IRB Institutional Review Board

#9
Additional Considerations when Developing a Protocol

The basic elements for developing any protocol involving human subjects are discussed in Guidelines for Developing a Basic Protocol. There are, however, specific areas of research that require additional consideration. The following topics are discussed in further detail in this section:

- Foreign collaborations
- Food and Drug Administration (FDA)-regulated studies
- Inclusion of vulnerable populations in research
- Federally sponsored studies
- Use of surveys, questionnaires, or interviews
- Use of advertisements, press releases, or bulletin board announcements
- Studies involving toxic or other potentially harmful agents

Researchers are encouraged to review the information provided in this section when first developing their research protocol. The IRB Office is available to answer any questions investigators may have regarding these types of studies.

Foreign Collaborations

Investigators and/or LLNL staff working on projects outside of the United States that employ humans as experimental subjects are responsible for obtaining copies of foreign approvals and other documentation necessary for LLNL IRB review. In addition, the investigator must assure the LLNL IRB that an ethics review board, fully constituted in the geographic vicinity of the actual work, has reviewed and approved the project, and that the major aspects of U.S. federal regulations were observed. This means that:

- The cognizant foreign institution's ethics review board comprises members that were selected according to the U.S. federal guidelines for IRB membership.
- If the local language is other than English, the experimental protocol and documents that are provided to subjects (e.g., informed consent documents, recruitment materials, questionnaires, etc.) must be written in the appropriate language, translated into English, and included in the application packet to the LLNL IRB.
- Minutes of the meeting during which the protocol was approved are translated into English and forwarded to the LLNL investigator.
- Investigators must be knowledgeable of and sensitive to issues, such as the expectations of the local volunteer population, the practices of the local collaborating experimenter(s), the meaning of informed consent, and possible coercion and enticement activities.
- The IRB Office must report all collaborations involving foreign countries to the DOE.

> ***Note:*** *Human subjects research involving projects outside the United States are typically complex. Investigators are encouraged to contact the IRB Office as early as possible for assistance.*

Studies Involving Products Regulated by the Food and Drug Administration

The FDA regulates all human subjects research involving drugs, medical devices, and biologics, including the ingestion or injection of radio-labeled compounds. FDA regulations require IRB review and informed consent (21 CFR parts 56 and 50, respectively) in much the same way that the DHHS or DOE does. However, the FDA has several additional reporting conditions that directly involve investigators.

If an investigator is the developer of the drug or device and no commercial manufacturer is involved, then either the investigator or the investigator's institution may be the sponsor for purposes of designing and organizing clinical trials. The sponsor is responsible for (1) submitting an investigational new drug (IND) or investigational device exemption (IDE) application to the FDA and (2) providing a copy of the FDA's response to the IRB. Sponsors also have important administrative and reporting requirements above and beyond those of investigators. LLNL employees or contractors contemplating the dual role of sponsor/investigator should consult with the IRB Office about these additional responsibilities.

Clinical trials conducted under an IND or IDE issued by the FDA must adhere to the protocol as submitted by the investigator. Any modification (e.g., extension to another age group, use of a different dose, or change in subject eligibility criteria), must be approved by the FDA and the IRB prior to implementation, unless immediate action is required to eliminate apparent immediate hazards to human subjects. Any changes made to eliminate an immediate hazard must be reported to the IRB Office within five business days.

> ***Note:*** *Deviation from the approved protocol may subject the investigator to sanctions by the FDA and/or the IRB, and, possibly, to charges of scientific misconduct.*

- **Sponsor–Investigator–IRB Interactions**

Investigators are generally expected to provide the communication link between the IRB and a sponsor. Such linkage is agreed to by the sponsors and investigators when they sign forms FDA-1571 and FDA-1572, respectively, for drug and biologic studies or an investigator agreement for device studies. However, the regulations do not prohibit direct sponsor to IRB contact. There are occasions when direct communication between the IRB and the sponsor may facilitate resolution of concerns about study procedures or specific wording in an informed consent document. In those cases, the investigator will be kept apprised of the discussion.

