IRB
Institutional
Review Board

#14
IRB Review Process

The IRB is responsible for ascertaining the acceptability of proposed research in terms of institutional commitments and regulations, applicable laws, standards of professional conduct and practice, and ethical and societal norms. When the LLNL IRB reviews research involving a category of vulnerable subjects (e.g., prisoners, children, or individuals institutionalized as mentally disabled), the Board will include in its reviewing body one or more individuals who have as primary concern the welfare of these subjects. If no members of the Board have the appropriate background, the Board will use consultants on an as-needed basis during the review process. Consultants are not allowed to vote on the approval or disapproval of the protocol under review.

The IRB examines subject recruitment procedures, proposed remuneration (in cash or in kind), and the informed consent process. The Board also evaluates the potential risks and benefits to participants outlined in each protocol. This review helps to ensure that investigators recruit subjects in an equitable, non-coercive manner, that subjects are fully informed about the risks and benefits entailed in participation, and that subjects are not exposed to disproportionate risks.

Levels of IRB Reviews

The review of applications to involve human subjects in research is a multi-step process. The process begins with the submission of an application to the IRB Office who screens the initial application packet and corresponds with the investigator if clarification is needed on any part of the application. Once the screening has been completed, the protocol is submitted to the Board for review.

New and continuing protocols may undergo one of two levels of Board review, full Board or expedited review. In some cases, the IRB Office, in consultation with the IRB Chair, may determine that a protocol requires only administrative review by the IRB Office. Amendments or modifications to currently approved protocols must also be reviewed by the IRB.

During the review process, the Board examines the protocol and supporting documentation to ensure that the investigator has addressed the risks and benefits posed to potential subjects participating in the research, the subject selection is equitable, and that the consent process will provide adequate information to prospective subjects so that subjects can make informed decisions regarding their participation in the research activity. Any issues or concerns identified during the IRB review will be communicated to the investigator. This communication most often takes the form of an e-mail correspondence from the IRB Office. Receiving correspondence from the IRB Office after a review by the IRB is typical and should not be viewed as a negative comment about the content of the research.

The Board review process allows investigators various levels of appeal from the time a study receives initial review through approval or disapproval. Any and all IRB decisions are contingent upon the response of the investigator.

Research that has been approved by the IRB may be subject to further appropriate review and approval or disapproval by LLNL management. However, management may not approve research if it has not been approved by the IRB.

Investigators should be aware that the review process can take up to two months. Because some sponsors require IRB approval prior to consideration of proposals for funding, and all require IRB review prior to release of funding for human subjects research activities, investigators are strongly advised to contact the IRB Office regarding IRB submission deadlines and the current IRB meeting schedule.

A discussion of the various types of review follows.

Research Requiring Review by the Convened Board (Full-Board Review)

Except for research qualifying for an expedited review, all protocols must be reviewed during convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it must receive approval from a majority of those members present at the meeting.

When submitting a study for full-Board review, investigators should allow three (3) weeks lead time for the processing of the human subjects application by the IRB Office staff prior to the IRB meeting. The IRB Office staff logs each submission and checks to ensure it fulfills all application requirements. The staff will inform investigators by telephone, e-mail, or letter if the application is missing elements. All complete applications are copied and distributed to all members of the Board. A thorough and intelligent analysis of the application requires that each Board member receive a complete set of materials to review prior to the meeting. The members receive materials approximately one (1) week prior to the scheduled meeting.

Investigators should be aware that initial Board review most often results in a request for additional information, clarification, or revisions to the protocol prior to the Board giving final approval of the research protocol.

Consideration, discussion, and a vote regarding the proposed research must occur during a properly convened meeting of the IRB. During the meeting, the investigator will be asked to briefly describe his/her research protocol and answer any questions that Board members may have. Following the Q&A period, the investigator is asked to leave and the Board continues their deliberations. These deliberations will include a detailed examination of the protocol, the consent form, and all supporting documentation, including any questionnaires or survey instruments and any recruiting materials.

