UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT
INFORMED CONSENT AND HIPAA AUTHORIZATION FORM

Protocol Title: 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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Why am I being asked to volunteer?

You are being invited to participate in this research study because you have what is called a “persisting pregnancy of unknown location” (PPUL): it has been determined that your pregnancy cannot continue normally, but the doctors do not know if the pregnancy is in your uterus (womb), or outside of your uterus (this is called an “ectopic pregnancy”). Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study
doctor and/or the research team about this form. If you decide to participate, you will be asked to sign this form.

What is the purpose of this research study?
When a woman has pain and/or bleeding during the first trimester of pregnancy, it is very important that doctors be able to determine whether the pregnancy can progress normally, or if it cannot. A pregnancy that cannot continue normally is called a “nonviable pregnancy.” In some cases, a nonviable pregnancy is a pregnancy that is located outside of the uterus, often in the fallopian tubes (called an ectopic, or “tubal” pregnancy). Ectopic pregnancy can be very dangerous, and should be treated as soon as possible. However, it is sometimes difficult with the current tests available for doctors to tell exactly where the pregnancy is located. This is called a “pregnancy of unknown location” or PUL.

There are currently three different management strategies for women who have a PUL: 1) not to take any action in the beginning, but to watch the patient closely to see if the pregnancy resolves on its own (or may need treatment later, if it does not resolve), 2) to empty the uterus, and then treat with a medication called methotrexate (MTX) if the pregnancy is still ongoing (i.e. it was not in the uterus), 3) to treat with MTX without emptying the uterus first. The way that MTX is given to patients in these management strategies (two injections a few days apart) is investigational, meaning it has not been approved by the US Food and Drug Administration.

The purpose of this research is to study these three different management strategies in pregnant women who have a persisting PUL (PPUL) to see which one is the most effective at resolving a PPUL without the women requiring any additional treatment afterwards.

How long will I be in the study? How many other people will be in the study?
You will be in this study from the time you sign this form to the end of your pregnancy. You will also be contacted to answer some questions every 6 months for 24 months after the end of your pregnancy. We are planning to enroll about 276 women in this study across all the sites. We plan to enroll about 50 women at the University of Pennsylvania. The timeframe for each treatment arm is of similar duration.
What am I being asked to do?

The study team will identify you as a potential study participant by looking at your medical records. Before you decide whether or not to participate in the study, the risks of all options for managing your PPUL will be explained to you. This will be done by a doctor who is treating you clinically. None of these management strategies are experimental.

Before any research activities can happen, you will be given time to read this consent form. The information in the form will be reviewed with you, and all of your questions will be answered. If you agree to participate in the study, you will be asked to sign this form.

You will then be randomly assigned (like rolling dice) to one of three management strategies for your PPUL (see below). Please note that all three of the treatment choices are currently standard of care (or considered to be reasonable medical management options) and are not in themselves experimental. The study is to find out which, if any, of the three strategies is best. The three strategies in the study are referred to as “arms”.

**Arm 1: Close monitoring:** You will not have your uterus emptied or receive MTX, but will be closely monitored to see if your pregnancy is resolving on its own (or may need treatment later). The progress of your treatment will be closely monitored in two ways. 1) You will be instructed to call the medical team with any change in symptoms (increase in pain or bleeding), and 2) you will have clinically scheduled visits to assess your progress and check your hCG (pregnancy hormone) level every 2 – 7 days (depending on the clinical course) until it has disappeared from your system.

**Arm 2: Uterine evacuation (surgery):** Your uterus (womb) will be emptied through a surgical procedure called a uterine evacuation, or a dilation and curettage (D&C, sometimes called a “D&E” for “dilation and evacuation”), and the level of hCG (pregnancy hormone) in your blood will be measured 12-36 hours after the procedure. If the level of hCG in your blood is not going down, you will then be treated with MTX as you have an ectopic pregnancy. Treatment with MTX involves one injection on the first day of treatment, and a second injection four days later (with more injections possible if necessary). The exact number of injections you may need depends on how fast or slowly your hCG (pregnancy hormone) disappears from your blood.

Analysis will be performed on the tissue from your uterus to confirm the location of the pregnancy (inside or outside the uterus), and the results of this analysis will be shared with you once received. These results may alter your treatment course.

**Arm 3: Medication (Methotrexate):** You will be treated with MTX without having your uterus emptied first. You will have one injection on the first day of treatment,
and a second injection four days later (with more injections possible if necessary). The exact number of injections you may need depends on how fast or slowly your hCG (pregnancy hormone) disappears from your blood.

