



## **Overview:**

All non-exempt human subjects research (HSR) projects must be reviewed by the procedures in this Standard Operating Procedure (SOP) regardless if the research is reviewed by the expedited review procedures or by a convened Institutional Review Board (IRB) (i.e., full board review).

## **Regulatory Guidance:**

The IRB is responsible for reviewing all non-exempt research in accordance with the Criteria for IRB Approval in the Health and Human Services (HHS) regulations (45 CFR 46, Subparts A, B, C, D); Department of Energy (DOE) policies, requirements, and guidance; and Food and Drug Administration (FDA) regulations 21 CFR Parts 50, 56, 812, when applicable. In addition, the IRB must consider additional regulations articulated in the Lawrence Livermore National Laboratory (LLNL) policies and procedures for the protection of research subjects from research risks.

### **I. Criteria for Approval**

The ethical review of research conducted by LLNL is the primary goal of the IRB. All IRB reviews will consider the ethical principles of the *Belmont Report*. Each of the regulatory requirements listed in the Criteria of IRB Approval below is based on one or more of the below ethical principles.

The IRB will approve a research protocol only if the following criteria for approval are satisfied:

- Risks to subjects are minimized.
- Risks to subjects are reasonable in relation to anticipated benefits.
- Selection of subjects is equitable.
- Informed consent will be appropriately sought from each prospective subject or the subject's legally authorized representative in accordance with, and to the extent required by, 45 CFR 46.116.
- Informed consent will be appropriately documented.
- Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- Appropriate safeguards have been included to protect vulnerable subjects (i.e., children, prisoners, and pregnant women) in accordance with 45 CFR 46, Subparts B, C, and D.

The determinations made by the IRB for expedited review approval of a study are documented in the IRB records (paper or electronic). The determinations made by the IRB for full board approval of a study are documented in the IRB minutes.

### **A. Assessment of Risks to Subjects**

1. The IRB will identify the risks associated with participating in the research study and differentiating them from the risks that the subjects would encounter if they were not in the study.
  - a. The risks will include physical, psychological, emotional, economical/financial risks, and those related to a loss of privacy or a breach of confidentiality.
  - b. The identification of risks is based on review of the protocol, supporting information submitted to the IRB for review, the IRB members' experience and knowledge, and from external sources such as a review of the literature.
  - c. The IRB must be able to determine whether the potential risks are minimal or greater than minimal risks so that the appropriate level of review can be applied to the research.

### **B. Risks to Subjects are Minimized**

1. Risks to subjects are minimized by using procedures which are consistent with suitable research design and which do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already performed on the subjects for diagnostic or treatment purposes.
2. The study design and study procedures will be evaluated to determine whether risks have been minimized to the extent possible that will still permit the ethical conduct of the study and that study objectives can be met.
3. Whenever possible, procedures should be utilized that will otherwise be performed on subjects if they were not enrolled in the study (e.g., for biomedical research using diagnostic or treatment that would be conducted in standard practice).
4. The IRB may minimize risks by any of the following:
  - a. Removing the risk by removing the procedure, intervention, or interaction that will cause the risks.
  - b. Substituting an alternative procedure, intervention, or interaction that is associated with less risks.
  - c. Adding precautions, procedures, interventions, or interactions that will manage or remove the risks.
  - d. Adding safeguards such as additional monitoring or testing that will identify the risks earlier and allow intervention or removal of the risks before they are exacerbated.

**C. Assessing Risks and Anticipated Benefits, If Any, to Subjects**

1. The LLNL IRB shall conduct a risk/benefit analysis. The LLNL IRB will ensure that risks to all subjects are minimized and are reasonable when compared to the benefits of participating in the research study or the knowledge that will be gained from participation in the study. The IRB shall carefully assess each risk and benefit to the study to determine if the benefits outweigh the risks and, therefore, justify the use of human subjects.
2. The IRB should not consider the possible long-term effects of potential knowledge that may be gained from the study when considering whether to approve the study (e.g., the possible effects of the research on public policy).

**D. Assessing Equitable Selection of Subjects**

In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons. Defining the appropriate group of subjects for a research project involves a variety of factors—requirements of scientific design, susceptibility to risk, likelihood of benefit, practicability, and considerations of fairness. IRBs are required to make a specific determination that the selection of subjects is equitable.

While studies of a captive group of subjects, such as government contractors, students, laboratory co-workers, and hospitalized patients may be useful and desirable and can be conducted in an ethical fashion, a scrupulous effort must be made to preserve the individuals' rights because of the possibility of coercion. Studies of volunteers in the investigator's own department or who are the investigator's students should be avoided and will be carefully scrutinized by the LLNL IRB because of the subtle coercive factors, or undue influence, that could be present in even the most harmonious situations.

The LLNL IRB shall consider the following points when assessing equitable selection of subjects:

1. Does the nature of the research require or justify using the proposed study population?
2. Will the solicitation of subjects avoid placing a disproportionate share of the risks and discomfort as well as inconvenience of the research on any single group of individuals?
3. Are women of childbearing potential eligible for participation or, if not eligible, has their exclusion been justified?
4. Has the selection process overprotected potential subjects who are considered vulnerable so that they are denied opportunities to participate in research?
5. Are any payments, or incentives to subjects reasonable, based upon the complexities and inconveniences of the study and the particular subject population?