The Board may come to one of four (4) determinations regarding a request to involve human subjects in research:

- **Approved as submitted**—An approval letter is sent to the investigator in a timely fashion.
- **Approved pending completion of minor modifications and/or clarifications**—The IRB staff will correspond with investigators regarding clarification of minor points and/or modifications to the protocol or consent form. An investigator's response to IRB correspondence may be approved by the Chair and/or Program Manager without review by the full Board. The Chair and/or Program Manager may not disapprove a response, but they may request additional information from the investigator or refer the response to the full Board for additional review. Investigators have the right to directly discuss with the Board requests for revision
- **Deferred**—Studies are deferred when the IRB has substantive concerns or significant requests for clarification. Responses to IRB correspondence in this category will be resubmitted to the full Board for further deliberation.
- **Disapproved**—The IRB retains the final authority for approval of proposed research with human subjects.

Results of Board decisions are reflected in correspondence sent to investigators within approximately three to five (3–5) working days following the IRB meeting. Letters or e-mails sent to investigators will describe any conditions required for approval, may request additional information, and will indicate the next step, if any, in the review process.

During the review process, the Board will also determine whether the protocol requires review more often than on an annual basis.

Research Eligible for Expedited Review

Expedited review, as defined by 45 CFR 46.110, allows the IRB Chair, an individual Board member, or a designated subcommittee of the IRB, to evaluate and approve specific types of minimal risk research. All studies received by the IRB Office are evaluated for possible expedited review. If the Office determines that a protocol qualifies for expedited review, and the IRB Chair concurs, the complete protocol packet is given to one or more Board members for review. Reviewers conducting an expedited review may exercise all the authority of a convened Board meeting except that they may not disapprove a study. When the reviewer(s) cannot approve the research under expedited review, the study will be referred to the full Board for review at the next scheduled meeting. Investigators should note that some of the expedited review categories may not apply to "vulnerable" populations, such as pregnant women, children, prisoners, or mentally incompetent persons.

Investigators will receive written notification of IRB action resulting from an expedited review. Such action may include approval or a request for further information. Information about research protocols approved under expedited review will be provided to Board members during a legally convened meeting of the full Board.

> ***Note:*** *Minimal risk is the probability and magnitude of harm or discomfort anticipated in the research are not greater, in and of themselves, than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.*

According to 45 CFR 46, research involving no more than minimal risk may receive expedited review. Additionally, the involvement of human subjects must fall into one or more of the following categories:

- The study of existing data documents, records, pathological specimens, or diagnostic specimens.
- Collection of blood samples by venipuncture, in amounts not exceeding 550 milliliters in an eight-week period, and not more than two times per week from subjects 18 years of age or older who are in good health and not pregnant, and weigh at least 110 lb.
- Research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required.
- Collection of excreta and external secretions including sweat, uncannulated saliva, placenta removed at delivery, and amniotic fluid at the time of rupture of the membrane prior to or during labor.
- Collection of hair and nail clippings in a non-disfiguring manner or deciduous teeth and permanent teeth, if patient care indicates a need for extraction.
- Collection of mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings, or sputum collected after saline mist nebulization.
- Collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of teeth and the process is accomplished in accordance with accepted prophylactic techniques.
- Recording of data from subjects 18 years of age or older using noninvasive procedures routinely employed in clinical practice. This includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy. It also includes such procedures as weighing, testing sensory acuity, electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, diagnostic echography, and electroretinography. It does not include exposure to electromagnetic radiation outside the visible range (e.g., x-rays, microwaves).
- Moderate exercise by healthy volunteers.
- Voice recordings made for research purposes, such as research of speech defects.
- Research on individual or group characteristics or behavior, or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.
- Review of minor changes in previously approved research or for cases where all protocol-related interventions have been completed and the protocol remains active only for long-term follow-up on subjects.

> ***Note:*** *The activities listed above should not be considered minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when specific circumstances of the proposed research involve no more than minimal risk to human subjects.*

The expedited review procedure may **not** be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections have been implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

The expedited review procedure may **not** be used for classified research involving human subjects.