FDA regulations require that a sponsor assure the FDA that a study will be conducted in compliance with the informed consent and IRB regulations (21 CFR 50 and 56). Sponsors, in turn, are expected to rely on the investigator who assures the sponsor, on form FDA-1572 for drugs and biologics or the investigator agreement for devices, that the study will be reviewed by the investigator's IRB.

The IRB will notify an investigator in writing of its decision to approve, disapprove or request modifications in a proposed research activity [21 CFR 56.109(e)]. The investigator should make this correspondence available to the sponsor, as this documentation provides the sponsor with reasonable assurance that the IRB has complied with 21 CFR 56 and that it will be responsible for initial and continuing review of the study.

A sponsor and/or investigator may reach an impasse with the IRB about study procedures or specific wording in an informed consent document. Any disagreements between a sponsor, the IRB, and an investigator should be resolved through appropriate communication among those parties, with the IRB having final say about what it will and will not approve. The FDA does not mediate such disagreements.

➢ Types of FDA-Regulated Products

The FDA regulations include specific instructions for the content of records that must be created and maintained in clinical investigations of drugs and devices [21 CFR 312.62 and 21 CFR 812.40].

Medical devices

A medical device is defined, in part, as any health-care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices include, among other things, surgical lasers, wheelchairs, sutures, pacemakers, intraocular lenses, and orthopedic pins. Medical devices also include diagnostic aids, such as reagents and test kits for in vitro diagnosis of disease and other medical conditions such as pregnancy.

Clinical investigations of medical devices must comply with the FDA's informed consent and IRB regulations. Federal requirements governing investigations involving medical devices were enacted as part of the Medical Device Amendments of 1976 and the Safe Medical Devices Act of 1990. These amendments to the Federal Food, Drug, and Cosmetic Act define the regulatory framework for medical device development, testing, approval, and marketing.

Except for certain low-risk devices, each manufacturer who wishes to introduce a new medical device to the market must submit a premarket notification to the FDA. The FDA reviews these notifications to determine if the new device is "substantially equivalent" to a device that was marketed prior to passage of the Amendments (i.e., a "pre-amendment device"). If the new device is deemed substantially equivalent to a pre-amendments device, it may be marketed immediately and is regulated in the same regulatory class as the pre-amendments device to which it is equivalent. If the new device is deemed not to be substantially equivalent to a pre-amendments device, it must undergo clinical testing and pre-market approval before it can be marketed unless it is reclassified into a lower regulatory class.

Device Classifications

In 1976, Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act gave the FDA the responsibility for assuring the safety and effectiveness of devices intended for human use. In implementing these Amendments, the FDA has classified devices according to their level of risk.

- **Class I devices**—devices for which safety and effectiveness can be assured so long as there is compliance with provisions for notification of defects, repair, replacement or refund, records, and reports. Device manufacturers are required to also avoid distribution of adulterated, misbranded, or banned devices.
- **Class II devices**—devices that require something more than proper labeling and quality assurance to ensure their safety and effectiveness.
- **Class III devices**—devices that are life-sustaining, life-supporting, implanted in the body, or of substantial importance in preventing impairment.

- **510(K) devices**—devices that are substantially equivalent to one marketed prior to the enactment of the Medical Device Amendments (1976). Such devices may be sold without additional proof of safety and efficacy under Section 510(K) of the federal Food, Drug, and Cosmetic Act. These devices are thus commonly referred to as "510(K)" devices. A sponsor planning to market the device must notify the FDA 90 days in advance of placing the device on the market. If the FDA agrees that the device is substantially equivalent to one already on the market, the device may then be sold without further research. Research activities involving a 510(K) device do not require an IDE, but do require approval by the LLNL IRB prior to the initiation of research.

If the FDA determines that a new device is not substantially equivalent to a pre- amendment device, the new device is automatically designated a Class III medical device and the sponsor is required to obtain pre-marketing approval from the FDA. Studies conducted to develop safety and effectiveness data for such devices must be conducted according to the FDA requirements of Investigational Devices (21 CFR 812).

