# Research Involving Pregnant Participants

This document provides background and guidance for those who would like to include pregnant participants in their research. Pregnant participants should not generally be excluded from research.

Vulnerable populations in research are defined as a group "either by capacity of context are compromised in their ability to provide valid consent or are at special risk of exploitation" or "are potentially vulnerable to coercion or undue influence." Pregnant participants were considered a vulnerable population under federal regulations until 2018. With the 2018 revisions to the Common Rule, pregnant participants are not considered a vulnerable population. This reclassification corrects the implied notion that pregnancy adversely affects a woman's decision-making ability.

Nevertheless, special requirements are in place in the federal regulations to provide additional safeguards for pregnant participants, human fetuses and neonates, Subpart B of 45 CFR 46. For any research proposing to include pregnant participants as subjects, COMIRB ensures that the protocol adheres to these regulations.

## What defines a pregnant woman?

The answer may seem obvious, but under 45 CFR 46.202(f), a woman is assumed pregnant if she "exhibits any pertinent signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery."

## What are the regulatory considerations for research in pregnant participants?

In summary, the major considerations are:

- Studies that enroll pregnant participants as inclusion criteria will need Attachment J included in the COMIRB Application. In order to approve research that included pregnant participants as in inclusion criteria, COMIRB must find that the proposed research falls into one of the permissible categories of research (cited below).
- Studies that list pregnant participants or participants who can become pregnant as exclusion criteria will be considered by COMIRB as studies that do not enroll pregnant participants.
- Studies that are minimal risk where pregnancy or pregnant participants are not the focus of the research and may incidentally include pregnant participants (i.e., not explicitly included or excluded) usually do not require Attachment J. If you are not sure if you need Attachment J, please reach out to COMIRB staff member for guidance.

## What are the approval criteria for research that intends to include pregnant participants in research?

As set forth in federal regulations 45 CFR 46 Subpart B, COMIRB may approve research involving pregnant participants if it finds all of the criteria below are met:

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals and clinical studies, including studies on nonpregnant participants, have been conducted for assessing potential risks to pregnant participants and fetuses.
2. The research holds out the prospect of direct benefit to the woman, the fetus, or both the woman and fetus.
3. Research interventions, tests, or procedures are no more than minimal risk to the pregnant woman or the fetus.
4. If more than minimal risk to the woman or fetus, there is potential for direct benefit to the pregnant woman or the fetus ("therapeutic research") and the risk to the fetus is the "least possible."
5. Research in pregnant participants provides biomedical knowledge that cannot be garnered from nonpregnant participants.
6. Each individual providing consent should be "fully informed regarding the reasonable foreseeable impact of the research on the fetus or neonate."
7. No inducements, monetary or otherwise, will be offered to terminate the pregnancy.
8. Individuals engaged in research will have no part in determining the viability of a neonate.

## Are there restrictions on the kind of research that include pregnant participants?

Yes. Although the approval criteria are open to some interpretation, there are restrictions on research in pregnant participants.

1. For research that is more than minimal risk but potential for direct benefit to the pregnant participants or fetus, the trial must be far enough along to have some amount of safety data.
2. The prospect of direct benefit to the pregnant woman does not necessarily justify research-related risks to the fetus.
3. In research with no direct benefit to the pregnant woman or the fetus, risk is capped at a low threshold to minimize unknown threat to the fetus.
4. In general, fetal protections are more restrictive than research in children.
5. Special provision from the Secretary of the Department of Health and Human Services may be sought if the research is so sensitive but there is potential to further understand or alleviate a serious problem affecting the health and welfare of pregnant participants or the fetus.

## Is paternal consent required for a pregnant woman to participate in research?

Subpart B is unambiguous that for most research studies, consent of the pregnant participants alone is sufficient in accordance with parameters outlined by the Common Rule. It is assumed that pregnant participants are altruistic towards the fetus. Furthermore, it is assumed there may be some extent of tolerated fetal risk that is justified in specific research study situations.

However, in cases where there is direct prospect of benefit to the fetus *but not the pregnant woman*, paternal consent is additionally required. The only exceptions are with rape, incest, or the father is unavailable, incompetent, or incapacitated.

There are no specific provisions for paternal consent in research providing direct benefit to the pregnant participants but potentially involving risk to the fetus. In this situation, we recommend the study team start by discussing the specifics with a COMIRB representative with experience in research in pregnant participants and fetuses.

## Are there any specific requirements for exclusion of pregnant participants in research for the State of Colorado?

There are no specific Colorado statutes that address the exclusion of pregnant participants in research.

## How do I include pregnant minors?

Including minors who are pregnant may require consent of the minor's parent(s). Depending on the nature of the research, the inclusion of minors who are pregnant may need to satisfy regulatory requirements for research in children. For more guidance about these requirements, please refer to the COMIRB guidance, Research Involving Children. If you are including minors who are pregnant, we recommend you discuss this with COMIRB.

## How do I include pregnant participants that are incarcerated?

Prisoners are considered a vulnerable population under the Common Rule (COMIRB Research in Prisoners Guidance). If you are including pregnant participants who are prisoners, we recommend you discuss with both COMIRB staff who have expertise in research in prisoners and expertise in research with pregnant participants.

## How do I include pregnant participants who are surrogates?

There is no federal guidance in conducting research in surrogate pregnancies. Given the many nuances and legal technicalities within surrogate pregnancies, we suggest you meet with COMIRB staff with expertise in this area, and possibly University legal counsel, before submission to COMIRB and/or funding agencies.

