

## Guidance and Procedure: Special Populations – Pregnant Women, Fetuses, Neonates or In Vitro Fertilization (October 24, 2011)

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### Brief Overview

The University supports a policy of providing pregnant women the same opportunities as non-pregnant women to participate in research unless the individual meets legitimate exclusionary criteria or the study poses more than minimal risk to the fetus. Research inclusive of pregnant women increases the likelihood that the knowledge gained can be extended judiciously to this population in society.

Because pregnant women, fetuses and neonates are vulnerable populations, additional protections beyond the basic requirements for protecting human subjects are described in the Department of Health and Human Services (DHHS) regulations ([45 CFR 46 Subpart B: Additional Protections for Pregnant Women, Fetuses or Neonates Involved in Research](#)). These regulations also cover research using human fetal tissue, placenta or post delivery fetal material. As required by federal regulation and the UCLA Office of the Human Research Protection Program (OHRPP), the UCLA Institutional Review Boards (IRBs) review and determine the risk category for all studies involving pregnant women, fetuses, or neonates, as well as research using human fetal materials and ensure that the regulatory conditions are met.

### Definitions

The following definitions are taken from [45 CFR 46.202](#):

- **Dead fetus:** A fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord
- **Delivery:** Complete separation of the fetus from the woman by expulsion or extraction or any other means.
- **Fetus:** The product of conception from implantation until delivery.

- **Minimal Risk:** The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
- **Neonate:** A newborn.
- **Nonviable neonate:** A neonate after delivery that, although living, is not viable.
- **Pregnancy:** Encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.
- **Secretary:** The Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.
- **Viable Neonate:** A newborn being able after delivery to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration.

### **Inclusion of Pregnant Women or Women of Child-Bearing Potential in Research**

***Pregnant women or fetuses may be involved in research if the IRB determines that all of the conditions outlined in §46.204 are met.*** Three of these conditions are described immediately below and the others are described in the consent table below.

- Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.
- The risk to the fetus
  - Is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus **or**
  - Is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.
- Any risk is the least possible for achieving the objectives of the research.
- No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
- Individuals engaged in the research will have no part in any decisions as to the timing, method or procedures used to terminate a pregnancy; **AND**
- Individuals engaged in the research will have no part in determining the viability of a neonate.

The researcher needs to describe in both the protocol and the consent form 1) whether the research is directed toward the mother's health or toward the fetus, and 2) the risks and risk levels to the woman and to the fetus. The IRB will review and assess this description.

During the course of a study, pregnant women or women of childbearing potential may be encountered coincidentally as potential participants. Alternatively, pregnant women and fetuses may be the target study population(s).

#### ***Pregnant Women Who Are Not the Target Study Population***

If research targeting a wide population includes women of childbearing potential, there is the possibility of pregnancy, coincidental to subject selection.

- The research protocol should define any conditions for 1) inclusion; 2) exclusion of pregnant women; or 3) women of childbearing potential who may be encountered during study enrollment.

- The consent form for treatment and intervention studies should describe any known risks to the participant (or to the embryo or fetus if the participant is or becomes pregnant). If the risks are not known because there is little experience in pregnant women, the consent form should clearly say so.
- Additionally, in some instances, researchers may need to advise participants to avoid pregnancy or nursing for a time during or following the research. Where appropriate, participants should be advised to notify the investigator immediately should they become pregnant. See below for more details.
- See UCLA OHRPP Guidance: [Commensurate Protections for Non-Federally Funded Human Subjects Research](#) for review considerations for *non-federally funded social science, behavioral, education, and health services research*.

### ***Pregnancy as an Exclusion Criterion***

If pregnant women are excluded, the application should describe the risks that require exclusion or, if applicable, state that pregnancy is exclusionary due to a lack of knowledge of the risks.

- For research that poses an unacceptable risk to the pregnant women or fetus, non-pregnant participants of childbearing potential should be:
  - Instructed on methods to avoid pregnancy during and after the study.
  - Advised about pregnancy testing that may be required before and during the study.
  - The consent form should clearly describe information about avoiding pregnancy and about pregnancy testing that may be required.

### ***Pregnant Women and/or Fetus as the Target Study Population***

The following is a brief description of the conditions that contribute to the research risk assessment that both the researcher and the IRB should make as well as a few key points regarding informed consent:

- **Research risk assessment:**
  - If the research holds the promise of directly benefiting the woman or fetus, a greater than minimal risk to the fetus is acceptable.
  - If the research does *not* hold the prospect of directly benefiting the woman or fetus, the research is allowed if the risk to the fetus is not greater than minimal.
- **Informed consent:**
  - The pregnant woman's consent is sufficient if:
    - There is the prospect of direct benefit to the woman, the woman and the fetus, or
    - There is no prospect of direct benefit for the woman or the fetus, but the risk to the fetus is not greater than minimal.
  - The pregnant woman *and* the father's consent is required if
    - There is the prospect of direct benefit solely to the fetus unless the father is unavailable, incompetent, or temporarily incapacitated, or the pregnancy resulted from rape or incest.
    - In cases where the father is not reasonably available, a statement to this effect must be signed by the mother and retained in the research files.

