

## **Overview**

Lawrence Livermore National Laboratory (LLNL) and the LLNL IRB are responsible for providing additional protections for vulnerable subjects who participate in human research conducted by LLNL.

This Standard Operating Procedure (SOP) applies to all human subjects research under the purview of the LLNL that plans to enroll vulnerable subjects.

Whenever the IRB identifies that a research subject may enroll vulnerable subjects (such as children, prisoners, pregnant women, neonates, elderly, subjects who lack capacity or are mentally-ill or disadvantaged, students, employees, economically disadvantaged, etc.), the IRB will consider additional protections to ensure that the research is conducted ethically.

## **Procedures**

### **Review of Research Involving Pregnant Women, Human Fetuses, or Neonates (45 CFR 46, Subpart B)**

1. Pregnant women/fetuses/neonates like other potential vulnerable populations:
  - a. require additional protections when they are research subjects;
  - b. at the same time, they should not be denied the opportunity to enroll or the prospective benefits of participating in research.
2. Distinction should be made between studies that are designed to study pregnant women or the characteristics of the pregnant woman and/or fetuses/neonates (i.e., the inclusion criteria is geared to enroll pregnant women, fetuses, and/or neonates in the research), and studies for which pregnant women may enroll by chance. With regard to the latter, Subpart B requirements need not be met although when studies pose potential risks to pregnant women, neonates, or fetuses appropriate safeguards should be considered for women of child-bearing potential.
3. The IRB will ensure that the requirements of Subpart B are appropriately satisfied prior to granting approval of any study designed to study pregnant women, fetuses, or neonates. In addition to the considerations made by the IRB in the scope of its review (in accordance with Section VIII.A), the IRB will also consider the following:
  - a. there is adequate expertise on the IRB to evaluate the risks and benefits related to the inclusion of pregnant women, fetuses and neonates. When additional expertise is needed the IRB will consider adding an appropriate consultant(s);
  - b. the determinations required by Subpart B are documented appropriately in the IRB records (in the IRB minutes for reviews conducted by the convened IRB or in the documentation for review for expedited reviews);
  - c. any involvement of pregnant women or fetuses meets all requirements as stated in 45 CFR 46.204;
  - d. any involvement of neonates meets all requirements as stated in 45 CFR 46.205;
  - e. any research involving, after delivery, the placenta, the dead, macerated fetal material, or organs excised from a dead fetus will be conducted in accordance with 45 CFR 46.206, federal, state, or local laws and regulations;

- f. proposals that are supported by the Department of Health and Human Services (HHS) and for which the inclusion of pregnant women, neonates, or fetuses is not approvable per Subpart B will be referred to the HHS Secretary for review. For other such proposals, the IRB will establish a separate panel composed of individuals with appropriate expertise to determine whether the research meets ethical and regulatory standards and whether the research should be approved. If the research is supported by another federal agency or sponsor, their requirements must be considered during this process;
- g. informed consent is obtained per provisions of Subpart B for pregnant women who have reached the age of majority or are legally emancipated;
- h. informed consent is obtained per provisions of Subparts B and D for pregnant minors (where research is related to prenatal care, consent of the pregnant minor may be acceptable);
- i. consent documents contain information regarding risks of breastfeeding, when risks to the pregnant woman or neonate is determined to be greater than minimal;
- j. consideration is given to excluding women of child-bearing potential when the woman's reproductive status is not relevant to the research and risks to the pregnant woman or fetus is determined to be greater than minimal.

#### **Review of Research Involving Prisoners (45 CFR 46, Subpart C)**

LLNL does not conduct research with prisoners. If LLNL will conduct prisoner research it will have to review the research in accordance with 45 CFR 46 Subpart C.

#### **Review of Research Involving Children (45 CFR 46, Subpart D)**

##### 1. Children like other potential vulnerable populations:

- a. Require additional protections when they are research subjects;
- b. At the same time, children should not be denied the opportunity to enroll or the prospective benefits of participating in research.

Federal guidelines require that children be included in certain research activities unless there is a justification for excluding them, while federal regulations require that additional precautions be taken when children are research subjects, depending on the degree of risk involved in the research. National Institutes of Health (NIH) policy, which guides the conduct of much human research due to funding relationships, has similar requirements.

The regulations also set forth requirements for obtaining parental permission and, where appropriate, assent by the children themselves. The IRB will review research that involves children in consideration of Subpart D of the applicable HHS and Food and Drug Administration (FDA) regulations, California state law, and institutional policy.

Information provided by the investigator regarding level of risk, prospect of direct benefit (when applicable), assent and parental permission, and inclusion of wards/foster children is evaluated by the IRB, which may concur with the investigator's determinations, make alternative determinations, or impose additional requirements.

##### 2. Determination of Risk/Benefit Category

When the IRB (or qualified reviewer for research that is eligible for expedited review) reviews research involving children, it will be determined which of the risk/benefit categories described in 45 CFR 46 (Subpart D) and 21 CFR 56 (Subpart D) the research fits into, whether assent will be required, the manner in which assent will be obtained, if required, the requirements for parental permission or approval of waiver thereof, and the appropriateness of the inclusion of wards/foster children if their involvement is

proposed for research that involves greater than minimal risk with no prospect of direct benefit. The IRB will consider information provided by the research team in the submission. The IRB's (or reviewer's, for research that is eligible for expedited review) determinations will be entered into the minutes for the meeting at which the research was reviewed, if full Board review is indicated, or in the IRB record, in the case of expedited reviews. Any concern with the information provided by the researchers should be included in the documentation of Subpart D findings.

