IRB Institutional Review Board

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Guidelines for Developing a Basic Protocol

A research protocol is intrinsic to planning ethically responsible research and to working with the Lawrence Livermore National Laboratory (LLNL) IRB. In developing a human subjects research protocol, investigators should contemplate systematically (in writing) the research rationale, methods, and procedures, and the steps that will be taken in response to ethical considerations. The LLNL IRB encourages investigators to view the protocol as a planning tool, not simply a bureaucratic hurdle. It is not a form to be tossed together at the last minute. Investigators are encouraged to think through the ethical considerations along with the methodological ones. Treating ethical considerations as an afterthought in the protocol development process may, unfortunately, lead to a research plan that is not workable or approvable from the IRB's perspective. Keeping that in mind, investigators are encouraged to consider the following guidelines when developing a protocol.

Abstract of the Project

The Department of Energy (DOE) requires that LLNL annually provide them with an abstract for each human subjects research project requiring IRB review. The abstract should provide a summary of the proposed project and consist of no more than 750 words. It should be written in non-technical language and should clearly explain the LLNL investigator's role in the research activity. The abstract will be included in the Laboratory's annual report. The DOE will post the abstracts on a public server. Therefore, it should not contain sensitive information.

Detailed Description of the Protocol

A detailed description of the protocol will include a discussion of the following eight topics:

- Purpose, Methods, and Procedures
- Subject Selection Process
- Discussion of the Benefits and Risks
- Privacy and Confidentiality Concerns
- Risk/Benefit Assessment
- Financial Considerations for Subjects, if applicable
- Disclosure of Investigator's Personal or Financial Interest in the Research Study and/or Sponsor
- Obtaining Informed Consent

Purpose, Methods, and Procedures

The purposes, methods, and procedures section of the protocol should include the following elements:

- The title and sponsor of the study.
- The purpose of the research and the hypotheses to be tested.
- The historical background of the research, if applicable, referencing key scientific literature.
- An account of the research method, design, and mode of analysis, detailed enough that reviewers can assess scientific validity, including a fully detailed account of procedures that directly affect subjects, their bodily materials, or data.
- The location of the research; specify the exact laboratory, community, institution, etc., where various components of the research are to be performed, the reason why that setting was chosen, and how the investigator happens to have access to it.
- The duration of the project and how this window of time may coincide with other time constraints, such as the duration of funding, etc.

Subject Selection Process

The research protocol should indicate how many subjects will be included in the study and, where relevant, the ethnic background, sex, age, and state of health of prospective subjects. It should explain why a particular population is being used, the source(s) from which subjects will be recruited, and a statement of the selection criteria.

In addition to the above information, investigators will also need to give careful thought and attention to their recruitment procedures. That information must also be presented to the IRB and detailed in the research protocol.

Further information and guidelines regarding recruitment and selection of subjects is discussed below.

Recruitment of subjects

Respect for potential subjects begins with recruitment procedures that ensure the voluntary participation of the subject. Recruitment is the dialogue that takes place between an investigator and a potential subject prior to the initiation of the consent process. In many cases, it is the introduction to the consent process.

Various recruitment tools can be used to inform potential subjects of a research activity and provide them with an opportunity to contact the investigator. Recruitment tools may include flyers, advertisements, press releases, brochures, verbal exchanges, emails, and postings on the Internet. The IRB must review and approve any recruitment tool. Copies of all recruitment materials should be included with the initial application. If the material is not ready at the time of initial application, investigators may submit the material as an amendment to an already-approved project. In all cases, recruitment tools must be approved prior to their use. Advertisements, press releases, etc., may qualify for expedited review. The content of advertisements should be limited to the following information:

- The name of the investigator and contact information.
- A simple and concise description of the purpose of the research.
- General eligibility criteria for participation.
- A truthful description of the possible benefits which may result from participation in the research.
- If subjects are paid for their participation.

Selection of subjects

The systematic selection of subjects based on easy availability, their subordinate position, or social, racial, sexual, economic, or cultural biases institutionalized in society results in an uneven distribution of the benefits and the burdens of research.

