



University of Pennsylvania ♦ Institutional Review Board Pregnancy Testing, Contraception, and Incidental Pregnancies In Greater Than Minimal Risk Research

This document has been drafted to assist study teams with ensuring they have addressed all of the potential facets of subject protections that are needed when pregnancy is considered exclusionary in greater than minimal risk research. The document is arranged so that researchers and regulatory support staff can develop a thorough understanding of each concept before submitting for initial review by the convened board.

The Thought Process

The broad exclusion of pregnant women from research trials may eventually result in an overall lack of applicable knowledge regarding how best to treat pregnant women with concomitant medical conditions. Thoughtful, responsible study design aimed at appropriate inclusion of pregnant women, when possible, while maintaining fetal safety, is an important goal. Before submitting a protocol for IRB review the Principal Investigator and any regulatory support staff who are charged with drafting or revising the study documents should consider and have a full understanding of the following concepts as they pertain to an individual study:

If pregnant women are excluded from the study:

- 1. What is the rationale?**
- 2. What methods are you applying to detect pregnancy?**
- 3. How will your team counsel women on preventing pregnancy?**
- 4. What will your team do if someone becomes pregnant?**

What is the rationale for excluding pregnant women?

In the IRB HSERA application on the population page, researchers must provide a response to the following:

Vulnerable Populations*

Specify if the study intentionally includes any of the following populations:

- Children
- Pregnant women (if the study procedures may affect the condition of the pregnant woman or fetus)
- Fetuses and/or Neonates
- Prisoners
- Other
- None of the above populations are included in the research study

If the answer to this question is “none of the above will be enrolled” the key exclusion criteria section of the HSERA application should include a clear rationale for excluding pregnant women. There are many valid reasons why pregnant women would not be included in a research study. Some of the most common reasons are:

- The study requires the use of devices, agents or procedures that pose safety concerns for the developing fetus, for infants who are breastfeeding, or for women who are pregnant.
- Due to the scientific complexity, presence of a pregnancy will have a confounding effect on research data being collected
- The research investigates conditions or disease states that do not affect women of child bearing potential

Understanding and communicating the true reasoning behind the exclusion of pregnant women on a particular study will help your team avoid complex issues during IRB review. Researchers are discouraged from excluding pregnant women due to inconvenience of meeting the regulatory requirements.

The HSERA application / protocol should include:

1. A clear statement in the exclusion criteria section as to the reason/rationale for exclusion of pregnant women or women of child bearing potential.

The consent form should include:

1. A clear statement that female subjects and female partners of male subjects should not become pregnant and the time period for how long to avoid pregnancy, supplemented with basic available information about the risk to the pregnant mother and/ or fetus.

What methods are you applying to detect pregnancy?

Regardless of the reason for exclusion, if women participating in a research study (or female sexual partners of male participants) should not become pregnant, it is important to have a clear plan in place in the protocol and clear instructions in the informed consent form for determining the presence of a pregnancy during screening for eligibility.

The IRB understands that sometimes, in order to be eligible for a study, subjects will already have an existing condition that would greatly reduce or eliminate the chances of a pregnancy occurring. Subjects with a history of surgical hysterectomy, oophorectomy, and ongoing chemotherapy or radiation treatments are unlikely to become pregnant. Unless the possibility of pregnancy can be ruled out for every single female subject, a plan for testing should be fully developed.

The HSERA Application / protocol should include:

2. The plan for testing for pregnancy for exclusion purposes in the procedures section
 - a) How will you test? (Urine? Serum? Self-report? Patient history? Please note Penn does not have a standard so researchers must choose)
 - b) How often will you test?
 - i. If an external sponsor requires testing at multiple time points - what is the schedule for the tests and what is the method for those tests at each time point?
 - ii. IRB recommends only testing ONCE upon screening for eligibility for investigator initiated projects provided that:
 - a. Thorough contraception guidance and counseling is provided throughout the study
 - b. The study agent is not known to be teratogenic
 - c. The study team will be considering: reported sexual activity, reported use of contraception, post-partum/post abortion/post miscarriage status, the timing of last normal menses, timing of eligibility pregnancy test, and timing of initiation of contraindicated study procedures.
 - d. If a, b and c are not met, frequent pregnancy testing should be built into the schedule of procedures to ensure safety.

The consent form should include:

2. A clear outline of the plan for testing for pregnancy

- i. What type of pregnancy test will be performed? (Urine? Serum? Self-report? Patient history?)
- ii. How often will you test? Time points should be specifically outlined if more than one

How will your team counsel subjects on preventing pregnancy?