The IRB may approve research involving children only if it meets the criteria in one of the four following categories:

- a. Research not involving greater than minimal risk (45 CFR 46.404; 21 CFR 50.51):  
The IRB, or designated expedited reviewer, will provide the basis for the determination of minimal risk. If consent cannot be waived in accordance with 45 CFR 46.116(d), the IRB, or designated expedited reviewer, will almost always require that the permission of only one parent is necessary for research in this category, and will determine whether assent is required for some or all minors. However, the IRB has the discretion to require that the permission of both parents must be obtained.

- b. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (45 CFR 46.405; 21 CFR 50.52):

For research to be approved under this category, the convened IRB must:

- i. find the risk is justified by the anticipated benefits to the subjects; and
- ii. find the relation of the anticipated benefit to the risk must be at least as favorable to the subjects as that presented by available alternative approaches.
- iii. provide the basis for the determinations of greater than minimal risk and prospect of direct benefit.
- iv. the IRB may determine that the permission of one or both parents is required for research in this category and will determine whether assent for some or all minors is required.

- c. Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition (45 CFR 46.406; 21 CFR 50.53):

For research to be approved under this category, the convened IRB must find that it meets the requirements of 45 CFR 46.406 and 21 CFR 50.53, as follows:

- i. the risks represent a minor increase over minimal risk;
- ii. the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
- iii. the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the subject's disorder or condition;
- iv. adequate provisions are made for soliciting and documenting assent of the children; and
- v. adequate provisions are made for soliciting the permission of both parents of each child unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. (45 CFR 46.407 and 408).

The IRB, at a convened meeting, will provide the basis for the determinations of greater than minimal risk and no prospect of direct benefit.

The permission of both parents is required for research in this category, unless one parent cannot reasonably provide permission, as allowed per Subpart D. The assent of the minors involved is required unless the Board determines that some or all are not capable of providing assent.

- d. Research not fitting into the aforementioned categories which presents a reasonable opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407; 21 CFR 50.54):
  - i. The IRB, at a convened meeting, will provide the basis for its determinations regarding risk level and potential for direct benefit.
  - ii. If the research is supported by HHS jurisdiction, and falls in this category, it cannot be performed without review by the Secretary of the HHS as outlined in 45 CFR 46.407.
  - iii. Research under FDA jurisdiction that falls in this category cannot be performed without review by the Commissioner of Food and Drugs as outlined in 21 CFR 50.54.
  - iv. If the research is HHS-supported or under FDA jurisdiction, the IRB staff will prepare a request for panel review promptly after the IRB review, and will provide such to the IRB Program Manager. The IRB Program Manager, or designee, will prepare a report for submission to OHRP to request a panel review as described in 45 CFR 46.407 or 21 CFR 50.54, as applicable.

Research in this category that is not federally funded and does not involve FDA-regulated products will be reviewed by a special panel convened by the LLNL IRB office to make the determinations that would be otherwise be made by HHS or FDA when evaluating research in this category.

The permission of both parents is required for research in this category, unless one parent cannot reasonably provide permission, as allowed per Subpart D. The assent of the minors involved is required unless the Board determines that some or all are not capable of providing assent.

#### **Assent Determination**

- a. After the Board makes the risk/benefit determination, they must consider the issue of child assent, as described in 45 CFR 46.408(a) (Subpart D). The Board must decide whether assent is necessary, and also whether and how it will be documented if it is necessary.
- b. Among the formats the Board may consider are the following:
  - i. waiver of assent;
  - ii. determination that the children lack the ability to provide assent;
  - iii. verbal assent, without documentation;
  - iv. verbal assent, with documentation by the investigator and/or the legally authorized representative(s);
  - v. written assent form, with subject signature; or
  - vi. subject signature block on consent form (for older children only).
- c. The federal regulations do not require that assent be sought from children starting at a specific age, but that their assent should be sought when, in the judgment of the IRB, the children are capable of providing their assent. IRBs are to take into account the ages, maturity, and psychological state of the children involved (see 45 CFR 46.408(a)).
- d. When the research offers the child the possibility of a direct benefit that is important to the health or well-being of the child and is available only in the context of the research, the IRB may determine that the assent of the child is not necessary (45 CFR 46.408(a)).

#### **Inclusion of Wards in Research**

- a. Special protections must be considered whenever children who are wards of the state or any other institution, agency, or entity are considered for inclusion in research that is greater than minimal risk with no prospect of direct benefit. Of primary concern are consent issues, i.e., who has authority to enroll a child who is a ward in research. Responsibility for ensuring that

in compliance with applicable statutes and the process described in the protocol that was approved by the IRB.

- b. Federal regulations do not require special provisions for wards enrolled in research that is either minimal risk or greater than minimal risk with the prospect of direct benefit. However, the IRB may impose additional requirements if the research and/or status of the child(ren) warrant additional safeguards. California state laws and any applicable California Department of Child Protective Services policies will be considered during review of research that involves wards.
- c. Wards may only be included in research that is greater than minimal risk and does not offer the prospect of direct benefit (45 CFR 46.406 or 45 CFR 46.406) when such research is either related to their status as wards or conducted in a facility at which most of the children are not wards.
- d. If it is proposed that wards will be enrolled in research that is greater than minimal risk and does not offer the prospect of direct benefit, an advocate or advocates who will serve to ensure the best interests of each child are being upheld must be appointed, in addition to obtaining permission from any other individual acting on behalf of the child, e.g., as guardian or in loco parentis. One individual may serve as an advocate for more than one child.

**REFERENCES:**

45 CFR 46 Subparts B, C and D  
21 CFR 50

## Document Review History

Revision Number	Date	Author	Summary of Changes
01	November 2019	IRB Office	New
02	October 2020	Ann-Marie Dake	Revisions and updates