Policy & Procedure Reportable Events	Document No.	HSC-2010-009
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1.0 PURPOSE

This guidance establishes how adverse, unanticipated, and/or reportable events that occur during human subjects research shall be documented for, and reviewed by, the Human Subjects Committee (HSC) of the Lawrence Berkeley National Laboratory (Berkeley Lab).

2.0 REVISION HISTORY

Date	Revision No.	Change	Reference Section(s)
01/31/10	1.0	New Procedure Drafted	Not Applicable
9/17/12	1.1	Reformat, terminology update	All
12/2018	2.0	Updated for consistency with the Revised Common Rule	All
06/2023	3.0	Updated throughout	All

3.0 DEFINITIONS

3.1 Research: A systematic investigation, including research development, testing and evaluation, designed to contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities. The following activities are deemed not to be research:

(1) Scholarly or journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.

(2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitory, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

(3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
(4) Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

3.1.1. Systematic Investigation: a study or examination involving a methodical procedure or plan.

3.1.1. Generalizable knowledge: The information is expected to expand the knowledge base of a scientific discipline or other scholarly field of study and yield one or both of the following:

- Results that are applicable to a larger population beyond the site of data collection or the specific subjects studied
- Results that are intended to be used to develop, test, or support theories, principles, and statements of relationships, or to inform policy beyond the study.

3.2. Human subject: a living individual about whom an investigator conducting research: (1) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies or analyzes the information or biospecimens or (2) Obtains, uses, studies, analyzes, or generates identifiable private information. In clinical research, a subject is someone who becomes a participant in research, either as a recipient of the test article or as a control.

3.2.1. *Intervention* includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

3.2.2. *Interaction* includes communication or interpersonal contact between investigator and subject.

3.2.3. *Private information* is information that is associated with individuals or groups of individuals and that could reveal details of their lives or other characteristics that could impact them. Private information includes:

- Information that is observed or recorded about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and
- Information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public, e.g., a medical record or a utility bill.

3.2.4. *Identifiable private information* is private information for which the identity of the subject is associated with the information or may readily be ascertained by the investigator

3.2.5. An *identifiable biospecimen* is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

3.3. Risk: The probability and magnitude of discomfort, harm or injury (physical, psychological, social, or economic) anticipated as a result of participation in a research study.

3.3.1. Minimal Risk: Risks are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

3.4. Protocol Lead Investigator: The researcher with primary responsibility for conducting human subjects research under a specific protocol.

3.5. Vulnerable subject: a subject potentially vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons. Certain circumstances may make some subjects situationally vulnerable (e.g., college students or employees) and certain groups may be vulnerable to group harms.

3.6. Reportable Event: Any occurrence of adverse events, unanticipated problems, complaints received, or non-compliance with applicable international, federal, or state regulations, or institutional policies during the conduct of a human subjects research project. Includes data breaches, protocol noncompliance, or unexpected negative impacts to participants or bystanders stemming from the research.

3.7. 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 (Unanticipated Problems Involving Risk and Adverse Events Guidance, OHRP, 2007).

3.7.1. A significant adverse event is an adverse event that is unexpected and substantively impacts the human subjects. Examples are events that actually or potentially interfere with the normal activities of daily life, such as nausea severe and prolonged enough so as to prevent eating for a day or more, or a headache sufficient to prevent a participant from driving, reading, or watching television.

3.7.2. 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.

3.8. Definitely Related: An adverse event that meets **all four** of the following conditions:

3.8.1. Has a reasonable temporal relationship to the intervention.

3.8.2. Could not readily have been produced by the research participant's normal state or have been due to environmental or other interventions.

3.8.3. Follows a known pattern of response to the intervention.
3.8.4. Disappears or decreases with reduction in or cessation of the intervention and recurs with re-exposure

3.9. Possibly Related: An adverse event with a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research. Typically meets **any** of the following conditions:
3.9.1. Has a reasonable temporal relationship to the intervention.
3.9.2. Could not readily have been produced by the research participant's normal state.
3.9.3. Could not readily have been due to environment or other interventions.
3.9.4. Follows a known pattern of response to intervention.

3.10. Unanticipated Problem: In general, to be classified as an unanticipated problem, any incident, experience, or outcome should meet *all three* of the following criteria:

1) 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;

2) Related or possibly related to participation in the research; and

3) Likely to place subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

4.0 POLICY

The policy of Berkeley Lab is to ensure that the Human Subjects Committee is notified promptly of all reportable events occurring during the conduct of or associated with human subjects research performed by or funded through the institution. In order to meet external reporting requirements, as well as to ensure the timely resolution of any reportable events, the following reporting timelines are required of investigators upon learning of a reportable event.

4.1. Immediate reporting to the HSC by phone or email as soon as possible under the circumstances, is required upon learning of the following events;
4.1.1. A suspected or confirmed data breach involving PII in printed or electronic form.
4.1.2. A serious adverse event

4.2. Reporting to the HSC by phone or email within 1 business day is required in any of the following situations;
4.2.1. Any significant adverse events, unanticipated problems, or complaints about the research either from participants or bystanders;
4.2.2. Any noncompliance with the requirements of the DOE Order 443.1C, 10 CFR Part 745, or 45 CFR Part 46.

4.3. Reporting to the HSC for the following situations is still required, however these scenarios may be reported in a reasonable timeframe based on the necessary

investigation to determine the severity and corrective actions. In most cases, reporting is expected within 3-5 business days.

