Title: Information to Evaluate Research Studies for Continuing Review
Standard Operating Policy: #10
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Subject: Information to Evaluate Research Studies for Continuing Review

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Policy:

It is the policy of the LLNL IRB that research activities be periodically reviewed at intervals appropriate to the degree of risk, but not less than once per year as required by the federal regulations.

Procedures:

Each study requires ongoing monitoring by the investigator and the IRB. Renewal of protocols through the IRB occurs at intervals specified by the IRB (and no less than annually). At IRB-defined intervals, the Principal Investigator (PI) reports to the IRB the study's progress and findings to date. This monitoring mechanism assures that continuing safeguards are in place to protect the rights and welfare of study participants. Periodic review of findings allows the IRB and investigator to determine whether the benefits and risks of the research have changed as the study has progressed. It is an opportunity to revisit and reapply the ethical principles and norms outlined in *The Belmont Report* and federal regulations for the protection of human subjects in research.

Federal regulations specify initial IRB review criteria that include determinations regarding risks, potential benefits, informed consent, and safeguards for human subjects. The same review criteria are required during continuing review, whether full committee or expedited review is conducted. It is, therefore, the responsibility of the IRB to determine at the time of continuing review that:

- Risks to subjects continue to be minimized and reasonable in relation to the anticipated benefits.
- Selection of subjects continues to be equitable.
- Informed consent continues to be appropriately obtained and documented.
- Adequate provisions for monitoring the data collected to ensure the safety of the subjects is provided, when appropriate.
- Adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data is provided, when appropriate.
- Appropriate safeguards for vulnerable populations are being provided.

Any significant new findings that may relate to the subjects' willingness to continue participation should be provided to the subjects either through a revised consent form or a letter to the research participants. Unanticipated risks are sometimes discovered during the course of research. Information that may impact the risk–benefit ratio should be promptly reported to, and reviewed by, the IRB to ensure adequate protection of the welfare of the subjects. Based upon such information, the IRB may need to reconsider its approval of the study, require modifications to the study, or revise the continuing review timetable.

Research may be restricted, modified, or halted altogether based on continuing review by the full IRB committee. Previously imposed restrictions may be relaxed or additional or new restrictions may be imposed. By regulation, the IRB has the authority and the responsibility to take appropriate steps such as terminating or suspending approval of research that is not being conducted in accordance with the IRB's requirements.

When study approval is terminated by the IRB, in addition to stopping all research activities, any subjects currently participating should be notified that the study has been terminated. Procedures for withdrawal of enrolled subjects should consider the rights and welfare of subjects. If follow-up of subjects for safety reasons is required by the IRB, the subjects should be so informed and any adverse events or outcomes should be reported to the IRB and the sponsor of the study.

Submission of Renewal Documents for IRB Review

To allow adequate time for IRB review and to prevent the study from falling into noncompliance due to an expired status, the LLNL IRB will issue the PI a courtesy renewal notice 60 days prior to expiration. Renewal documents will be due to the IRB 14 days in advance of the expiration date. Should a PI fail to receive the renewal form, it is the PI's responsibility to contact the Human Research Protection Office to obtain a second copy. It is critical that investigators track the status of their studies on a regular on-going basis.

For continuing review of research, whether full committee or expedited, the IRB must be provided sufficient information to determine whether the proposed research continues to fulfill the criteria for approval. Therefore, PIs shall submit to the IRB the following documents and information for continuing review (contained with the renewal form):

1. The full protocol which was approved by the IRB during the past year.
    a. A protocol must contain the relevant information required to determine whether the research continues to fulfill the criteria for approval.
2. A status report on the progress of the research.
    a. The number of participants currently enrolled, number planned to enroll in the coming year, number declined to participate in the past year of approval.
    b. Activities during the past year, specifically results to date and any problems encountered during the past year.
    c. Future activities, specifically plans for the coming year and minor and major proposed changes to the research.
3. A summary of any unanticipated problems involving risks to participants or others since the last IRB review. The information submitted to the IRB shall include serious adverse events, which occurred at LLNL, and related sites, during the past year. If available, attach the Data and Safety Monitoring Board report.
4. A summary of any withdrawal of participants from the research since the last IRB review. Include the reasons for withdrawal.
5. A description of complaints about the research since the last IRB review.
6. A summary of any relevant/recent literature, published by the team and specific to this study, since the last IRB review.
7. A summary of any interim findings since the last review.
8. A copy of all modifications/amendments since the last IRB review.

9. Any other relevant information, especially information about risks associated with the research.
10. The current informed consent document in use.
11. Newly proposed consent documents with all proposed changes underlined and/or highlighted.
12. A summary of participant benefits.
13. A current risk-benefit assessment based on study results.
14. If applicable, sponsor report if the study was audited during the past year.
15. Enough information to review the progress of the entire study.
16. If applicable, any relevant multicenter trial reports.

For continuing review of research by full committee, the IRB Chair, primary and secondary reviewers (if assigned), and all other IRB members will be provided the complete renewal documents including any protocol modifications or amendments previously approved by the IRB. In addition, any IRB member can readily access the complete IRB study record prior to or at the meeting. Relevant IRB minutes may also be accessed prior to the IRB meeting.