In making this assessment, the IRB takes into account the purposes of the research and the setting in which the research will be conducted and is particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons [45CFR 46.111(3)].

#### **E. Assessing Methods for Obtaining Informed Consent of Subjects or Legal Representatives**

Informed consent will be sought from each prospective subject or the subject's legally authorized representative in accordance with, and to the extent required by, 45 CFR 46.116.

Communication between subject and investigator should embody aspects similar to those in a good patient–doctor relationship. Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension. The discussion with the potential participant by the principal investigator (PI) or co-investigator should include the purpose of the research, the procedures to be followed, and the discomforts, risks and possible benefits, if any. The signing of the consent document should signify that a thorough discussion has taken place and will continue to take place during the conduct of the study.

**Note:** Since informed consent is such an integral activity for the ethical conduct of research and there are many considerations for effectively obtaining consent from subjects, a separate section is devoted to the topic in SOP #11: *Recruitment and Informed Consent*.

#### **F. Assessing Data Monitoring Plans**

When appropriate, the research plan should make adequate provision for monitoring the data collected to ensure the safety of subjects.

1. For all studies that are greater than minimal risk, the IRB will review a safety monitoring plan that details how the study will monitor the data to ensure safety of subjects.
2. The IRB will determine whether the safety monitoring plan can be managed by the investigator and research team or whether there should be an additional review of safety data by a separate committee or process (e.g., data monitoring committee/data safety monitoring board) and/or the sponsor. Some considerations for when a monitoring committee will be required include moderate to high risk research (especially studies that may include death as a risk), inclusion of vulnerable subjects, large number of subjects, and double-blind study designs.
3. When considering a separate monitoring committee, the IRB may determine that the monitoring board should be entirely independent from the research team(s) and/or the sponsor to remove all potential conflicts of interest. Additional considerations for when a monitoring committee will be necessary include requirements by the FDA or National Institutes of Health (NIH) or the sponsor for research regulated or supported by them.
4. The IRB shall also determine whether additional monitoring may be required by LLNL when the PI is also the PI of a multicenter study. In such situations, the IRB may determine that the monitoring plan should provide details of how safety data will be collected in a timely manner from all performance sites and how the plan will ensure the safety and well-being of subjects at all sites.

#### **G. Assessing Privacy and Confidentiality Protections**

When appropriate, provisions to protect the privacy of subjects and to maintain the confidentiality of data should be included in the protocol.

The IRB will determine the adequacy of the provisions to protect subject privacy and maintain data confidentiality. If the research study involves greater than minimal risk as a result of a potential breach of confidentiality, a data protection plan will be required for review by the IRB.

During the course of a study, the highest standards should be maintained with regard to the privacy and confidentiality of information, including interviews, emails, telephone conversations, and other records concerning the subject. Although more investigators and staff may be involved in the conduct of a study than might occur in the usual course of treatment of a patient, confidentiality standards should not be relaxed.

#### **H. Assessing Special Considerations for Projects Involving Vulnerable Populations**

When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards should be included in the study. The IRB review process will determine if the proposed safeguards are adequate to protect the rights and welfare of these subjects.

### **II. Assessing Suitable Study Design**

A human research study should be well designed according to proper scientific principles and be preceded by adequate laboratory and/or animal studies. A study which will not yield valuable data is unacceptable.

The LLNL IRB shall consider the following points when assessing suitable study design:

- A. Has the rationale and basis for the study hypothesis been provided in the background information?
- B. Is the scientific design adequate to answer the research questions posed?
- C. Is the sample size (number of subjects) adequate?
- D. Is the method proposed for selecting and assigning subjects to treatment groups unbiased?
- E. Are the study endpoints and methods of data analysis appropriate for the study?

### **III. Approving Research at the Time of Initial Review**

A. The IRB can take any of the follow actions:

1. Approve the research study;
  - a. Without any conditions; or,
  - b. With conditions (also referred to as “conditional approval or approval contingent upon changes or stipulations for approval”);
    - The IRB may require an investigator make specific changes to the protocol or informed consent.
    - The IRB may require an investigator to submit additional documents.
    - The IRB Chair or other individuals (with expertise or qualifications) may review materials submitted by the investigator and determine that the conditions have been satisfied.
    - Further review by the IRB at a subsequent convened meeting would not be necessary.
    - The IRB should specify whether any conditions need to be satisfied before an investigator can initiate research activities.

2. Defer, or table, the study for further review at a future date after the required modifications are submitted by the investigator.

### 3. Disapprove the research.

For FDA regulated studies, FDA recommends the IRB notify the sponsor of any decision to disapprove the research and the reason(s) for the disapproval determination.

## IV. Effective Date of the Initial IRB Approval

For studies reviewed by the full board, the effective date is the date of the IRB meeting that the IRB either approved the study without any changes or approved with conditions that can be confirmed by the Chair or designated reviewer. The expiration date of the initial approval is the day before the one-year anniversary after the effective date.

