



Title: Adverse and Unanticipated Events
Standard Operating Procedure: #13
Department: Human Research Protection Program/Institutional Review Board
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Subject: Reporting of Unanticipated Problems Involving Risk to Participants or Others

Policy:

45 CFR 46 calls for prompt reporting to the IRB(s), appropriate institutional and agency officials, and OHRP.

OHRP guidance recommends that the PI report an unanticipated problem to the IRB(s) within 2 weeks and that the PI or PI's organization report the unanticipated problem to OHRP within 6 weeks [or within 1 month of notifying the IRB(s)].

DOE Order 443.1B also requires prompt reporting to the DOE HSR Program Manager, SC-23 (and the HSR Program Manager, National Nuclear Security Administration (NNSA) for NNSA sites), and coordination with and approval from the HSR Program Manager(s) in determining plans to correct the unanticipated problem.

While DOE Order 443.1B does not define "prompt," the DOE Program Manager requests that the HSR Program Manager(s) receive notification within 48 hours of learning of any unanticipated problem that *does not involve* Personally Identifiable Information (PII).

If potential loss or compromise of PII *is involved*¹, as soon as investigator learns of the incident he/she shall report the incident:

- To the IRB IO.
- To the IRB Office within the Human Research Protection Office.

The IRB Office shall then report the incident to the:

- DOE-Cyber Incident Response Capability (DOE-CIRC) at doecirc@doecirc.energy.gov or 866-941-2472; *and* The DOE HSR Program Manager(s).

All unanticipated problems involving risks to participants or others and adverse events shall be reported to the IRB according to the following schedule:

- Adverse Events that are serious, unanticipated, and possibly or definitely related, must be reported within 5 working days of the Investigator's knowledge of the event.
- Unanticipated problems involving risks to participants or others must be reported within 5 working days of the Investigator's knowledge of the problem.

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

¹See *Standard Operating Procedure #14, Department of Energy Requirements for Protecting PII at the National Laboratories*.

Definitions:

Adverse Event: 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. A significant adverse event is an adverse event that is unexpected and substantively impacts the human subjects.

Definitely Related: Meeting **all four** of the following conditions:

- Has a reasonable temporal relationship to intervention.
- Could not readily have been produced by the research participant's normal state or have been due to environmental or other interventions.
- Follows a known pattern of response to intervention.
- Disappears or decreases with reduction in or cessation of intervention and recurs with re-exposure.

Possibly Related: Meeting **any** of the following conditions:

- Has a reasonable temporal relationship to intervention.
- Could not readily have been produced by the research participant's normal state.
- Could not readily have been due to environmental or other interventions.
- Follows a known pattern of response to intervention.

Serious: Events are classified as serious if they meet any of the following criteria:

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

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:

I. Investigator Responsibilities

The Investigator submits reports of serious, unanticipated, and possibly or definitely related adverse events and unanticipated problems involving risks to participants and others as follows:

- A. A "Problem Report" is submitted to the IRB as soon as possible, but no later than **5 working days** after the investigator first learns of the event or problem. This form contains the investigator's assessment of causality (related or not related to the study) and a description of the actual event; and
- B. In the report, the investigator will either justify why no changes to the protocol or consent form are needed or attach proposed modifications to the report.

II. IRB Chair/Designated Committee Member Responsibilities

- A. All reports made under the policy are provided to the Chair or an IRB Member who has been designated by the Chair to conduct expedited reviews.
- B. The reviewer will review the report to determine what action, if any, is required. Actions may include, but are not limited to:
 - 1. Providing information concerning the problem or event to subjects, research staff, or whoever else is affected.
 - 2. Requiring modifications to the study.

3. Shortening the protocol approval period.
 4. Recommending suspending or terminating approval of the study.
- C. If modifications are required and all modifications are minor, the Chair will review the modifications under an expedited review.
- D. If the reviewer:
1. Cannot make a determination as to whether any actions are or are not required.
 2. If modifications are required that are substantive in nature.
 3. If the reviewer determines that the study should be suspended or approval terminated.
- The Report will be referred to the full IRB Committee for review.
- E. If participants are at immediate risk of harm and there is insufficient time to wait for review by the convened IRB, the reviewer will request that the IRB Chair or the IRB Manager suspend the study until review can be completed.

III. IRB Committee Responsibilities

- A. The IRB will review the report to determine what action, if any, is required. Actions include, but are not limited to:
1. Providing information concerning the problem or event to subjects, research staff, or whoever else is affected.
 2. Requiring modifications to the study.
 3. Revising continuing review timetable.
 4. Suspending or terminating approval of the study.

References:

45 CFR 46.103(b)(5)(iii)
21 CFR 56.108(b)(1)
IRB Guidebook (OHRP)