Investigational Device Exemptions (IDEs)

An investigational device is a medical device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. Clinical investigations undertaken to develop safety and effectiveness data for medical devices must be conducted according to the FDA regulations (21 CFR 812). Certain clinical investigations of devices (e.g., certain studies of lawfully marketed devices) may be exempt from [21 CFR 812.2(c)].

Unless exempt from the FDA regulations, an investigational device must be categorized as either "significant risk" (SR) or "non-significant risk" (NSR). (Examples of each kind, published by the FDA, are included in Appendix 8.) The subsequent determination of whether a device is an SR or NSR is made by the sponsor. The proposed study is then submitted either to the FDA (for SR studies) or to the IRB (for NSR studies).

The IRB's SR/NSR subsequent determination has significant consequences for the study sponsor, the FDA, and prospective research subjects. SR device studies must be conducted in accordance with the full IDE requirement (21 CFR 812), and may not commence until the FDA has approved the IDE application and the IRB has approved the study. Submission of the IDE application enables the FDA to review information about the technical characteristics of the device, the results of any prior studies (laboratory, animal, or human) involving the device, and the proposed study protocol and consent documents. Based upon the review of this information, the FDA may impose restrictions on the study to ensure that risks to subjects are minimized and do not outweigh the anticipated benefits to the subjects and the importance of the knowledge to be gained.

In contrast, NSR device studies do not require submission of an IDE application to the FDA. Instead, the sponsor is required to conduct the study in accordance with the "abbreviated requirement" of the IDE regulations [21 CFR 812.2(b)]. Unless otherwise notified by the FDA, an NSR study is considered to have an approved IDE if the sponsor fulfills the abbreviated requirements. The abbreviated requirements address, among other things, the requirements for IRB approval and informed consent, record-keeping, labeling, promotion, and study monitoring. NSR studies may commence immediately following IRB approval.

Once the final SR/NSR decision has been rendered by the IRB (or the FDA), the IRB will determine whether or not the study should be approved, using the same criteria it would use in considering approval of any research involving an FDA-regulated product (21 CFR 56.111). Some NSR studies may qualify as "minimal risk" studies, and thus may be reviewed through an expedited review procedure (21 CFR 56.110). However, the FDA considers all SR studies to present more than minimal risk, and thus, full IRB review is necessary. In making its determination on approval, the IRB should consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures.

Additional information about device studies can be found on the FDA's Website.

- **Studies involving SR devices**—Sponsors are responsible for making an initial risk assessment regarding an investigational device. An SR device, by definition, is an investigational medical device that presents a serious risk to the health or safety of the research subjects. Such a device is:
  - Intended for use as an implant; or
  - Purported to be useful in supporting or sustaining human life; or
  - Intended for a use that is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise preventing impairment of human health; or
  - One that otherwise presents a serious risk to the health, safety, or welfare of subjects.
- **Studies involving NSR devices**—Investigators should clearly explain in their applications to the IRB why the sponsor believes the device presents no significant risk to study participants and provide supporting information, such as reports of prior investigations. The investigator should also inform the IRB whether the FDA or any other IRB has made a risk assessment and what the results of those assessments were. The IRB will then make an independent assessment of the risk of the investigational device to be used in the study. If the IRB agrees that the device poses no significant risk to research subjects, the investigator will not be required to obtain an IDE from the FDA to conduct the study. If the IRB instead believes that the device poses significant risk to research subjects, the investigator will be notified by the IRB Office. The investigator is then required to notify the sponsor of the IRB's decision within five business days, and the sponsor must then notify the FDA of the IRB determination.

Following the IRB determination of the risk involved, the IRB will review the protocol to make a risk/benefit assessment and consider the acceptability of the consent form, as described elsewhere in this document.