Consent Decision Chart for Pregnant Women and Fetuses				
Risk	Direct benefit to mother only	Direct benefit to mother and fetus	Direct benefit to fetus only	No direct benefit or societal benefits only
More than minimal	Mother's consent	Mother's consent	Mother and father's consent	Not approvable by IRB
No more than minimal	Mother's consent	Mother's consent	Mother and father's consent	Mother's consent

For minors, that is, children who are pregnant, assent and permission are obtained in accord with the special provisions of the regulations for children, that is, [Subpart D](#). See [UCLA OHRPP Guidance on the Inclusion of Children and Minors in Research](#).

## Contraception and the Risk of Reproductive Harm

Prospective study participants should be warned about possible reproductive or lactation risks from study treatments. **These risks and the steps to be taken to minimize them should be discussed in both the application and the consent form.** The general discussion that follows is adapted from a more specific discussion in the [NIH Guidance on Informed Consent for Gene Transfer Research: Reproductive Considerations](#).

- **Study Specific:** Discussions of reproductive harm, and measures taken to minimize harm, should be study-specific. Factors to be considered include:
  - Direct teratogenic effects
  - Possible germline effects
  - Effects on a woman's ability to continue the current pregnancy
  - Effects on fertility and future pregnancies
- **Gender Appropriate:** Reproductive harms and steps to be taken to avoid or minimize them may be unique to one gender or may be different for men and women. Consent forms and the protocol should be written to address concerns appropriate to each subject population involved in the study.
- **Exclusion and Testing:** While some risks legitimately justify exclusion of particular subject groups, in many studies prospective subjects should have the right to make their own choice about the level of risk they will tolerate—after they have been fully informed of the risks and possible benefits of study participation.

If exclusion of pregnant women, nursing women, or people who wish to start a pregnancy is justified for a particular study, the application and consent form should explain the reasons for the exclusion and the steps to be taken to avoid problems, such as pregnancy testing prior to treatment and periodically during the study.

- **Abstinence and Methods of Contraception:** Methods required by the protocol and described in the consent form should be adequate to address the specific risks of the study.
  - **The time period** when steps should be taken—before, during, or after treatment—should be made clear in the application and consent forms.
  - **Choices of methods** should be as broad as is consistent with subject safety. Subjects should be told the short- and long-term advantages and disadvantages of the allowable methods.
  - **Barrier methods** should be used where body fluids may transfer infectious agents, vectors, or medications.
- **Banking Sperm and Ova:** Where appropriate, researchers should address the advisability of banking sperm and ova, including the likely additional costs for participants.

- **If Pregnancy Occurs:** The application and consent documents should discuss what will happen if a study participant or the partner of a participant becomes pregnant. Typically, the participant should contact the investigator, who can then discuss risks and provide counseling about additional steps to be taken. If the researchers will want to monitor any offspring long term, this should be mentioned in the consent documents. For some studies it would appropriate to provide special consent forms for participants who become pregnant and wish to continue in the study; the special consent form discusses risks and any special additional precautions or follow up.
- **Sample Consent Form Wording:** The sample consent form wording that follows is adapted from the [NIH Gene Transfer guidelines](#) cited above. The NIH guidelines include a number of additional examples that will be useful in many different kinds of studies and for both women and men. The wording in any example will need to be adapted to the particular study:

**Example 1 (for women):** You should not be in this study if you are a pregnant or nursing mother or if you are planning a pregnancy soon. The [*study treatments—Name relevant treatments.*] may cause harm to the mother and to unborn or breast-feeding children. You should not become pregnant during the study. If you can give birth or father a child, you must use an adequate form of birth control. If you are able to become pregnant, you must have a negative pregnancy test within [*time*] before you get the first [*treatment*], and you will be tested for pregnancy every [*interval*] during the study. If you become pregnant while in this study, you should tell the study doctor immediately. The study doctor will counsel you about your choices, and, if you decide to stay in the study, will ask you to sign a new consent form.

**Example 2 (for men):** You should not exchange body fluids with another person after you start the [treatment] and for [time period] after the [treatment] stops. The best way to avoid exchanging fluids is to abstain from sexual activity for the [time period] you are in active treatment. Other, less effective ways to avoid exchanging fluids include barrier contraceptive methods such as [specify].

