



Standard Operating Procedure: #10
Modification to Approved Study
Revision Date: November 2020

Overview:

All modifications to a currently approved IRB protocol require IRB review and approval prior to the initiation of the change.

The only exception to this requirement is when a change is necessary to eliminate apparent immediate hazards to the subject. In such a case, the IRB should be promptly informed of the change following its implementation and should review the change to determine that it is consistent with ensuring the subjects' continued welfare.

Changes Implemented in Order to Avoid Harm

If a change was temporarily implemented without prior IRB approval to avoid immediate harm to subjects, the Principal Investigator (PI) must notify the IRB within five (5) working days, via email. The PI should provide all relevant information concerning the change/modification that was implemented, the potential risks/harms to the subjects, and the current status of the subjects or subjects' well-being.

The PI must submit *Form LL6657: Request for Amendment or Modification* if long-term implementation of the change is needed, along with revised study documents, as applicable.

The proposed change will be designated as a minor or substantive change. This determination will dictate the level of review required, whether full board or expedited review.

Minor Changes:

Minor changes are defined as changes in research-related activities that do not significantly affect the risk/benefit ratio of the study and/or changes that do not significantly alter the study design. The IRB Chair may request additional information from the PI to make this determination. The IRB can use the expedited review procedure to review and approve minor changes, even if the study was initially approved by the full board.

Minor changes include, but are not limited to:

- The addition of research activities that would be considered exempt or expedited if reviewed independent of the main research protocol.
- Changes in PI (in most situations) or other research personnel.
- A minor increase or decrease in the number of subjects.
- Narrowing the inclusion criteria.
- Broadening the exclusion criteria.
- Changes to the dosage form (*e.g.*, tablet to capsule or oral liquid) of an administered drug when the dose, route of administration, and pharmacokinetics of the drug remain constant.
- Decreasing the number of biological sample collections, provided that such a change does not affect the collection of information related to safety evaluations.
- An increase in the number of study visits for the purpose of increased safety monitoring.
A decrease in the number of study visits, provided the decrease does not affect the collection of information related to safety evaluations.
- Changes in remuneration.

- Changes to improve the clarity of statements or to correct typographical errors, provided that such a change does not alter the content or intent of the statement.
- The addition or removal of qualified investigators.
- The addition or deletion of study sites.

Substantive Changes:

Any change to a study that affects the risk/benefit ratio of the study in a manner that may elevate the risk so that it is greater than minimal risk or significantly affects the nature of the study is defined as a Substantive Change. Substantive changes must be reviewed by the full board. Changes that are not minor are scheduled for review by the Full Board at a convened meeting.

Substantive changes include, but are not limited to:

- Broadening the range of inclusion criteria.
- Narrowing the range of exclusion criteria.
- Addition of a new subject population (e.g., control group, additional cohort, etc.).
- Addition of research procedures that involve greater than minimal risk to subjects (e.g., addition of a new drug to a treatment regimen; addition of invasive procedures; change in route or frequency of drug administration, etc.).
- Extending substantially the duration of exposure to the test material or invention.
- The deletion of laboratory tests, monitoring procedures, or study visits directed at the collection of information for safety evaluations.
- Addition of new, significant risks to the protocol and/or the Informed Consent Document(s).
- Changes, which, in the opinion of the IRB Chair or his/her designee, do not meet the criteria or intent of a minor modification.
- The addition of a qualified investigator with a disclosable conflict of interest.

Procedures:

1. The PI submits *Form LL6657: Request for Amendment or Modification*.
2. The IRB Project Manager will prereview the submitted form. If required, revisions and/or clarification will be requested from the PI. Upon verification of revisions and determining that the form and pertinent documentation is complete, the IRB Program Manager will determine if the modification is a minor or substantive change
3. The review process follows the procedure for review of Expedited (See SOP #7 *IRB Review of Human Subjects - Expedited*) or Full Board (See SOP #8 *IRB Review of Human Subjects – Full Board*)

Principal Investigator (PI) Leaving LLNL

1. The PI is responsible for ensuring that his/her research-related duties are appropriately transitioned or completed before officially exiting their position.
2. The PI must contact the LLNL IRB within 60 days of leaving LLNL.
3. The PI must submit *Form LL6657: Request for Amendment or Modification* transferring the study to another PI or *Form LL6713: Human Subjects Research Protocol Closure*.

If the subjects are still participating in the research study, the IRB recommends the PI provide the subjects with a letter to update them of the change in PI and to update them regarding changes in relevant email

addresses and telephone numbers (*e.g.*, for study-related questions) and addresses (*e.g.*, to withdraw authorization).

4. All changes must be reviewed and approved by the IRB Office *prior* to the change being implemented (except to eliminate hazards to subjects).
5. All study related records will remain at LLNL, unless specifically approved by LLNL.

The protocol and all application documentation will follow SOP #18: *Retention of IRB Records*.

References:

45 CFR 46.108(3)(iii)



Document Review History

Revision Number	Date	Author	Summary of Changes
01	September 2017	Ann-Marie Dake	Complete Revision
02	November 2018	Dawn Whalen	Document control process added
03	November 2019	IRB Office	Complete Revision
04	November 2020	Ann-Marie Dake	Revisions and updates