Investigators should clearly explain in their protocol whether the sponsor believes that a device poses a significant risk to subjects when used in the context of the research activity, and if so, why. In addition, investigators should inform the IRB of results of any FDA or other IRB risk assessment of the device. Supporting information, such as reports of prior investigations or risk determinations, should be provided by the sponsor. The IRB will make an independent assessment of the risk of the investigational device to be used in the study. If the IRB agrees that the device poses significant risk to research subjects, the investigator will be required to obtain an IDE from the FDA to conduct the study. Following the IRB determination of the risk presented, the IRB will make a risk/benefit assessment and determine the acceptability of the consent form in accordance with normal review procedures (see IRB Review Process).

Additional information regarding how to obtain an IDE can be found on the FDA's Website.

When submitting a research protocol involving a medical device, the investigator must complete and attach Form LL6656, IRB Determination of Risk for Investigational Devices, and, when one exists, an Investigator's Brochure.

- ***Investigational drugs***

Research involving experimental or licensed pharmaceuticals is regulated primarily by the FDA and provides a transition from "promising" basic or laboratory research to "accepted" therapeutic or diagnostic procedures for patients. FDA guidelines for the investigational use of a new drug can be found at the following Website: Investigational New Drug (IND) Application.

Investigational drugs include the following:

- Products that are not generally recognized as being safe and effective for any use under the conditions prescribed, recommended, or suggested by the FDA.
- Products that are already approved by the FDA as safe and effective for specific indications but are being studied for new indications (or doses, strengths, or frequency) other than those that have been approved (e.g., off-label use).

Federal law prohibits the distribution of new drugs until the FDA has reviewed clinical data, determined that a particular product is safe and effective for a specific use in human patients, and issued a pre-market approval. To test a new drug in clinical trials, the investigator must obtain an exemption from that law. Thus, a drug sponsor is required to apply and receive FDA approval for an IND exemption before tests with human subjects may begin.

The FDA notifies the sponsor of the date it receives the application. Upon receipt of the application, the FDA requires 30 days for scientists to review the materials and if necessary, request additional information, require modifications or disprove the application. The LLNL IRB will not provide formal approval for a study until the 30 days have elapsed and the FDA has either provided an IND number or advised the sponsor that an IND is not required [21 CFR 312.40(b)].

If the investigator is the developer of the drug and no commercial manufacturer is involved, then either the investigator or the investigator's institution may be the sponsor for purposes of designing and organizing clinical trials. The sponsor is responsible for submitting an IND application to the FDA and providing a copy of the FDA's response to the IRB. Sponsors also have important administrative and reporting requirements above and beyond those of investigators. LLNL investigators contemplating the dual role of sponsor/investigator should consult with the FDA's Center for Drug Evaluation and Research website to better understand the considerable time and resources associated with sponsorship.

Types of Drug Trials

The FDA has defined 4 types of drug trials, ranging from initial investigations of new drugs conducted with healthy volunteers to post-market studies to delineate additional information about the drug's risks, benefits, and optimal use. Additional information about the four phases is provided below.

- **Phase 1 drug trials**—Drug trials that include the initial introduction of an investigational new drug into humans. Typically, these studies are closely monitored and conducted with healthy volunteers even when the drug is intended for use in patients with a particular disease. Phase 1 trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses (to establish a safe dose range), and, if possible, to gain early evidence of effectiveness. The ultimate goal of Phase 1 trials is to obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled, sufficiently valid Phase 2 studies. Other examples of Phase 1 studies include studies of drug metabolism, structure-activity relationships, and mechanisms of actions in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects involved in Phase 1 investigations is generally in the range of 20–80.
- **Phase 2 drug trials**—Drug trials that include controlled clinical studies conducted to evaluate the drug's effectiveness for a particular indication in patients with the disease or condition under study, and to determine the common short-term side effects and risks associated with the drug. These studies are typically well-controlled, closely monitored, and conducted with a relatively small number of patients—usually no more than several hundred subjects.
- **Phase 3 drug trials**—Drug trials that involve the administration of a new drug to a larger number of patients in different clinical settings to determine its safety, effectiveness, and appropriate dosage. They are performed after preliminary evidence of effectiveness has been obtained, and are intended to gather necessary additional information about effectiveness and safety for evaluating the overall benefit/risk relationship of the drug, and to provide an adequate basis for physician labeling. In Phase 3 studies, the drug is used the way it would be administered when marketed. When these studies are completed and the sponsor believes that the drug is safe and effective under specific conditions, the sponsor applies to the FDA for approval to market the drug. Phase 3 trials usually involve several hundred to several thousand patient–subjects.
- **Phase 4 drug trials**—Concurrent with marketing approval, the FDA may seek agreement from the sponsor to conduct certain post-marketing (Phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in Phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