## V. Notification of IRBs Initial Review Determination to the Investigator

After the review, the investigator will receive a letter with the IRB decision:

For studies **approved** – an approval letter with the date of approval and expiration date of IRB approval will be sent to the PI.

For studies **approved with conditions (i.e., “Action Item”)** – IRB conditional approval indicates that the IRB has approved the protocol pending submission and approval of minor revisions. The Initial Review Determination letter will describe the revisions requested by the IRB. The investigator needs to respond to revisions requested by the IRB. The IRB Program Manager may forward the responses to the IRB Chair for additional review.

For studies **tabled/deferred** - (Convened IRB only) Indicates that the IRB withholds approval pending submission of major revisions/additional information that must be re-reviewed by the IRB at a convened meeting. The IRB Program Manager will send the investigator a letter listing the reasons for tabling the study and include a description of the revisions or clarifications requested.

For studies **disapproved** – (Convened IRB only) A vote to disapprove research indicates that the IRB will not allow the research to be conducted. Disapproval of a protocol usually occurs when the IRB determines that the risk of the procedures outweigh any benefit to be gained or if the proposed research does not meet the federal criteria for IRB approval. Disapproval generally indicates that even with major revisions to the application the issues preventing approval will not be resolved.

The IRB Program Manager will send the investigator a letter describing the reasons for disapproving the protocol. The investigator will be given an opportunity to respond to the IRB’s decision to disapprove the research. The investigator’s responses will be reviewed at a subsequent convened meeting of the IRB.

For any of the above actions, the copy of the notification letter will be kept in the IRB study file. The approved informed consent document(s) will be released with the IRB approval letter and will be stamped with the IRB number, date of IRB approval and the date IRB approval expires.

## VI. Appeal of IRB Decisions/Determinations

Investigators may appeal the IRB’s decision/determination of any new study, modification or continuing review of an existing study, or review and determinations regarding allegations of noncompliance/review of noncompliance.

An investigator may appeal to the IRB for a formal re-review of a decision whenever there has been more than two unsuccessful efforts by the investigator and the IRB to resolve the investigator’s concerns and the investigator believes that the IRB’s decision is due to: inadequate or inaccurate information; or IRB non-compliance with LLNL IRB SOPs, state law, or federal regulation.

At the discretion of the IRB Chair, the investigator may make such an appeal in person and/or in writing to the IRB. The appeal request consists of sending the IRB Program Manager a cover letter outlining the basis for the appeal and documents that support the appeal. The IRB Program Manager reviews the appeal request to determine whether an appeal is appropriate. This may include consultation with the investigator, the IRB Chair, select members of the IRB, or the Institutional Official, as needed. The IRB Program Manager informs the investigator by email if the request has been accepted for review.

If the decision being appealed was made by the convened IRB, the appeal is heard and considered by the convened IRB. This may be a regularly scheduled IRB meeting, or it may be an ad-hoc meeting convened for this specific purpose. If the decision being appealed was made by the Expedited or Exempt (both minimal risk) process, then the IRB Chair will hear the appeal.

The following outlines the process for appeals heard by the convened IRB. The IRB Chair may hold a closed session of the IRB without the investigator, to establish the key issues and questions to consider.

- The investigator is invited to present information and rationale to the IRB.
- There is a question-and-answer session with the investigator.
- The investigator leaves the meeting room.
- The IRB members and other meeting attendees discuss the appeal.
- The IRB Program Manager prepares anonymous written ballots to distribute to the members for voting when the discussion has ended. After voting, the ballots are read by the IRB Chair. The IRB motions and then votes whether to take one of the following actions:
  - Approve the appeal and modify the original decision; or
  - Disapprove the appeal and uphold the original determination; or
  - Defer the appeal and obtain additional information or consultation to make a final decision.
- The IRB's appeal determination, and any other considerations or requirements associated with it, are communicated to the investigator in a letter within 10 business days of the IRB's determination. If appropriate, the determination may also be communicated by email or telephone call with follow-up email by the IRB Program Manager or IRB Chair.
- A decision by the IRB to disapprove, suspend, or terminate a project is not subject to reversal by the LLNL IO or any other officer of LLNL, state, or federal government.
- Only one appeal will be allowed on a given matter. The concluding IRB decision of an appeal is final and cannot be appealed.

**References:**

*45 CFR 46.108; 45 CFR 46.109; 45 CFR 46.110*  
*45 CFR 46.111; 45 CFR 46.116; 45 CFR 46.117*  
*45 CFR 46 Subparts B, C, and D*  
*21 CFR 50 Subparts A, B, and D*  
*21 CFR 56.108, 21 CFR 56.109, 21 CFR 56.111*  
*The Belmont Report*



## Document Review History

Revision Number	Date	Author	Summary of Changes
01	September 2017	Ann-Marie Dake	Complete Revision
02	November 2018	Dawn Whalen	Document control process added
03	November 2019	IRB Office	Complete Revision