The IRB will closely examine research that selects subjects solely due to their easy availability, subordinate position, or susceptibility to manipulation.

> ***DOE Order 443.1B, Protection of Human Research Subjects***
> *Protected Classes. Research involving fetuses, pregnant women, and in vitro fertilization; prisoners; or children shall be conducted in accordance with 45 CFR Part 46 Subparts B, C, and D. Care should also be taken to ensure the proper protections are in place for DOE or DOE site Federal and/or contractor employees who become human subjects of research.*

The IRB will seek assurance that potential subjects are not coerced into participating in research, nor must they fear the loss of some benefit to which they are otherwise entitled if they choose not to participate. A person in authority, such as a supervisor recruiting coworkers, must take special precautions to ensure that a potential subject's decision to participate in research is not based on subtle pressures such as fear of a poor appraisal or loss of job.

Investigators proposing to recruit and select subordinates, students, or other coworkers as research subjects must justify the necessity for the inclusion of these individuals in the protocol. The LLNL IRB strongly discourages the recruitment of subordinates and will closely scrutinize the precautions that are put in place to prevent the appearance of coercion or undue influence in the recruitment of these subjects. The protocol should clearly articulate how the recruitment will avoid the appearance of coercion when selecting subjects who are in a dependent relationship to the investigator.

Discussion of the Benefits and Risks

The research protocol must include a discussion of both the possible benefits and risks of the research. The investigator should consider only those risks and benefits that may result from the research. Evaluating the possible long-range effect of applying the knowledge gained through the research should not be included in this discussion. (See The Consent Process for further discussion of risks and benefits.)

A realistic discussion of the benefits of research must take into account any possible benefits a subject might derive from participation in research that would justify asking a person to undertake the risks of the study. Payment for participation in research is not considered a benefit. As appropriate, a discussion of benefits should also include what the investigator expects to learn from the research, and what

value it will have for the participant's community, the research institution, the funding agency, or science.

The discussion of risks must include inconveniences or discomforts and, where possible, an estimate of the likelihood and magnitude of harm. Biomedical research often presents some risk of physical injury to subjects. Although most of these risks are transient, some adverse effects of study participation (especially those resulting from medical procedures, drug research, or device research) may result in permanent injury to subjects. For all research with the potential to cause physical harm, investigators must list in writing all risk possibilities. As appropriate, the investigator should describe alternative methods that could have been used to minimize risk, stating why they were rejected. By clearly detailing procedures to address situations of physical harm, the IRB can be assured that the investigator has made efforts to minimize physical risks to the greatest extent possible.

Some research proposals involve the handling of sensitive information that may result in injury to subjects through a breach of confidentiality. These breaches may result in embarrassment within a subject's business or social group, loss of employment, or criminal prosecution. The IRB is especially concerned about information regarding drug and alcohol use, mental illness, sexual behavior, and illegal activities. For these situations, investigators must clearly detail strong safety precautions to ensure that the research does not cause social or economic risks to the subjects.

Privacy and Confidentiality Concerns

Privacy refers to a person's interest in controlling other's access to data about him/herself. Confidentiality is an extension of the concept of privacy; it refers to data (some record about the person, such as notes or a videotape of the person) and to how data are to be handled in keeping with the subjects' interest in controlling the access of others to information about themselves. Ideally, confidentiality is handled in an informed consent agreement between investigator and subject; the agreement states what may be done with private information that the subject conveys to the investigator. The terms of the confidentiality agreement need to be tailored to the particular situation.

Investigators are required to maintain and protect the privacy and the confidentiality of all personally identifiable information of all human subjects participating in research, except as may be required by law or released with the written permission of the subject. Subjects have the right to be protected against invasion of their privacy, and to expect that their personal dignity will be maintained and the confidentiality of their private information will be preserved. The more sensitive the research material, the greater the care required in obtaining, handling, and storing data.