## What about research under FDA regulations?

There are no explicit FDA regulations regarding pregnant participants in research. The FDA states that "in general, pregnant women are excluded from drug development clinical trials" but concedes that it may be "scientifically and ethically appropriate to include pregnant women

in a clinical trial." The FDA published draft guidance in April, 2018: Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials Guidance for Industry.

Research done as an IND in pregnant participants still needs to follow the FDA preclinical animal requirements. These animal requirements include female reproduction toxicity and genotoxicity studies. Any research done with *FDA-approved* products meet subpart B requirements of preliminary animal studies since this is already an FDA requirement with application for drug approval.

## What if my research is at the VA?

Research involving pregnant participants can be conducted in the VA when certain conditions beyond COMIRB are met. The research must be either 1.) relevant to the health of Veterans, 2.) relevant to the VA – as a health care provider – in a period of local or national emergency, or 3.) support the mission of another federal agency through an interagency agreement or similar.

With a VA proposal, you will also need to provide adequate description of the relevance and justification to the inclusion of pregnant participants in relation to the health of Veterans. The VA Facility Director must also certify that the specific VA facility where the research will be conducted has the capability to respond to obstetrical emergencies if determined greater than minimal risk.

If data are to be collected on the fetus, contact the VA research office to determine if a CRADO waiver is required beyond COMIRB requirements.

## What do I do if a subject becomes pregnant?

If a subject becomes pregnant during the course of the study in a study where pregnancy is an exclusion criterion, the investigator must promptly notify COMIRB by submitting a UAP. Contact COMIRB immediately to discuss if research interactions and interventions with the pregnant subject must be suspended or adjusted. If the investigator and/or sponsor wishes to have the pregnant subject continue to participate in the research, COMIRB must promptly re-review the study for inclusion of pregnant participants as a protocol amendment.

Federal regulations allow exception to continue research related interventions if minimal risk and/or it is in the best interests of the pregnant woman and fetus for safety reasons. In these instances, pregnant participants may remain in the research study while COMIRB is reviewing the protocol amendment. If you have any doubts or questions about continuing research, discuss promptly with COMIRB staff.

## What do I do if a partner of a research participant becomes pregnant?

In some drug trials, the risk of paternal transmission of risk to the fetus is unknown. In those cases, contraception is required for enrolled male research participants. If the partner becomes unexpectedly pregnant, the investigator must promptly notify COMIRB by submitting a UAP. In general, continued follow-up is desired for safety and monitoring considerations. If not already approved by COMIRB, a separate consent for the unintended pregnant partner must be submitted to COMIRB as a protocol amendment for consent to collect safety data and add any

appropriate research monitoring. As with any study, data collection on the fetus, neonate, or beyond require additional application amendments and consent.

Sponsors often include consent forms for pregnant partners at initial review. Since these consent forms rarely become necessary, COMIRB recommends that study teams wait until a pregnancy occurs, and then submit an amendment as described above. COMIRB can review these amendments quickly. If a sponsor insists on approving a pregnant partner consent at initial review, study teams are required to complete Attachment J in the COMIRB application and will be required to submit these additional consent forms for reapproval at every continuing review.

## What does COMIRB require for studies that include pregnant participants?

- Make sure your protocol falls under one or more of the permissible categories of research detailed above.
- The protocol must outline additional risks, and mitigation of risk, for both the pregnant woman and the fetus.
- In the COMIRB application, indicate that you are enrolling pregnant participants and answer the additional questions in the section related to the inclusion of pregnant participants (Attachment J).
- The consent must have language specific to pregnant participants and the fetus (if applicable).
- If it is a VA study, please attach the approval letter and/or a description of the approval status.

## What does COMIRB require for studies that exclude pregnant participants?

- If a study is more than minimal risk, routine pregnancy testing may be required.
- In minimal risk studies, self-report of pregnancy status may be acceptable.

## What is the COMIRB reviewer looking for in a protocol?

COMIRB has reviewers that have experience with research in pregnant participants. In the Preliminary Studies section of the protocol, they will be looking for the justification and additional safety measures to include pregnant participants or include participants who become pregnant.

The protocol may need to describe routine research procedures in more detail than normal. In the protocol describe:

- Justification for the inclusion of pregnant participants in the study.
- How the recruitment and selection of pregnant participants will be done.
- How the project will obtain informed consent and address any risk assessment to the fetus.
- Plans for ensuring follow-up examination or care of participants after the end of their pregnancy including infant follow-up, if necessary.
- How risks specific to pregnant participants (and the fetus, as applicable) are minimized.

Research in pregnant participants is necessary but can be challenging. If you are not experienced in this area, you will need to involve faculty who are, or work with a co-PI mentor that is.

## Requirements of Other Federal Agencies

For research subject to requirements of the Environmental Protection Agency (EPA), the EPA prohibits research involving the intentional exposure of pregnant participants, nursing participants, or children to any substance (40 CFR 26).

For research subject to requirements of the Department of Defense (DoD), the DoD applies Subpart B only to research involving pregnant participants that is greater than minimal risk, and includes interventions or invasive procedures involving the woman, fetus, or neonate (DoD Instruction 3216.02).

## Contact COMIRB

Pregnant participants should not generally be excluded from research. When thinking of doing this type of inquiry, we encourage you to contact COMIRB and ask to speak to a representative with experience in research with pregnant participants with any questions or advice prior to submitting a protocol. This action could greatly refine the protocol for this setting and facilitate the review process.