Research concerning new treatments for certain life-threatening conditions (e.g., cancer, AIDS, emergency-room interventions) may progress differently through the four phases. Investigators interested in studies involving such products should contact the FDA for further information.

➢ *Studies involving exposure to internal and external ionizing radiation*

For research involving exposure to ionizing radiation from internal radionuclides or external radiation sources, the FDA regulations require that the research be reviewed and approved by a Radioactive Drug Research Committee (RDRC) as well as by the IRB. LLNL does not have an RDRC. Therefore, the actual dosing of radio-labeled compounds or otherwise exposing research subjects to ionizing radiation is not allowed on-site at LLNL.

Exposing human research subjects to radio-labeled compounds or ionizing radiation must occur at a collaborating institution, and with the approval of that institution's IRB and their RDRC. The LLNL IRB will require copies of all documentation submitted to the collaborating institution's RDRC, as well as a copy of the RDRC approval letter. This documentation must be included in the application packet that is submitted to the LLNL IRB, and will be reviewed by members of the IRB's Subcommittee on Dosimetry and Toxicology prior to full-board review.

Any human research involving ionizing radiation requires that investigators use an IRB-reviewed and approved consent form. The consent form should clearly outline, in layperson's terms, the quantity, significance, and risk, if any, of the radiation absorbed dose. The dose is usually compared with background radiation, the occupational exposure limit of 5000 mrem per year, or radiation doses received from familiar medical procedures (e.g., a chest x-ray). The explanation should be written in terms that are understandable to a person with an eighth-grade education.

Emergency Use of an FDA-Regulated Test Article

FDA regulations allow for the emergency use of an investigational drug, biologic, or device when an individual is in an immediately life-threatening situation for which no standard acceptable treatment is available, and there is not sufficient time to obtain IRB approval for use of the FDA- regulated test article [21 CFR 56.102(d)]. Medical personnel faced with the need for the emergency use of an investigational drug, biologic, or device will do so only under approved LLNL Health Services procedures. The FDA does require that emergency use of a test article be reported to the IRB within five business days (21 CFR 56.104).

On occasion, a sponsor will agree to allow the emergency use of a test article, but requires "an IRB approval letter" before the test article can be shipped. Under this circumstance, and on a case-by-case basis, the IRB may provide a letter stating that the IRB is aware of the proposed emergency use and that the use appears to meet the requirements of 21 CFR 56.102 (d).

Notifying the IRB of the emergency use of an FDA-regulated product should not be construed as IRB approval for future use. If medical personnel anticipate there may be subsequent need for the investigational product, a research protocol should be submitted to the IRB for review and approval.

Inclusion of Vulnerable Subjects in Research

Children

California law identifies children as those who have not yet reached their 18th birthday (i.e., 0–17 yr.). Investigators who intend to involve children in human subjects research should familiarize themselves with the federal regulations (45 CFR 46, Subpart D), which require "additional safeguards . . . to protect the rights and welfare" of children involved in research as they are "vulnerable to coercion and undue influence." Investigators are also encouraged to review The Consent Process for information about obtaining assent from children.

Federal regulations allow the IRB to approve research involving children only if special provisions are met and the research falls into one of four categories, based on the degree of risk and benefit to individual subjects. Those categories are discussed in the following sections.