You have a 1/3 chance of being assigned to Arm 1, and 1/3 chance of being assigned to Arm 2, and a 1/3 chance of being assigned to Arm 3.

After you are assigned to your group, all of your care will be managed by the clinical team, not the research team. While Dr. Barnhart is the director of the study, he will not be your treating physician. Clinical questions about treatment should be addressed to your clinical team. No matter what your initial treatment assignment is, you may receive additional treatments or interventions if the doctors caring for you feel they are necessary to safely ensure the pregnancy has completely resolved. This includes surgical interventions or medications. These possibilities will be discussed with you by members of the clinical team. All of these treatments require that it is determined that the pregnancy of unknown location has resolved.

It is standard of care for all three study arms to have your blood drawn regularly to measure changes in your hCG level. We will ask the clinical staff person who is drawing your blood to draw up to two extra tubes (about 10 - 15 mL, or 2-3 teaspoons) at each blood draw for us to use for research. These samples will be studied to look for biomarkers (proteins or other substances in the blood) that can possibly tell us something about pregnancies of unknown location. These blood samples may be used for genetic testing in the future. Any genetic testing would be for exploratory research only, and would not be used to test for or diagnose any kind of genetic condition or disease. Genetic testing would only be performed on your samples after they are no longer able to be identified as yours. You will not know the results of this testing.

“Risks of genetic testing:

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information.

This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.
Be aware that this Federal law does not protect you or your family against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Also, GINA does not prohibit discrimination of individuals with a genetic disorder that has been diagnosed. However, in order to do everything possible to keep this from happening, the results of this test will NOT be given to anyone outside the study staff. This means that it will not be made available to you, your family members, your private physician, your employer, your insurance company or any other party as allowed by law."

Soon after your pregnancy has resolved, you will be asked to answer some questions about your experiences with your particular treatment arm for this study. Additionally, we will contact you every 6 months for the next two years to ask questions about your fertility and future pregnancies.

**What are the possible risks or discomforts?**

All three management strategies in this study are used as part of clinical standard of care, and are not experimental. Each strategy has different risks associated with the treatment plan, and all risks will be explained to you by the clinical team providing your care

**Arm 1: Close monitoring:** Women assigned to this group may be at a higher risk for rupture of an ectopic pregnancy, but may avoid the side effects of surgery and/or MTX.

Of note, as many as half of all women who have a pregnancy of unknown location (PUL) have an ectopic pregnancy. An ectopic pregnancy, if not treated, can result in rupture of the fallopian tube. This will result in internal bleeding that may require emergency surgery, blood transfusion or even death. These risks are not due to the study, but are part of the condition your doctor has determined that you currently have. If the final diagnosis is not an ectopic pregnancy, the likelihood of disrupting a viable healthy intrauterine pregnancy is exceedingly small.

**Arm 2: Uterine evacuation (surgery):** Women assigned to this group will be exposed to the risks of the surgical procedures used to empty the uterus (bleeding, infection and uterine perforation). Some women will still require MTX and be exposed to the side effects of that medication (nausea, abdominal pain, mouth sores). However, women in this group whose pregnancy is resolved by uterine evacuation will not require treatment with MTX, and therefore would avoid the risks associated with that medication.

**Arm 3: Medication (Methotrexate):** Women assigned to this group may avoid the risks of surgery, but will all be exposed to the side effects of MTX.

*IRB Approval from 4/7/2014 to 12/11/2014*
What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

Your PPUL will be managed as per the clinical standard of care to the arm of treatment that you are assigned to. No other research procedures will be performed while you are in the study. Although this study is comparing three “standard of care” regimens, and your care during the study will not be different from what you would receive clinically, you may benefit from the close monitoring, treatment, and evaluation provided to you through study participation.

However, the data may contribute to our understanding of the best management strategy of a PPUL. The knowledge gained from this trial may be used to further improve the management of women with a PPUL. A benefit of the study will be to determine which, if any, treatment is best.

What other choices do I have if I do not participate?

You do not have to participate in this study to receive treatment for your pregnancy. All three management strategies described in this consent form are available clinically, and are available to you even if you do not participate in this study. Choosing not to participate will not have any affect on your clinical care.

Will I be paid for being in this study?

You will receive compensation for your time when you complete and return the questionnaires after your treatment. Compensation for the first questionnaire regarding treatment (to be completed 2 to 3 weeks after treatment) is $50. Thereafter, every six months for 24 months (four times), a questionnaire to assess fertility is completed. Compensation each time is $25 for completion of the questionnaire.

Will I have to pay for anything?