If pregnant women are being excluded, it is important to develop an appropriate plan for counseling subjects about the importance of contraception. If there is a washout period after study participation for which pregnancy should continue to be avoided, this should be made clear in the consent form.

The HSERA Application / protocol should include:

3. A clear indication of contraception requirements for subjects who are eligible:
 - i. A plan for female participants
 1. A complete list of acceptable forms of contraception (IUD, Implant, Injection, Pills, Patch, Ring, Condoms and other barrier methods, Abstinence, Sterilization)
 2. The time frame for utilization of contraception
 - ii. A plan for male participants (including considerations for female partners of male participants)
 1. A complete list of acceptable forms of contraception (for each)
 2. The time frame for utilization of contraception (for each)

The consent form should include:

3. A clear and consistent outline of contraception requirements for subjects who are eligible:
 - i. A plan for female participants
 1. A complete list of acceptable forms of contraception (IUD, Implant, Injection, Pills, Patch, Ring, Condoms and other barrier methods, Abstinence, Sterilization)
 2. The time frame for utilization of contraception
 - ii. A plan for male participants (including considerations for female partners of male participants)
 3. A complete list of acceptable forms of contraception (for each)
 4. The time frame for utilization of contraception (for each)

What will your team do if someone becomes pregnant?

While incidental pregnancies are a rare occurrence, the IRB strongly encourages investigators to consider and accurately communicate the steps that will be taken in the event a subject or a female partner of a male subject becomes pregnant during portions of the study that could pose a risk. Regardless of the plan for obtaining information for research purposes, researchers are responsible for referring subjects who become pregnant to an OB/GYN specialist for care and should offer to provide relevant information about research participation that might affect the pregnancy. Information about referral for care in the event of an incidental pregnancy should always be included in the protocol and consent form if pregnancy is an exclusion criteria for safety reasons. If the pregnancy will not be followed and no data will be collected about the pregnancy course or outcome for research purposes, the only information needed in the protocol and consent is the information related to referral for care. The outline provided below pertains only to preparing a plan for pregnancy course and outcome collection for research purposes.

The HSERA Application/ protocol should include:

4. A prospective plan regarding procedures for incidental pregnancies
 - i. A clear statement that a modification will be submitted for approval of incidental pregnancy plan in the event of an incidental pregnancy **OR**
 - ii. A clear statement indicating what happens if a subject becomes pregnant while on study if a plan has already been prepared:
 - Complete Withdraw from study and no follow up?
 - Allowed to continue for follow up and data collection only?
 - Allowed to continue in full capacity?
 - Will data be collected about the pregnancy course and/or outcome?

The consent form should include:

4. A clear statement informing subjects about what the study team will require if a pregnancy occurs in alignment with the protocol e.g. :
 - i. If you become pregnant you will no longer be able to participate
 - ii. If you become pregnant you will be allowed to continue for follow up and data collection on the mother only or mother and pregnancy
 - iii. If you become pregnant you will be allowed to continue the study to completion and we will plan to collect data about the pregnancy throughout the study and after outcome.

What should be included in an incidental pregnancy plan?

In the red section above, we have outlined the importance of incidental pregnancy plans for both ensuring pregnant subjects receive appropriate care as well as plans for collecting information for research. Implementation of a prepared incidental pregnancy plan for a large multi-site/industry sponsored protocol is typically very straight forward. However, the IRB understands that the situation is often very different for development of investigator initiated studies. For investigators who plan to submit a modification for approval of collection of research data at the time a pregnancy is identified, an IRB approvable incidental pregnancy plan may include the following (if a plan is not provided by the Sponsor in the protocol):

- Plan for following pregnancy through to outcome (*note: the term outcome should be utilized because the outcome of the pregnancy may not be a live birth)
 - This could be accomplished by the following mechanisms:
 - Data review related to pregnancy and outcome (i.e. medical record)
 - If this method is to be used this needs to be clearly outlined in the consent form and HIPAA authorization form in the event of incidental pregnancy
 - Soliciting the information directly from the participant
 - If this method is to be used this needs to be clearly outlined in the consent form in the event of incidental pregnancy
 - Soliciting the information directly from the female partner of a male participant
 - Appropriate permission/authorization must be obtained from the female partner prior to engaging them in the research
 - Asking the male participant for information regarding the pregnancy and outcome without permission/authorization of the female partner is prohibited

- Regardless of when the incidental pregnancy plan is provided, if a pregnant subject will be allowed to continue on the study, a subpart B determination will be required, thus the associated supplemental form should be submitted for review
- A description (either in the protocol or the application) for how the data related to pregnancy and outcome will be utilized, including any plans for reporting the pregnancy to appropriate oversight agencies or any other clinical reporting responsibilities.