When reviewing continuing research under an expedited procedure, the IRB Chair and/or his/her designee will receive and review all of the above referenced documentation, including the complete IRB study record.

Requests for Clarification/Revisions/Documents by the IRB

A pending or deferred status is given to all studies in which the IRB requests clarification, revisions, and/or documents during continuing review. IRB approval is not granted until all requested changes are completed by the PI and reviewed by the IRB. Investigators should be aware that if the study is expired, this review process will not extend the expiration date or grant a "grace period," as the federal regulations do not allow such extensions or grace periods.

Minor or major revisions or clarification to the study will be transmitted to the PI within one to two working days after IRB review. This will include instructions for resubmission to the IRB and whether full committee review or review only by the IRB Chair and/or his/her designee is required. If all concerns have been addressed to the satisfaction of the IRB, approval documents will be issued to the PI.

If the PI fails to submit a response to the IRB, the study will be closed out at the expiration date. If the study was already expired at the time of receipt by the IRB, the IRB will close out the study if it does not receive a response within 30 days from the date of the communication of the IRB. Notification of closeout will be transmitted to the PI in writing.

Frequency of Continuing Review

Appropriate continuing review intervals are determined on a study-by-study basis. When determining the appropriate review interval, the IRB will consider factors including, but not limited to:

- Risks to subjects
- Involvement of vulnerable populations
- Research for which participants would be exposed to additional risks (e.g., Phase I studies, breach of confidentiality, disproportionate number or severity of adverse events)
- Research conducted internationally
- Involvement of recombinant DNA or other types of gene transfer studies
- Use of waiver of informed consent
- Classified research
- Recommendations from other ancillary committees
- Previous suspensions or administrative holds of the research due to compliance, record- keeping, or other concerns

The IRB will decide the frequency of continuing review for each study protocol necessary to ensure the continued protection of the rights and welfare of research subjects. The following three scenarios explain the date by which continuing review must occur:

- Scenario 1: The IRB reviews (whether full committee or expedited review) and approves a protocol without any conditions or revisions on October 1, 2017. Continuing review must occur within one year of the date of the review, that is, by October 1, 2018.
- Scenario 2: The IRB reviews a study (whether full committee or expedited review) on October 1, 2017 and approves it contingent on specific minor revisions that the IRB chair or his/her designee can verify. On October 31, 2017, the IRB chair or designee confirms that the required minor revisions were made. Continuing review must occur within one year of the date of the convened or expedited review, that is, by October 1, 2018.
- Scenario 3: The IRB reviews a study at a convened meeting on October 1, 2017 and has serious concerns or lacks significant information that requires IRB review. The protocol is reviewed at subsequent meetings on October 15 and October 29, 2017. At their October 29, 2017 meeting, the IRB completes its review and approves the study. Continuing review must occur within one year of the date of the convened meeting at which the IRB reviewed and approved the protocol, that is, October 29, 2018. Studies reviewed under expedited procedures, where serious concerns or revisions have been identified, are typically referred by the IRB reviewer to the full IRB committee for review.

Note: Review of a modification/amendment during the year of approval, does not alter the date by which continuing review must occur.

Expiration of IRB Approval

There is no grace period extending the conduct of the research beyond the expiration date imposed by the IRB. Therefore, the study expires and extensions are not granted. If the IRB does not re-approve the research prior to the expiration date, study activities must cease, pending re-approval of the research. A final notice will be issued to the PI approximately one week prior to expiration. Unless the PI wishes to close the study, the PI must immediately submit the renewal documents to the IRB and address (1) why the PI did not adhere to the renewal notice, and (2) address whether any subjects were entered into the study during the expired status of the study.

Should stopping the study place currently enrolled subjects at a health risk, the PI is to immediately contact the IRB Chair to discuss continued treatment. The IRB addresses these situations on a case-by-case basis. **Enrollment of new subjects cannot occur on or after the expiration date.**

On March 27, 1997, President Clinton issued a memorandum on *Strengthening Protections of Human Subjects of Classified Research* (Clinton Memorandum), which requires a special review process for classified human subjects research. In July 2015, the Director of DOE-IN, in coordination with and approval by the DOE-IO, on behalf of DOE and NNSA, instituted a reconstituted IRB-C to improve the process for protecting human subjects in research as it pertains to intelligence-sensitive projects in accordance with the Clinton Memorandum. This IRB-C is composed of only Federal employees, except for unaffiliated member(s) who are not current DOE Federal (*in accordance with the Clinton Memorandum*) or DOE/NNSA M&O contractor employees. The scope of the IRB-C is to review and approve intelligence and intelligence-related projects, regardless of funding source or classification, conducting HSR and/or HTM. This will now include all such projects conducted by/at DOE site(s). The IRB-C will operate within a Special Compartmented Information Facility (SCIF).

Department of Energy, Office of Intelligence and Counterintelligence,
DOE-IN Policy Number 202, Effective 15 November 2016

References:

45 CFR 46.109
45 CFR 46.110(b)(1)
45 CFR 46.111
Institutional Review Board Management and Function by Elizabeth A. Bankert and Robert J. Amdur, Chapter 7 Protocol Renewal, Second Edition