length of your shortest typical cycle? __ Days
3. What is the length of your longest typical cycle? __ Days

Conception Information

4. Did you try to conceive during the last 6 months?
   ☐ No, I did not and I do not want to become pregnant
   ☐ Yes, I tried to conceive all 6 months
   ☐ Yes, I tried to conceive but not all 6 months
5. Did you use a contraceptive over the last 6 months? ☐ Yes ☐ No → *Skip to Question #6*

   5a. Which type(s) of contraceptive did you use?
   ☐ Contraceptive pill/patch/ring
   ☐ Intrauterine device
   ☐ Condom or diaphragm
   ☐ Tubal ligation
   ☐ Male vasectomy
   ☐ Other: specify_____

6. Specify which months you tried to conceive

☐ January	☐ July
☐ February	☐ August
☐ March	☐ September
☐ April	☐ October
☐ May	☐ November
☐ June	☐ December

7. Date of positive pregnancy test __/_____/2 0 _____ (Month Day Year)

Pregnancy Information ……

8. Have you been pregnant during the last 6 months?
   ☐ Yes, I became pregnant spontaneously
   ☐ Yes, I became pregnant after fertility treatment
   ☐ No, although I tried to, I did not become pregnant
   → ***Skip to Question #10***
   ☐ Not applicable; I do not want to become pregnant → ***Skip to the End***

9. First day of last menstrual period
   __ __/_____/2 0 _____
   Month Day Year

10. Type of fertility treatment
    ☐ Ovulation Induction with hormone PILLS
    ☐ Ovulation Induction with hormone INJECTIONS
    ☐ Intrauterine insemination (IUI) with
    ☐ In vitro fertilization (IVF/ICSI)

11. How is the pregnancy going?
    ☐ I don't know yet; I did not visit a general practitioner, midwife, or gynecologist yet → ***Skip to Question #13***
    ☐ The pregnancy is vital and inside the womb → ***Skip to Question #13***
    ☐ I had a miscarriage → ***Skip to Question #14***
    ☐ I had an ectopic pregnancy →***Skip to Question #15***
    ☐ I had an induced abortion → ***Skip to Question #16***
    ☐ I gave birth to a child → ***Skip to Question #17***

12. Estimated date of delivery
    __/ __ / 2 0 _____
    Month Day Year

13. Has an ultrasound been done? ☐ Yes ☐ No

    13a. Date of ultrasound
    __/ __ / 2 0 _____
    Month Day Year

Miscarriage Information

14. Date of miscarriage
    __/ __ / 2 0 _____
    Month Day Year

    14a. Did you have a D&C? ☐ Yes ☐ No → *Skip to End*

    14b. Date of D&C
    __/ __/ 2 0 _____
    Month Day Year

Ectopic Pregnancy Information

15. In which tube was the pregnancy located?
    ☐ Left
    ☐ Right
    ☐

☐ Other site: specify_____

15a. How was the ectopic pregnancy treated?
☐ Surgery
☐ Medical treatment with Methotrexate
☐ No treatment, spontaneously resolved

15b. Was the tube removed?
☐ Yes was removed
☐ No, the tube was not removed

Induced Abortion Information

16. Date of abortion __ __/_____/20__ _
Month Day Year

Delivery Information

17. Date of birth __ __/_____/20__ _
Month Day Year

17a. Gestation age at birth (# weeks) __ weeks

17b. Did you have live birth? ☐ Yes ☐ No

17c. Baby's birth weight __ pounds __ ounces

17d. Complications _____

Additional Remarks

Please explain:_____

_____

_____

Signatures

To the best of your knowledge the above information is correct.

Subject's Signature:_____Date:_____/_____/2 0 __
Month Day Year

The above information has been verified with the subject and is complete.

