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Overview

Pregnant women, fetuses and neonates are vulnerable populations, and additional protections are described in the regulations (45 CFR 46 Subpart B ^[1]) enforced by the Office for Human Research Protections (OHRP). These regulations also cover research using human in vitro fertilization, as well as human fetal tissue, placenta or post delivery fetal material.

UCSF 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.

Inclusion of Pregnant Women or Women of Childbearing Potential

During the course of a clinical 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).

Some common types of research involving pregnant women include the following:

Pregnant women are not the target study population

If research targeting a wide population includes women of childbearing potential, there is the possibility of pregnancy. The research protocol should define any conditions for inclusion or exclusion of pregnant women or women of childbearing potential.

The consent form for treatment and interventional 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. See suggested consent form language below and in the consent form templates.

See the detailed IRB Requirements for additional conditions imposed by the regulations.

Pregnancy is 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 told about:

- Methods of contraception
- Pregnancy testing requirements

Additional details are provided below.

Pregnant women as the target study population

The IRB must consider the potential risks and benefits to the woman and the fetus:

- 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 may be required from only the pregnant woman or from the pregnant woman and the father. Review the complete regulatory requirements below.

The Risk of Reproductive Harm and Contraception Requirements

Prospective study participants should be warned about possible reproductive or lactation risks from study treatments. **Discuss these risks and the steps to be taken to minimize them in both the consent form and IRB Application.**

The points that follow are adapted from a more specific discussion in the NIH Informed Consent Guidance for Human Gene Transfer Research: Reproductive Considerations [2], which also contains sample consent form language.

Study-specific and gender-appropriate discussions of reproductive harm

Include study-specific discussions of reproductive harm and measures taken to minimize harm. 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

In addition, reproductive harms and steps to be taken to minimize them may be unique to one gender, or may be different for men and women. Address concerns appropriate to each subject population involved in the study.

Exclusion criteria and pregnancy testing requirements

Prospective subjects in many studies should have the right to make a choice about the level of risk they will tolerate after having been fully informed of the study's risks and possible benefits.

However, if the study's risks justify the exclusion of pregnant women, nursing women or people who wish to start a pregnancy from a study, 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.

Required methods of contraception

Methods of contraception required by the study should be adequate to address the study's specific risks. Clarify the time period when steps should be taken ? before, during and/or after treatment.

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, address the advisability of banking sperm and ova, including the likely additional costs for participants.

What 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 female participant is withdrawn from the study as a result of a pregnancy, the researcher may want to obtain information about the progress and outcome of a pregnancy for safety purposes. This information should be included in the consent form and may occur as long as the participant does not withdraw consent. Additionally, the investigator should submit a Protocol Violation/Incident Report [3] via iRIS to the IRB if either the participant or the participant's partner becomes pregnant.
- If both the participant who becomes pregnant and the investigator wish to continue the participant's enrollment in the study, a single subject modification [4] (i.e., an enrollment exception) should be submitted to the IRB.

Sample Consent Form Wording: The sample consent form wording that follows is adapted from the NIH Gene Transfer guidelines [2] 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 and subject population.

Examples

Example 1: 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 the 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.

Example 2: 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*].

Regulatory Requirements

Definitions

As described in 45 CFR 46.202 [5]:

Dead fetus: A fetus that does not exhibit a heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, or 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 neonate able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration.

Click on the link to expand the regulatory requirements for research involving each participant population.

Pregnant women or fetuses prior to delivery

45 CFR 46.204 [6]

All conditions must be met:	Informed consent requirements:
Where appropriate, prior animal studies and clinical studies with non-pregnant women have been conducted and provide data for assessing potential risks to pregnant women and fetuses.	The consent form clearly explains the reasonably foreseeable impact of the research on the fetus, and

Any risk is the least possible for achieving the objectives of the research;

Consent will be obtained from the appropriate individuals as follows:

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**,

If there is no such prospect of benefit, the risk to the fetus 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.

The pregnant woman or her legally authorized representative if:

- The research holds out the prospect of direct benefit to the pregnant woman, or,
- The research holds out the prospect of a direct benefit both to the pregnant woman and the fetus; or
- The research does not hold out the prospect of direct benefit for the woman or the fetus, but the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means.

No inducements, monetary or otherwise, will be offered to terminate a pregnancy.

The pregnant woman and the father if:

- The research holds out the prospect of a direct benefit solely to the fetus unless the father is unavailable, incompetent, or temporary 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.

Investigators will have no part in decisions about the timing, method, or procedures used to terminate a pregnancy or decisions regarding the viability of a fetus.

For minors who are pregnant, assent and permission are obtained in accord with the provisions of the Protections for Children Involved as Participants (Subpart D). For UCSF guidance on research involving minors, see the Children and Minors in Research ^[7] page.

Neonates of uncertain viability

45 CFR 46.205 ^[8]

All conditions must be met:

Informed consent requirements:

Where appropriate, prior animal studies and clinical studies with non-pregnant women have been conducted and provide data for assessing potential risks to pregnant women and fetuses.

The consent form clearly explains the reasonably foreseeable impact of the research on the neonate.

Investigators engaged in the research will have no part in ending the pregnancy or in determining the viability of a neonate.

Informed consent is obtained from either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, consent is obtained from either parent's legally authorized representative. If the pregnancy resulted from rape or incest, the father's consent or his legally authorized representative need not be obtained.

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 IRB determines that:

- The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
- The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research

Nonviable neonates

45 CFR 46.205 [8]

All conditions must be met: Informed consent requirements:

Vital functions of the neonate will not be artificially maintained;

The informed consent of both parents of the neonate will be obtained. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent will suffice. If the pregnancy resulted from rape or incest the consent of the father is not needed.

The research will not terminate the heartbeat or respiration of the neonate;

The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice.

There will be no added risk to the neonate resulting from the research;

The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.

Viabile neonates

A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of the Federal Policy for Protection of Human Participants (Subpart A) and Protections for Children Involved as Participants (Subpart D) [9]. See the IRB's guidance on Children and Minors in Research [7] page for more info.

After delivery, the placenta, the dead fetus or fetal material

45 CFR 46.206 [10]

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 identifying data are associated with the material in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent privacy protection measures are applicable.

Additional guidance on fetal tissue transplantation research is available on the OHRP website.

Research not otherwise approvable

45 CFR 46.207 ^[11]

The Secretary will conduct or fund research that the IRB does not believe meets the requirements of Sec. 46.204 or Sec. 46.205 only 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:

- That the research in fact satisfies the conditions of Sec. 46.204, as applicable; OR
- 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 in accord with the informed consent provisions of Federal Policy for Protection of Human Subjects (Subpart A).

Research involving human in vitro fertilization

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

- The American Society for Reproductive Medicine (ASRM) ^[12]
- The American College of Obstetricians and Gynecologists (ACOG) ^[13]

Important Note: Research may require review by the Human Gamete, Embryo and Stem Cell Research (GESCR) Committee ^[14] at UCSF.

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Links

- [1] <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>
- [2] <http://osp.od.nih.gov/sites/default/files/resources/IC2013.pdf>
- [3] <http://irb.ucsf.edu/protocol-violation-or-incident>
- [4] <http://irb.ucsf.edu/modification>
- [5] <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.202>
- [6] <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.204>
- [7] <http://irb.ucsf.edu/children-and-minors-research>
- [8] <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.205>
- [9] <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.204>
- [10] <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.206>
- [11] <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.207>
- [12] <http://www.asrm.org/>
- [13] <http://www.acog.org/>
- [14] <http://irb.ucsf.edu/stem-cell>