Research involving no more than minimal risk

When the IRB finds that no greater than minimal risk to children is presented, it may approve the proposal **only if** adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

If the IRB finds that more than minimal risk to children is presented by an intervention or procedure but that the intervention or procedure has the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, the IRB may approve the research only if (1) the risk is justified by the anticipated benefit to the subjects, (2) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches, and (3) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

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

If the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not have the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, the IRB may approve the research **only if** (1) the risk represents a minor increase over minimal risk, (2) 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, (3) the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition, **and** (4) adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.

Research not otherwise approvable that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

If the IRB does not believe the research proposal meets any of the requirements set forth above, it may still approve the application but **only if** (1) 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 children, **and** (2) the Secretary of the Department of Health and Human Services DHHS, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, or law) and following an opportunity for public review and comment, has determined either:

1. The research, in fact, satisfies one of the conditions set forth above, or
2. The research satisfies the following conditions: (a) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (b) the research will be conducted in accordance with sound ethical principles; and (c) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.

For further information and guidance regarding children as research subjects, investigators should carefully review the applicable federal regulations found in 45 CFR 46, Subpart D, "Additional DHHS Protections for Children Involved as Subjects in Research." Investigators should also review assent/parent permission requirements.

Pregnant Women and Fetuses

If it is possible that pregnant women and their fetuses may be involved in a study, the protocol should include an assessment of the advantages and consequences of their inclusion in the study. This type of research poses special concerns for the IRB.

The fetus is unique and yet has an inextricable relationship to the mother. A fetus cannot consent to participate as a research subject. In the early 1970s, Congress required that the National Commission for the Protection of Human Subjects study the subject of fetal research. The Commission, in its findings, did not define the "personhood" of the fetus; however, it did recognize the genetic heritage and vulnerability of the fetus and affirmed that it should be treated respectfully and with dignity, regardless of its life prospects. The Commission also affirmed the legitimacy and importance of fetal research for improving the health of fetuses both in the present and future. In 1975, the DHHS fully implemented the recommendations of the National Commission (45 CFR 46, Subpart B). The rule has been amended several times, most recently in 2001.

In addition to the general requirements for review of research by the IRB, prior research with animal subjects and, if reasonable, research with non-pregnant persons should form the basis of the risk/benefit assessment for fetal research. Investigators who propose research involving human fetuses are required to assure the IRB that they are seeking information not obtainable in any other fashion. There are three types of fetal research: (1) the study is directed toward pregnant women in which the fetus is indirectly involved in the research; (2) the study is directed toward the fetus; and (3) studies in which both the pregnant woman and the fetus are the subjects of the research activity.

The IRB may only approve in utero research when one of the following two criteria is met in addition to all other applicable institutional, federal, state, and local requirements:

1. The purpose of the research is to meet the health needs of the fetus and is conducted in a way that will minimize risk (e.g., a new technique for fetal transfusions for Rh incompatibility); or
2. The research poses no more than minimal risk to the fetus and the purpose of the activity is the development of important biomedical knowledge that is unobtainable by other means.

After lengthy review, the National Commission determined that there is no difference between the moral status of a fetus destined for abortion and that of a fetus that is expected to be carried to term. Therefore, only those research procedures that are acceptable for a fetus going to term may be performed in anticipation of abortion, to preserve the mother's right to change her mind about ending the pregnancy. To address the numerous concerns that are raised by research activities involving the use of fetuses, the federal regulations have provided the following clarifications in the areas of ex utero, in utero, and fetal tissue, as discussed below:

Research involving the fetus ex utero (neonate)

The federal regulations indicate that a neonate (delivered fetus) is viable if, in the judgment of physicians, it is likely to survive to the point of sustaining life independently, given the benefit of available medical therapy. If the neonate is viable, the regulations for research involving children apply.