The study does not cover any of your medical care for your PPUL. You and/or your insurance provider will be responsible for all costs incurred during the management of your PPUL, including the costs of your monitoring bloodwork, MTX medication, or any surgical interventions you receive. Any future research done on your blood samples will be paid for by the study.

What happens if I am injured from being in the study?
Costs for the treatment of research-related injuries will be charged to your insurance carrier or to you. Some insurance companies may not cover costs associated with research studies. If for any reason these costs are not covered by your insurance, they will be your responsibility. You will also be responsible for any deductible, co-insurance and/or co-pay.

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, contact the study investigator, Dr. Barnhart, as soon as possible. The investigator’s contact information is listed on the front page of this form.

**When is the Study over? Can I leave the Study before it ends?**

This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by your physician, the study Sponsor, or the United States Food and Drug Administration (FDA) without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.

- You have not followed study instructions.

- The Sponsor, the study Principal Investigator, or the FDA has decided to stop the study.

If you decide to participate, you are free to leave the study at anytime. Withdrawal will not interfere with your future care.

**Who can see or use my information? How will my personal information be protected?**

The investigators and the research team will be able to see your medical records as authorized by you. Results of laboratory tests and clinical procedures done for the monitoring or treatment of your PPUL will be placed in your medical record and will be accessible to employees of the health system that are not part of the research team. This information may also be viewed by your insurance company during routine audits.

**Privacy and confidentiality measures:**

Your records that are used in the research at University of Pennsylvania will include your study identification number, your initials, and visit date and will be
kept in a secured area in a locked file cabinet. Your samples collected for research purposes will be labeled with your study identification number, initials, and visit date and will be stored in a -80 freezer in a locked room.

For research records sent to the Data Coordination Center at Yale University, you will be identified by your study identification number and study visit date. The list that matches your name with your code number will be kept in a secured area in a locked file cabinet. Your blood specimens will not identify you and you cannot be linked to your specimen.

To help protect your privacy, a Certificate of Confidentiality has been obtained from the federal government. This Certificate means that the researchers cannot be forced (for example by court subpoena) to share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the U.S. government that is used for checking or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food an Drug Administration (FDA).

The Certificate, however, does not prevent you or a member of your family from voluntarily releasing the information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. This means that you and your family should actively protect your own privacy.

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

**Electronic Medical Records and Research Results**

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, results of
research-related procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any results of procedures performed as part of this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). Results of research procedures performed as part of your participation in the study (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.

Once placed in your EMR, these results are accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc).

What information about me may be collected, used or shared with others?

The following information may be used or disclosed for this research project:

- Name, address, telephone number, email address, date of birth
- Medical record number
- Information from your medical records pertaining to your medical history, pregnancy outcome, and information related to all assessments and treatments for this pregnancy

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- do the research
- oversee the research
- see if the research was done right.

Who may use and share information about me?

Representatives of the following people/groups within the University of Pennsylvania may use your health information and share it with other specific groups in connection with this research study.
The Principal Investigator, Dr Kurt Barnhart
The University of Pennsylvania Institutional Review Board
The University of Pennsylvania Office of Clinical Research
The members of the research team working with Dr Kurt Barnhart
Other authorized personnel at University of Pennsylvania, who may have access to your information to perform their daily duties (laboratory personnel, financial personnel, etc).

Who, outside of the School of Medicine, might receive my information?

The above people/groups may share your health information with the following people/groups outside the University of Pennsylvania for their use in connection with this research study. These groups while monitoring the research study, may also review and/or copy your original University of Pennsylvania records.

• The office of Human research Protections in the U.S. Department of Health and Human services
• Food and Drug Administration
• Data Coordination Center at Yale University
• Reproductive Medicine Network of The Eunice Kennedy Shriver National Institute of Child Health and Human Development
• National Institute of Health

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

• You have given written authorization
• The University of Pennsylvania’s Institutional Review Board grants permission
• As permitted by law

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

What will happen to the blood sample that I donate to the study?

The sample of blood you donate to the study will have your name removed and will be and stored in a freezer with other samples. The samples will be stored until they are used by the investigators at the University of Pennsylvania, or their collaborators. These samples will be analyzed to look for new markers in blood that may serve to help diagnose or treat future women. The specific tests to be performed have not yet been determined. You will not be able to remove your sample once donated.

Who can I call with questions, complaints or if I’m concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.
When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent and HIPAA authorization form will be given to you.

I have been adequately counseled and informed.

Name of Subject (Please Print)  Signature of Subject  Date

Name of Person Obtaining Consent (Please Print)  Signature  Date