> ***Note:*** *Standard requirements for informed consent (or its waiver, alteration or exception) apply regardless of the type of review – expedited or convened – utilized by the IRB.*

Review of Classified or Sensitive Human Subjects Research

Classified projects require Central DOE Institutional Review Board Classified review and the LLNL IRB will also need to approve the project. Sensitive projects require review by the convened IRB. Normal review in an unsecured environment is preferred as long as the research can be accurately and comprehensively described to the IRB, and no classified or sensitive information is relevant to the protection of human subjects. If the research cannot be subjected to normal review, the IRB Chair may determine that it should be reviewed at a meeting of the IRB conducted in a secure environment. A majority of the members of the IRB, including at least one nonscientist, must be present at this meeting. Each member present must have the appropriate security clearance.

Amendments and Modifications to Currently Approved Research

Substantive changes in research during the period for which IRB approval has already been given shall not be initiated by investigators without IRB review and approval. The only exception to this policy is if it becomes necessary to revise a protocol to eliminate apparent immediate hazards to the subject. These changes must be reported immediately to the IRB Office.

Amendments or modifications to previously approved research, submitted between scheduled continuing reviews that involve only minor changes in previously approved protocols or minor changes in consent forms may qualify for expedited review. Only changes that do not increase the risk to research subjects may receive an expedited review. Modifications to approved protocols that may affect the risk to subjects are forwarded to the full IRB for review. (See Making Modifications to Currently Approved Research for further information about modifying currently approved research.)

Continuing Reviews

All protocols that have been approved by the IRB will be reviewed on a continuing basis at intervals appropriate to the degree of risk as determined by the IRB, but not less than once per year. The IRB will determine the frequency of continuing review when it grants final approval to a proposed study. A standard approval letter will be used to notify the investigator of the approval and length of approval for each proposal. The IRB may be called into an interim review session by the Chair at the request of an IRB member or investigator to consider any matter concerned with the rights and welfare of any subject.

Additional Types of Review

The IRB will determine whether a project requires more than annual review and may require an appropriate monitoring procedure that could include monitoring of the consent process, observation of the research procedures, verification from a third party that there have been no material changes in the research since the previous review, and review of research-related records.

Review Criteria

Protocols

In light of the information provided in the research plan of the protocols, the IRB determines whether protection of human research subjects is adequate, in accordance with the following criteria.

Risks

The IRB will identify the risks associated with the research and will determine whether risks, if any, to a subject are reasonable in relation to the anticipated benefits and the importance of the knowledge that may reasonably be expected as a result. The IRB must also determine if risks to subjects are minimized by (1) using procedures that are consistent with sound research design and do not unnecessarily expose subjects to risk and (2) using procedures that are already being performed on the subjects for diagnostic or treatment purposes, whenever appropriate.

Where appropriate, the IRB will determine whether the research plan makes adequate provision for monitoring the data collected to assure the safety of the subject, and that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

The IRB is also required to ensure that potential subjects will be provided with an accurate and fair description of the risks or discomforts and the anticipated benefits and to determine intervals of periodic review.

The IRB will not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

Subject selection

The IRB will determine that the selection of subjects is equitable. In making this assessment, the IRB shall take into account the purposes of the research, the setting in which the research will be conducted, and the population from which subjects will be recruited.

Where some or all subjects are likely to be vulnerable to coercion or undue influence, such as persons who are economically disadvantaged, or employees for whom the research investigator has supervisory responsibility, the IRB will determine that appropriate additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Incentives for participation

The IRB will review any proposed reimbursement (in cash or in kind) that the subject will receive as a result of participating in the research activity. The Board must determine that payments do not represent "undue inducement" by leading to a decrease in either the voluntariness or the understanding with which subjects agree to participate. The Board must also determine that payments to subjects do not result in economically disadvantaged populations bearing an unduly large share of the risks and burdens of research participation.

Qualifications of Research Personnel

Procedures requiring special skills on the part of the investigators, licensure, accreditation, and/or experience in qualifying the investigator for the performance of the proposed procedures are reviewed by the IRB. In addition, the IRB will consider the facilities and equipment used to conduct the research and maintain the rights and welfare of the subjects.

Termination of IRB Approval

The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval will include a statement of the reasons for the IRB's action and will be reported promptly to the investigator, appropriate institutional officials, OHRP, any other sponsoring federal agencies, and/or private sponsors, if appropriate.