Federal regulations define a nonviable neonate as follows: "an expelled or delivered neonate which, although it is living, cannot possibly survive to the point of sustaining life independently, even with the support of available medical therapy. Although it may be presumed that an expelled or delivered neonate is nonviable at a gestational age less than 20 weeks and weight less than 500 grams, a specific determination as to viability must be made by a physician in each instance." If a neonate is nonviable, 45 CFR 46, Subpart B applies to the research activity.

Consent for research involving fetuses in utero

Because of the father's continuing responsibility for his offspring, the consent of both parents generally is required for research involving the fetus. The consent of the father is not required, however, in the following circumstances:

- The research is designed to meet the health needs of the pregnant woman.
- The father is not competent.
- The father's identity or whereabouts cannot reasonably be ascertained.
- The father is not reasonably available.
- The pregnancy resulted from rape.

Research involving fetal tissue

The use of dead fetuses, fetal material, and the placenta is gaining considerable attention due to the lifting of a moratorium on federally funded research involving the therapeutic transplantation into humans of fetal tissue obtained from induced abortions, and from recent controversy over the use of fetal stem cells.

When the fetal tissue is derived from an abortion, the decision to terminate a pregnancy and the actual abortion procedures must be kept independent from the retrieval and use of fetal tissue. The timing and method of abortion should not be influenced by the potential uses of fetal tissue for transplantation or medical research.

Fetal tissue from induced abortions should not be used in medical research without the prior consent of the pregnant woman. However, the decision and consent to terminate pregnancy must precede discussion of the possible use of the fetal tissue in research and any request for such consent that might be required for that use. A woman's consent to donate fetal remains is sufficient for the use of fetal tissue. Consent should be obtained in compliance with state law and the Uniform Anatomical Gift Act.

Payments and other forms of remuneration associated with the procurement of fetal tissue are prohibited, except payment for reasonable expenses occasioned by the actual retrieval, storage, preparation, and transportation of the tissue.

Potential recipients of fetal tissues, as well as research and health care participants, should be informed about the tissues in question. This information should be provided to the prospective subjects in the consent form.

The pregnant woman should be prohibited from designating the transplant recipient of the fetal tissue. Anonymity between donor and recipient should be maintained, so that the donor does not know who will receive the tissue, and the identity of the donor is concealed from the recipient and transplant team. Experimental transplants performed with fetal tissue from induced abortions provided by a family member, friend, or acquaintance should be prohibited.

Prisoners

Prisoners are considered vulnerable because they are in a restrictive, institutional environment that affords little opportunity for making choices, earning money, communicating with outsiders, or obtaining medical care. The National Commission for the Protection of Human Subjects found that prisoners often volunteer for medical research as a means of access to a competent medical examination, because health care is woefully inadequate in most prisons.

Because their autonomy is limited, prisoners may participate only in certain categories of research, and special precautions are needed to ensure that their consent to participate in the research is both knowing and voluntary (45 CFR 46.302). Prisoners may participate in the following kinds of research:

- Studies of the possible causes, effects, and process of incarceration and criminal behavior, if those studies present no more than minimal risk or inconvenience to the subjects.
- Studies of prisons as institutions, or of prisoners as incarcerated persons, if those studies present no more than minimal risk or inconvenience to the subjects.
- Research on conditions affecting prisoners as a class (e.g., research on hepatitis, drug addiction, sexual assaults, and other conditions more prevalent in a prison population than elsewhere), but only after the Secretary of DHHS, has consulted with experts in medicine, ethics, and penology and published a notice approving the proposed research in the Federal Register.
- Research on practices that are intended, and reasonably likely, to enhance the well-being of the subjects; however, if some of the prisoners will be assigned to control groups which will not benefit from the research, then the study must first be approved by the Secretary of DHHS, after consultation with appropriate experts, as described above.

Coworkers

Under the guidance of DOE Order 443.1, *Protection of Human Subjects in Classified Research,* LLNL employees are vulnerable to perceived, even if not intended, pressures to appear cooperative and supportive of their supervisor's work. Potentially affected groups include office staff, lab technicians, postdoctoral fellows, students, and contractors. Various procedures have been suggested to reduce the possibility of unintended coercion, while still permitting these individuals to participate as subjects in research, and include:

- Posting IRB-approved advertisements throughout the Laboratory to recruit subjects from a broad base of employees and contractors, and
- Avoiding any personal solicitations of coworkers by investigators, or fellow coworkers.