Coordinator's Signature:_____ Date:__/__/2 0 _____
Month Day Year

16 Appendix E: Data and Safety Monitoring Plan

Optimal treatment for women with a Persisting Pregnancy of Unknown Location - a Randomized Clinical Trial of women at risk for an ectopic pregnancy: Active Treatment versus No Treatment

The "ACTorNOT TRIAL"

DATA AND SAFETY MONITORING BOARD (DSMB) CHARTER

1. Purpose and Responsibilities of the DSMB

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

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

Basic Responsibility of DSMB	Method DSMB for ACTorNOT will use to complete task
Familiarize themselves with the study protocol	• Review study protocols and informed consent forms.
Monitor adverse events	• Adverse Event: Review quarterly progress reports prepared by the DCC on behalf of RMN. • Serious Adverse Events: Review report submitted by the DCC on behalf of RMN within one week of the event if life threatening or fatal, or within two weeks otherwise. The DSMB will submit a report of their review to the NICHD Committee Coordinator within 7 business days if the SAE is life threatening or fatal, or within two weeks otherwise.
Monitor data quality	• Conduct interim evaluations of the data.
Oversee participant recruitment and enrollment	• Review interim progress reports prepared by the DCC on behalf of RMN.
Develop an understanding of the Study's risks and benefits	• Review study protocols and related literatures. • Review interim reports of subject accrual and outcome measures provided by the DCC. • Assess the need to perform further in-depth evaluation of the benefits and risks of the study after reviewing each report.

Ensure the proper reporting occurs	• Review and approve the meeting and reporting schedule listed in Section 5 of this DSMB charter.

2. Contacts

NICHD
Louis DePaolo, PhD, Program Officer
Charisee Lamar, PhD, MPH, RRT Committee Coordinator
Esther Eisenberg, MD, MPH, Project Scientist

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

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

Lead Investigator(s)
Kurt T. Barnhart, MD, MSCE

3. DSMB Members, Organizational Chart, & Communications

Members

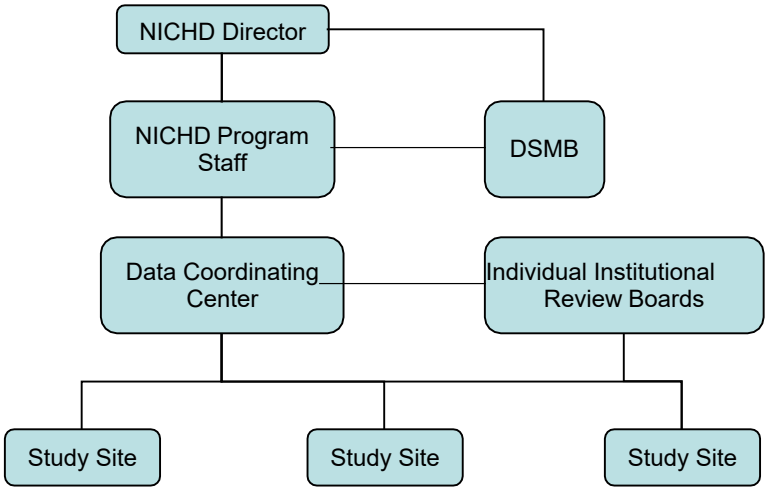
The DSMB for the ACTorNOT study is comprised of the members listed in the table below. In addition, their high level roles and responsibilities are identified in the table.

Name of Member	Role on DSMB	High Level Responsibilities
Frank Witter, MD	Chair of DSMB Voting member	• Chair the DSMB discussion and prepare written recommendations to NICHD. • Ensure the safety of study subjects, the integrity of the research data. • Provide NICHD with advice on the ethical and safe progression of studies conducted in the RMN. • Advises on research design issues, data quality and analysis, and research participant protection for each prospective and on-going study.
Rev. Phillip Cato, PhD	Voting member	• Ensure the safety of study subjects, the integrity of the research data. • Provide NICHD with advice on the ethical and safe progression of studies conducted in the RMN. • Advises on research design issues, data quality and analysis, and research participant protection for each prospective and on-going study.
PonJola Coney, MD	Voting member	
Lurdes Y.T. Inoue, PhD	Voting member	
Stacey A. Missmer, ScD	Voting member	
Robert E. Brannigan, MD	Voting member	

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

Organizational Chart

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



Communication

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

4. Conflict of Interest and Compensation

It is extremely important that all members of the DSMB state any real or apparent conflicts of interests at the onset of the study. Members of the DSMB shall read the NICHD Clinical Research Guidance Document regarding Conflict of Interest and provide their signed summary of any COI for the study, at its onset, to the NICHD Committee Coordinator, Dr. Charisee Lamar. A table summarizing anyCOI within the DSMB is provided in the Appendix.