Information through which subjects may be identified includes their names, employee numbers, hospital ID numbers, social security numbers, driver's license numbers, home addresses, email addresses, photographs, videotapes, and the like. Individuals also may be identified by description, for example, as the personnel manager in a particular company, the sixth-grade teacher in a certain school, or the pediatric nurse at a local hospital. If information or data to be collected may be traced back to individual subjects, safeguards should be provided to ensure confidentiality.

Investigators will be asked by the IRB to describe how the data and links to subjects will be stored and maintained. They should also consider whether or not they will (1) provide information about subjects to others not involved in the research and (2) provide information they have learned about the subjects to the subject. Finally, investigators should consider to what extent a breach of confidentiality or invasion of privacy would constitute harm. If harm is a possibility, investigators must provide adequate provisions to protect participants from those harms and inform subjects of the possible harm.

Guidelines for protecting confidentiality

- *Limit recording of personal information to that which is essential to the research.*
- *Store personally identifiable data securely and limit access to the principal investigator and authorized staff.*
- *Code data as early in the research as possible, and, when appropriate, develop a plan for the ultimate disposition or destruction of the code linking the data to individual subjects.*
- *Apply for federal Certificates of Confidentiality in all situations for which certificates are reasonable and available. (Contact the IRB Office for further information.)*
- *Do not disclose personally identifiable data to anyone other than the research team without the written consent of the subjects or their legal representative. (Exceptions may be made in case of emergency need for intervention or as required by regulatory agencies.)*

Risk/Benefit Assessment

The IRB requests that researchers assess the relative weights of the study's risks and benefits in the protocol application. Important research may necessarily contain risk. Such research is acceptable if (1) it is well-designed, (2) it will contribute to generalizable scientific knowledge, (3) it is conducted by a competent investigator, and (4) risk/benefit assessment and planning have occurred. The IRB will not approve studies in which the risks outweigh the benefits.

Financial Considerations for Subjects

If subjects are to be paid for their participation in the research activity, the investigator should provide information regarding the total dollar amount that subjects will be paid for participation in the study, and should give any other relevant information such as prorating if a subject does not complete the study, or bonus payment at the end of the study. Subjects should not be required to complete the entire study before receiving any reimbursement. However, most research studies at LLNL do not involve payment to research volunteers.

If a protocol involves more than minimal risk, the IRB will require that the investigator provide appropriate information about any compensation and/or medical treatment that would be available if an injury or illness occurs. (See Basic Elements of the Consent Form for further information regarding injury compensation.)

Participation in some research studies can lead to additional monetary costs for study subjects. Procedures billed to insurance companies may require a significant co-payment on behalf of the subjects. Insurance companies may refuse to pay for "investigational" therapies, subjects may be responsible for transportation costs, and subjects may lose wages during research participation. Investigators should attempt to minimize any economic costs to subjects. If the research involves additional actual costs to individuals, the anticipated costs should be described to subjects during the consent process.

Disclosure of Investigator's Personal or Financial Interest in the Research Study and/or Sponsor

*(*This section was adapted from the Association of American Medical Colleges "Guidelines for Dealing with Faculty Conflicts of Commitment and Conflicts of Interest in Research," which was adopted by their Executive Council on February 22, 1990.)*

The term "conflict of interest" in science refers to situations in which financial or other personal considerations may compromise, or have the appearance of compromising, an investigator's professional judgment in conducting or reporting research. The bias such conflicts may conceivably impart not only affects collection, analysis, and interpretation of data, but also the hiring of staff, procurement of materials, sharing of results, choice of protocol, and the use of statistical methods. Conflicts of interest are particularly important to consider in biomedical and behavioral research because of the impact such conflicts can have on human health.

It is not possible to completely eradicate the potential for conflict of interest because there are certain rewards that are inherent in the structure of the research enterprise. Such rewards may be completely unrelated to relationships with industry or private sponsorship.

For example, positive research results may contribute to opportunities for publication, promotion, tenure, grant renewals, and so forth. In addition, positive results are often more gratifying and lead to greater personal satisfaction than negative outcomes. These influences are integral to doing business as a researcher and are indeed the motivating forces for diligent scientists. If abused, however, these influences can be as much a source of conflict in the search for truth as interests of a pecuniary nature. Such conflicts become detrimental when the potential rewards, financial or otherwise, cause deviation from absolute objectivity in the design, interpretation, and publication of research activities, or in other academic and professional decisions.

