

**Overview:**

Federal Regulations and the DOE Order require prompt reporting of any unanticipated problems or adverse events to the LLNL IRB. The DOE Program Human Subject Managers request to be notified within 48 hours of learning of any unanticipated problem that does not involve Personally Identifiable Information (PII). The LLNL IRB will coordinate with the reporting Principal Investigator (PI) to further inform the LLNL Institutional Official (IO), the DOE Human Subject Program Managers and OHRP (where applicable) and to develop a plan to correct the unanticipated problem.

Specifically, the body of the order requires reporting to the DOE and NNSA HSP Program Managers:

- a. Immediately upon learning of loss/breach of PII and serious adverse events.
- b. Within 48 hours of learning of unanticipated problems, significant adverse events, and complaints about the research, as well as suspension or termination of IRB approval; and known or potential incidents of non-compliance with the requirements of this Order, 10 CFR Part 745, or 45 CFR Part 46.

The potential loss or compromise of PII should be reported to the LLNL IRB Office as soon as the PI learns of the incident. The IRB Program Manager will then report the incident to the LLNL IO and the DOE-Cyber Incident Response Capability (DOE-CIRC) at 1-866-941-2472; *and* the DOE HSR Program Manager(s), both Office of Science and NNSA.

A summary of all adverse events associated with the study must be reported to the LLNL IRB at the time of continuing review.

**Definitions:**

**Adverse Event: Per DOE O 443.1C.** Any unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (Unanticipated Problems Involving Risk and Adverse Events Guidance, OHRP, 2007). A significant adverse event is an adverse event that is unexpected and substantively impacts the human subjects. A serious adverse event ( Unanticipated Problems Involving Risk Adverse Events Guidance, OHRP, 2007) is any adverse event temporally associated with the subject's participation in research that meets any of the following criteria: a) results in death; b) is life-threatening; c) requires inpatient hospitalization or prolongation of existing hospitalization; d) results in a persistent or significant disability/incapacity; e) results in a congenital anomaly/birth defect, or f) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

**Serious events:**

- Any death.
- Any life-threatening event (*e.g.*, an event that places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred—does not include an event that, had it occurred in a more severe form, might have caused death).
- Any event that requires or prolongs hospitalization.
- Any event that results in persistent or significant disability/incapacity.
- Any congenital anomaly/birth defect diagnosed in a child of a subject who participated in the study and received study drug.
- Other medically or psychologically important events that, in the opinion of the investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

**Unanticipated Problem**

Per DOE O 4431C: In general, to be classified as an unanticipated problem, any incident, experience, or outcome should meet all three of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
- Likely to place subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. (DOE O 4431C)

**Unanticipated:** Any adverse experience, the frequency or severity of which is not consistent with the current consent form or investigator brochure. (See DOE Order 443.1C.)

**Unanticipated Problem Involving Risk to Participants or Others**

Any unanticipated event involving any aspect of a research study involving anyone (participants, research staff, or others not directly involved in the research) that increases a risk to the persons involved. These can occur in biomedical and non-biomedical research.

Examples of Unanticipated Problems Involving Risks to Participants or Others:

- Adverse emotional reactions to study procedures, such as depression or threat of harm to self or others, or that require medical, psychological, or legal intervention to prevent such outcomes.
- Unanticipated medical/physical reactions or injuries temporally related to a study.
- A participant unexpectedly becomes pregnant.
- A lab reports that blood studies performed the previous week were in error.
- Unanticipated identification of incidences of child abuse, threats of harm, sexual harassment, or other reportable events.
- An investigator loses a laptop computer that contains confidential information about study participants.
- A failure to follow approved protocol procedures that results in increased risks.

## Procedures:

1. PI contacts the IRB Office as soon as possible, but no later than five (5) working days after the PI learns of the event or problem. Note: The DOE O 443.1C requests notification within 48 hours of learning of the event or problem. This notification can be made by telephone or email.
2. The IRB Chair and Program Manager discuss the contents of the email and/or telephone conversation(s) and communicate with the PI if additional information is required.
3. The IRB Chair and/or Program Manager will determine what action, if any, is required:
  - Clarification / modification to the protocol
    - The IRB Program Manager will communicate to the PI to submit *Form LL6657: Request for Amendment or Modification*
    - The IRB Program Manager will ensure all information is received

If the modifications are minor, the IRB Chair can approve the changes following the IRB discussions:

- i. An approval letter will be generated and signed by the IRB Chair.
- ii. The approved protocol package will include:
  1. Signed approval letter
  2. Submitted form
  3. Pertinent documentation related to the application (i.e. consent forms, study materials, etc.)
- iii. The IRB Program Manager will send an email to notify PI that the study has been approved. The email will have the approved protocol package attached.
- iv. The approved protocol will be entered into the DOE IRB database.
- v. All applications approved under expedited review will be communicated to the IRB at the next regularly scheduled meeting. If the meeting is cancelled, the information will be distributed to the IRB via email. The *Expedited Review Summaries* will include:
  1. Protocol Number and Title of Study
  2. Names(s) of Principal Investigators(s)
  3. IRB Reviewers and their comments, if applicable
  4. Applicable Expedited Review Category(ies)
  5. Study synopsis
  6. Protocol approval date
- vi. The protocol and all application documentation will follow SOP #18: *Retention of IRB Records*.

- Shorten the protocol approval period
 

The IRB Program Manager will determine the new expiration date for the protocol

  - i. An approval letter will be generated and signed by the IRB Chair.
  - ii. The approved protocol package will include:
    1. Signed approval letter
    2. Submitted form
    3. Pertinent documentation related to the application (i.e. consent forms, study materials, etc.)
  - iii. The IRB Program Manager will send an email to notify PI that the study has been approved. The email will have the approved protocol package attached.
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    4. Protocol Number and Title of Study
    5. Names(s) of Principal Investigators(s)
    6. IRB Reviewers and their comments, if applicable
    7. Applicable Expedited Review Category(ies)
    8. Study synopsis
    9. Protocol approval date
  - vi. The protocol and all application documentation will follow SOP #18: *Retention of IRB Records*.
  
- Recommend suspending or terminating the protocol approval
 

The protocol will be referred to a Full Board review at the next regular scheduled meeting. If timing of the change is required prior to the scheduled meeting, an *ad hoc* meeting may be called. See SOP #8 *IRB Review of Human Subjects – Full Board*.  
NOTE: the IRB will determine if the protocol should be modified, revise the review timeline, and/or suspend/terminate the protocol.
  
- Cannot make a determination as to what action should be taken
 

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NOTE: the IRB will determine if the protocol should be modified, revise the review timeline, and/or suspend/terminate the protocol.

**References:**

**DOE Order 443,1C**  
 45CFR 46.108(4)(i)  
 21 CFR 56.108(b)(1)

## 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