Prior to each meeting, all members of the RMN DSMB will have an opportunity to state whether they have developed any new conflicts of interest since the meeting. As a new COI is identified it must be documented in the table in the Appendix and a new signed summary of the COI should be provided to the NICHD Committee Coordinator. The Coordinator will forward the COI documentation to the DCC for record-keeping purposes.

If a new conflict is reported, the Coordinator and staff will determine if the conflict limits the ability of the DSMB member to participate in the discussion.

All DSMB members will be compensated for their role in supporting the committee. Compensation will include an honorarium for meeting attendance and any travel costs.

5. Meeting Schedule

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

6. Blinding

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

7. Report Schedule and Content

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

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

Brief DSMB reports will include the following summaries:

- overall actual versus projected enrollment accrual
- overall randomization update
- overall study drop-out rate
- serious adverse events
- primary outcome measures update

Full DSMB reports will include the following summaries:

- recruitment update (number screened) overall and by site
- enrollment update (enrolled defined as randomized to a treatment) overall and by site

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

8. Efficacy Outcome Summary

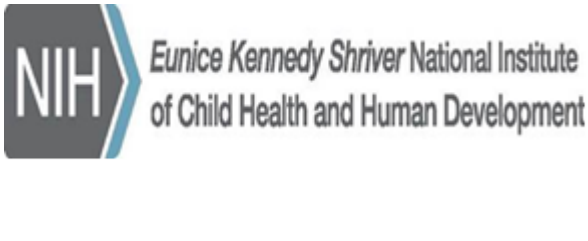
An interim analysis will be scheduled for safety after one half (225) subjects complete the trial. If safety or efficacy is an issue, one arm will be dropped or the study stopped.

References

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

Appendix: Summary of COI within the DSMB

DSMB Member Name	Date Submitted Signed COI	Was a COI Identified?	Will the Member Remain part of the Committee?
Rev. Phillip Cato, PhD			
PonJola Coney, MD			
Lurdes Y.T. Inoue, PhD			
Stacey A. Missmer, ScD			
Robert E. Brannigan, MD			
Frank Witter, MD			



Reproductive Medicine Network
Funded by *Eunice Kennedy Shriver* NICHD

Conflict of Interest Statement

Optimal treatment for women with a Persisting Pregnancy of Unknown Location - a Randomized Clinical Trial of women at risk for an ectopic pregnancy: Active Treatment versus No Treatment

The "ACTorNOT TRIAL"

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

for the _____
(insert project or study name)

agree to the following statements.

□ I agree to:

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

In addition:

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

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

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

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

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

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

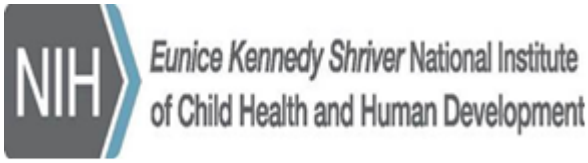
□ I will not engage in activities that could be viewed as real or apparent COI, including but not limited to:

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

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

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

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



Reproductive Medicine Network
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Reproductive Medicine Network (RMN)
Data and Safety Monitoring Board (DSMB)
Confidentiality Agreement

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

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

I agree that I will not distribute or publish RMN records. I further agree that I shall not make use of Network materials except for the express purpose of advising the RMN Steering Committee and the NICHD.

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

Name (Print or Type): _____

Signature:_____Date: _____

17 Appendix F: Investigator Signature of Agreement

Investigator Signature of Agreement

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

Title: Optimal treatment for women with a Persisting Pregnancy of Unknown Location (PPUL) – A Randomized Clinical Trial of women at risk for an ectopic pregnancy: Active Treatment versus Expectant Management (No Treatment)
The "ACTorNOT TRIAL"

Version: 6.0

Principal Investigator:

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

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

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

_____
Principal Investigator's Signature Date

_____
Printed Name Date