### Research Involving Neonates (Viable, Uncertain Viability, or Nonviable)

Neonates of uncertain viability and nonviable neonates as well as viable neonates may be involved in research if all the following conditions are met. Section [§46.205 Research involving neonates](#) of the federal regulations describes these conditions.

Conditions for Approval of Research Involving Neonates		
Neonates of Uncertain Viability	Nonviable Neonates	Viable Neonates
<ul style="list-style-type: none"> <li>• Where scientifically appropriate, prior animal studies and clinical studies been conducted and provide data for assessing potential risks to neonates.</li> <li>• Investigators engaged in the research will have no part in ending the pregnancy or in determining the viability of a neonate.</li> <li>• Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following <b>additional conditions</b> have been met:               <ul style="list-style-type: none"> <li>○ The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, <b>and</b></li> <li>○ Any risk is the least possible for achieving that objective, <b>or</b></li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>○ Vital functions of the neonate will not be artificially maintained;</li> <li>○ The research will not terminate the heartbeat or respiration of the neonate;</li> <li>○ There will be no added risk to the neonate resulting from the research;</li> <li>○ The purpose of the research is the development of important biomedical knowledge that cannot</li> </ul>	<p>A neonate, after delivery, that has been determined to be viable may be included in research following the requirements for the inclusion of children and minors in research.</p> <p>For UCLA guidance on research involving minors see <a href="#">OHRPP Guidance: Children and Minors</a>.</p>

<ul style="list-style-type: none"> <li>○ The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means <b>and</b></li> <li>○ There will be no added risk to the neonate resulting from the research.</li> </ul>	<p>be obtained by other means.</p>	
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<b>Consent Requirements for Research Involving Neonates</b>		
<b>Neonates of Uncertain Viability</b>	<b>Nonviable Neonates</b>	<b>Viable Neonates</b>
<ul style="list-style-type: none"> <li>• The consent form clearly explains the reasonably foreseeable impact of the research on the neonate.</li> <li>• Informed consent is obtained from <ul style="list-style-type: none"> <li>○ Either parent of the neonate <b>or</b>,</li> <li>○ If neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, consent is obtained from either parent's legally authorized representative.</li> <li>○ If the pregnancy resulted from rape or incest, the father's consent or his legally authorized representative need not be obtained.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• The informed consent of both parents of the neonate will be obtained.</li> <li>• However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent will suffice.</li> <li>• If the pregnancy resulted from rape or incest the consent of the father is not needed.</li> <li>• The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice.</li> </ul>	<p>The same considerations apply as for research involving minors. See <a href="#">OHRPP Guidance: Children and Minors</a>.</p>

### **Research Involving, After Delivery, the Placenta, the Dead Fetus or Fetal Material**

Section [§46.206](#) of the federal regulations states the following:

- Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.
- If information associated with material described above is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and human subjects protection regulations apply.

### **Research Not Otherwise Approvable Which Presents an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting the Health or Welfare of Pregnant Women, Fetuses, or Neonates**

Section [§46.207](#) of the federal regulations states the following: The Secretary will conduct or fund research that the IRB does not believe meets the requirements of [§46.204](#) or [§46.205](#) if:

- The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; **and**
- The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the [FEDERAL REGISTER](#), has determined either:
  - (1) That the research in fact satisfies the conditions of [§46.204](#), as applicable; or
  - (2) The following:

- The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;
- The research will be conducted in accord with sound ethical principles; **and**
- Informed consent will be obtained as described in federal regulations and UCLA policies.

## Research Involving Human in Vitro Fertilization

Although there is currently no federal funding of human in vitro fertilization (IVF) research, some UCLA investigators may be involved in privately-funded research on IVF as a treatment for infertility. The organization shown below offers background information, historical perspectives on the regulatory issues and ethical guidance for IVF research:

- [The American Society for Reproductive Medicine \(ASRM\)](#)

**IMPORTANT NOTE:** Investigators seeking information on human stem cell research should refer to the [UCLA Embryonic Stem Cell Research Oversight \(ESCRO\)](#) website.

## Regulations & References

### *Federal Regulations*

- 45 CFR 46, [Subpart B, Additional Protections for Pregnant Women, Fetuses or Neonates Involved in Research](#)
- 45 CFR 46, [Subpart D, Additional Protections for Children Involved as Subjects in Research](#)
- 40 CFR 26, [EPA Policy for Protection of Subjects in Human Research Conducted or Supported by EPA](#)

### *UCLA OHRPP Guidance*

- [Commensurate Protections for Non-Federally Funded Human Subjects Research](#)
- [Research Involving Children and Minors](#)
- [EPA Checklist](#)