The IRB does not encourage recruitment procedures that target employees from the investigator's own lab or office. The IRB, however, will consider requests to recruit coworkers on a case-by-case basis

Studies Sponsored by Federal or State Agencies

Investigators must submit a complete copy of the federal or state grant/proposal to the IRB when requesting review of human studies. Some agencies do not require IRB review until the investigator has been notified that funding for the research is likely. Investigators should check with their sponsors for guidance. However, investigators are strongly encouraged to contact the IRB Office at the beginning of the protocol development process to avoid delays in receipt of funding.

Use of Surveys, Questionnaires, or Interviews (by Phone or in Person)

The IRB considers interviews, surveys, and questionnaires part of the experiment. They must, therefore, be reviewed and approved by the IRB prior to use. Normally this is done as part of the IRB's review and approval of the entire protocol, so investigators should assure that these accompanying documents are submitted to the IRB. Investigators may submit draft versions of these documents for the initial IRB review. The IRB, however, is required to review any subsequent modifications. If the IRB approves the protocol prior to the review of the finalized document, the investigator will receive an approval notice indicating that the surveys, etc. cannot be used until the final version has been reviewed and approved by the IRB. If a protocol requires an interview, the investigator must attach a script of the interview, including the introduction, questions, and closing comments.

Subjects assume that information requested in surveys, interviews, and questionnaires is relevant, necessary, and specific to the research project; they should not constitute "fishing trips." The IRB will expect that the investigator can clearly explain the necessity of each question to any subject or the IRB.

Use of Advertisements, Press Releases, or Bulletin Board Announcements

Many recruitment techniques are used to identify potential research subjects. Common recruitment techniques include the use of contact letters, flyers, posters, newspaper ads, and press releases. Television and radio spots, websites, e-mail messages, and electronic mailers are also considered direct advertisements. All direct advertising must have IRB approval before being used for recruiting subjects. It is considered part of the informed consent and subject selection process. In this regard, all direct advertising must:

- Be reviewed by the IRB for the information contained and the mode of communication.
- Not be coercive or use undue pressures.
- Not be misleading to subjects.
- Not overemphasize payment or overstate benefits.

Studies Involving Toxic or Other Potentially Harmful Agents

Careful consideration is required for the use of human subjects in research that involves exposure to potentially toxic materials or potentially harmful physical agents (e.g., laser or microwave radiation, noise, heat, etc.). To allow the LLNL IRB to fully evaluate the risks and benefits of the proposed work, investigators must submit detailed information documenting the expected exposure of subjects to these agents and must have their detailed dose calculations independently reviewed and validated. Any qualified independent party, within or outside the Laboratory, can perform this review.

Subject Matter Experts will be contacted to obtain assistance in identifying qualified people to perform these calculations. (Please contact the IRB Office for referral.)

Documentation provided to the IRB must cover the following:

- The assumptions used in subject selection, the agent and quantity used, the route of exposure, the frequency or duration of exposure, any assumptions regarding the amount of material absorbed, and any personal protective equipment used.
- The calculations that yielded the estimated dose and the quantitative risk associated with the exposure, whenever possible.
- References to community or occupational standards and, where possible, common exposures.
- A statement that the reviewer has no direct involvement in the research.
- A brief (2- to 4-sentence) summary of the qualifications of the reviewer.

If the proposed subjects are employees of LLNL or a collaborating institution, and the proposed exposure is to chemical agents involving inhalation only, and for which there is an existing Occupational Safety and Health Administration (OSHA)/U.S. Department of Labor Permissible Exposure Limit or American Conference of Governmental Industrial Hygienists Threshold Limit Value, the analysis may be based on exposure rather than absorbed dose.