The mere appearance of a conflict may be just as serious and potentially damaging as an actual conflict. Reports of conflicts based on appearances can undermine public trust in ways that may not be adequately restored even when mitigating facts of a situation are brought to light. Apparent conflicts, therefore, should be evaluated and managed with the same vigor as known conflicts.

Some examples of problematic situations include investigators who:

- Undertake basic or clinical research when the investigator or the investigator's immediate family has a financial, managerial, or ownership interest in the sponsoring company or in the company producing the drug/device under evaluation.
- Accept gratuities or special favors from research sponsors.
- Enter into a consultantship arrangement with an organization or individual having an economic interest in related research.

Investigators should contact the IRB Office or the Laboratory's Ethics Office if they have any questions or concerns regarding real or potential conflicts of interest with their research.

Obtaining Informed Consent

In the past, it was generally accepted that written informed consent, obtained at a single contact between an investigator and a subject, was sufficient to meet legal and ethical obligations to patients and research subjects. This view was modified in the 1970s. Informed consent is now understood as an ongoing process that starts with the initial presentation of a research activity to a prospective subject by the investigator and continues through the research activity until the subject ends his/her participation or the study closes. Indeed, the process continues to evolve.

Prospective subjects are rarely aware of research activities prior to an initial presentation by the principal investigator, or a member of the study team, and many subjects make their decision regarding whether to participate in the research at this point. As a result, it is critical that the initial presentation provide subjects with a clear understanding of the research, its procedures and attendant risks and benefits. Investigators are encouraged to provide sufficient time for a potential subject to reflect on the nature of participation during this important initial presentation of the research activity. When subjects are presented with numerous research and clinical options, the consent process should include a clear description of the possible ramifications resulting from each option presented. The presentation should not include specific "leading" information about whether to participate in any particular project.

Providing a potential subject with understandable information in the initial session will improve comprehension and enhance the potential for a more informed consent by the subject when agreeing to participate in the research.

The next phase in the consent process is the presentation of the consent form to subjects. According to federal regulations [45 CFR 46.117(b)], a consent form may be either of the following:

1. A written consent document that contains the elements of informed consent as described in Elements of Consent. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator must give either the subject or the representative adequate opportunity to read it before it is signed.

2. A short form written consent document stating that the elements of informed consent as described in Elements of Consent have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there must be a witness to the oral presentation. Also, the IRB must first approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary must be given to the subject or the representative, in addition to a copy of the short form.

When a written consent form is being used, the member of the study team who is obtaining consent should ask the subject if s/he understands the information contained in the form after the subject has read it. In situations where the ability of the subject to understand the form is in question (e.g., the form includes complex scientific information or the subject is possibly educationally or mentally challenged), the person obtaining the consent should ask questions of the subject to ensure an understanding of the basic elements of the consent form.

An effective way to assess the subject's comprehension of the consent form is to request that the subject summarize the risks of participation, how the subject may withdraw, and what alternatives exist to participation in the research.

The consent process does not end with the signing of a consent form. Research is an ongoing process that involves the constant reevaluation of current information and procedures. It is important that investigators apprise subjects of new research information that may have an impact on the subject's willingness to continue participation in the study. Investigators should note, however, that the IRB must review and approve communications with subjects relating to their participation in the study prior to communicating that information to the subject.

In conclusion, it is difficult to be confident that volunteers truly understand the nature of their participation in research when they are confronted with complex scientific details in a brief and isolated consent session. By adopting the concept of an ongoing consent process, subjects will have an improved understanding of the risks and anticipated benefits (to themselves, others, and society) as a result of their participation in the research. Creating an ongoing consent process will facilitate an exchange of information between subjects and investigators in an increasingly complex scientific environment. By providing subjects with the opportunity to give effective and ongoing informed consent, in a process that incorporates the free exchange of information between both the investigator and the subject, investigators will be living up to the highest standards for the conduct of ethical research at LLNL.