4.3.1. Any adverse events that are correlated with the research either temporally or situationally, including mild events that are only possibly related to the research. Examples include;

- Adverse emotional reactions to study procedures, such as depression or threat of harm to self or others, or reactions that require medical, psychological or legal intervention
- Surveys being hacked by fraudulent respondents in order to receive the financial incentive.
- Study personnel witnessing incidences of child abuse, threats of harm, sexual harassment, or other events that invoke mandated reporter status.

4.3.2. Any noncompliance with institutional policy or deviation from the procedures as written in the protocol approved by the reviewing IRB. NOTE: Protocol deviations must be reported whether they are intentional or accidental.

4.4. In addition, a summary of all reportable events associated with the study must be reported to the HSC at the time of the continuing review or annual check-in, as applicable.

5.0 PERSONS AFFECTED

5.1. All protocol lead investigators (PLIs) participating in, conducting or with oversight over research projects involving human subjects.

5.2. The Human Subjects Committee (HSC); including the Chair and those HSC members designated by the Chair to review reportable events.

5.3. Compliance Specialists and other Human and Animal Regulatory Committees (HARC) office staff

5.4. Human subjects participating in research that falls under this guidance

6.0 RESPONSIBILITIES

6.1. **PLIs** shall comply with this guidance and report relevant events as described in 7.1 (below).

6.2. The **HSC Chair** or **designated member (designee)** shall comply with this guidance and review reports of adverse events as described in section 7.2 (below).

6.3. The **HARC office staff** shall comply with this guidance and immediately notify the investigator of protocol suspension through the Human/Animal Research Protocol Management (HARP) system if requested to do so by the reviewer or HSC Chair.

6.4. The **full HSC** will review reports of adverse, unanticipated and/or reportable events referred to it by the Chair or designee, as described in 7.3 (below).

7.0 PROCEDURES

7.1. Event Reporting

7.1.1. The PI shall submit Reports through the following methods:

- All immediate reporting should be done through phone or email to properly address the issue in a timely manner.
- All reportable events must additionally be logged in the HARP system by creating a New Reportable Event. The timing of this report should be reasonable so as to avoid the loss of information over time, however in some cases it is understood that the majority of the immediate response is best handled through other communication methods. These events in the system are for long-term record keeping, and when applicable, should include uploads of the reports generated through email or other means.

7.1.2. In the Report, the PLI will include the PI's assessment of causality (related or not related to the study); a description of the actual event; and either a justification why no changes to the protocol or consent form are needed or a description of proposed modifications to the protocol or consent form.

7.2. Review of the Reported Event

7.2.1. All Reports submitted under this guidance are immediately provided by HARC staff to the Chair or their designee.

7.2.2. The Chair or designee shall review the Report to determine what immediate action, if any, is required. The report is then referred to the full committee in the case of a Full IRB Review study, or to an expedited or exempt reviewer for those categories of HSR. The Institutional Official is additionally informed of the event at this stage.

7.2.3. Upon review by the committee/designated reviewer, subsequently required corrective actions may include, but are not limited to:

- Providing information concerning the problem or event to subjects, research staff, and/or whoever else is affected;
- Requiring modifications to the study;
- Shortening the protocol approval duration;
- Recommending suspension or termination of study approval.

7.2.4. All required modifications will be processed in the same manner as would normally be used for the review based on the category of HSR.

7.2.5. If ***any*** of the following conditions apply, then the Report shall be referred to the full HSC for review even in the case of an expedited or exempt study:

- The Chair or designee cannot make a determination as to whether any actions should be required;
- Modifications are required that are substantive in nature;

- The Chair or designee determines that the study should be suspended or approval terminated;
- Even though the reportable event does not meet the definition of serious, it appears to form part of a pattern of continuing or repeated non-compliance; or
- The Chair or designee determines that a report to the Department of Energy is needed.

7.2.6. If participants or others are at immediate risk of harm and there is insufficient time to wait for review by the convened HSC, the reviewer will request that the HSC Chair or a HARC Compliance Specialist suspend the protocol in HARP and notify the investigator until review can be completed.

7.3. Reporting outside the HSC

7.3.1. As soon as is reasonable, at a minimum within 2 business days, the Chair or designee shall report the occurrence as well as corrective actions to be taken, to the Site Office for LBNL and the Department of Energy Human Subjects Protection Program manager:

- any significant adverse events, unanticipated problems, and complaints about the research;
- any suspension of termination of IRB approval of research;
- any noncompliance with the requirements of the DOE Order 443.1C, 10 CFR Part 745, or 45 CFR Part 46.

7.3.2. When the following occurs in a non-exempt research activity funded by a federal Common Rule agency, the Chair or his/her designee shall report the occurrence to the Office of Human Research Protections and to the LBNL Office of the Chief Financial Officer for reporting to the funding agency:

- any unanticipated problems involving risks to subjects or others
- any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB; and
- any suspension or termination of IRB approval.

7.3.3. For research activities funded outside of the federal Common Rule agencies, the PI will be required to self-report to their program managers as appropriate based on the specific language of the funding contract.

Regulations

DOE Order 443.1C
10 CFR Part 745
pre-2018 Requirements at 45 CFR 46.103(a) and (b)(5), and 45 CFR 46.113,
2018 Requirements at 45 CFR 46.108(a)(4) and 45 CFR 46.11345 CFR 46.103(b)(5)(iii)
21 CFR 56.108(b)(1)

References

US Department of Health & Human Services. IRB Guidebook. http://www.hhs.gov/ohrp/irb/irb_guidebook.htm. Accessed January 19, 2010.

https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html#AA

https://www.hhs.gov/ohrp/compliance-and-reporting/guidance-on-reporting-incident/index.html