

University of California, San Diego
Human Research Protections Program
Institutional Review Board
Standard Operating Policies and Procedures

Section 3.13
Reporting Adverse Events and Unanticipated Problems

Policy

Federal regulations [45 CFR46.103(b)(5) and 21 CFR56.108(b)(1)] require the IRB to ensure that investigators promptly report “any unanticipated problems involving risk to subjects or others” (UPR). The IRB defines UPRs as any problem or event, which in the opinion of the Principal Investigator was: 1) unanticipated, 2) suggested that subjects were at greater risk than was previously know or recognized, AND 3) at least possibly related to the research procedures.

In addition, the US Food and Drug Administration under Subpart C - IRB Functions and Operations 56.108 Subpart C (b)(1) requires written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of any instance of serious or continuing problems involving risks to human subjects or others. This institution includes the notification of this requirement on the cover sheet for all IRB approval letters.

The Research Plan must have procedures for reporting unanticipated problems that involve risks to human subjects or others. The IRB will consider the following definition when determining whether a reported event represents an unanticipated problem involving risks to subjects or others: *Unexpected* (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-relate 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 (in this guidance document, possibly related means that there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and *Suggests that the research places subjects or others at greater risk of harm* (including physical, psychological, economic, or social harm) that was previously know or recognized.

The following events meet the IRB’s definition of UPR and should be reported within 10 working days:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.

4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio of the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Incarceration of a participant in the course of a study.
7. A change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
8. In FDA clinical trials, adverse events that are serious, unexpected, and reasonably related to the study treatment or intervention and that are expected to result in a change to the protocol or consent documents and/or dissemination of new information to subjects and any unanticipated adverse device effect occurring during the trial.
9. Any other event that indicates participants or others might be at risk of serious, unanticipated harms that are reasonably related to the research.
10. An event that requires prompt reporting to the sponsor.
11. Sponsor imposed suspension for risk.

The convened IRB will review unanticipated problems involving risks to participants or others (UPR) that include both minimal risk and more than minimal risk.

The convened IRB will have sufficient information to determine whether each reported problem represents a UPR. A range of some appropriate actions that may be considered by the IRB are listed, including revision of the protocol or informed consent forms, notification of subjects, re-consenting, or requiring changes in research procedures, suspension, or termination.

Confidentiality, for both subjects and investigators, to the extent allowed by law will be maintained in the reporting of adverse events.

The written report of the UPR submitted by the investigator will be presented to the IRB by the Primary Discussant who will provide assessment of the report. All associated documents will be available for IRB review. If additional information is required by the IRB in order to make a final determination concerning the event, the investigator will receive such a request in writing from the IRB. In addition, and if necessary, the IRB may directly audit the research and medical records pertaining to the event or interview witnesses.

The IRB will determine whether each reported problem represents an unanticipated problem involving risks to subjects or others, an unexpected death, or an expected outcome based on the subjects medical history or the nature of the study as described in the protocol and informed consent. The IRB will determine appropriate actions for mitigating unexpected problems. Unanticipated problems involving risks to human subjects or others will be promptly reported to OHRP, FDA, and the appropriate University officials. The IRB may additionally require that such problems be communicated to the other participants in the study, and that all study participants be re-consented if the information regarding risks would be reasonably expected to affect their willingness to continue in the study. Other potential actions include revising the protocol and informed consent form for future subjects, requiring changes in study procedures, or suspending the study temporarily or permanently.

The Director, Human Research Protections Program, is responsible for reporting unanticipated problems involving serious risks to subjects, instances of serious or continuing noncompliance with regulations or committee requirements, and any suspension or termination or committee approval, to the US Food and Drug Administration, OHRP and appropriate institutional officials, in compliance with guidance provided by federal regulations and University policy.

Information about serious adverse events *not* deemed to be UPRs at this site needs to be reported at least annually as part of a “re-submission” of the study or Continuing Review submission. The information to be provided regarding non-UPRs includes subject ID; description of event, date of event; any costs (if known); who paid the costs (if known); and PI’s assessment of the event (e.g., likelihood the event caused by the study including unlikely and definitely unrelated).

Definitions

1. Unanticipated (unexpected) problems/events are those that are *not* already described as potential risks in the consent form, *not* listed in the Investigator’s Brochure or *not* part of an underlying disease. Anticipated (expected) problems/events do NOT meet the IRB’s definition of UPRs.
2. Serious problems/events are those, which in the opinion of the Principal Investigator involve risk to subjects or others. Examples may include death, hospitalization, disability as well as breach of confidentiality. Non-serious problems/events do NOT meet the IRB’s definition of UPRs.
3. A Serious Adverse Event is defined by the FDA as any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. FDA Federal Regulations require IND sponsors to report serious AEs via expedited reporting.
4. Problems/events that are unanticipated and serious should be reported to the IRB within 10 working days *only* if in the opinion of the Principal Investigator they are possibly, probably or definitely related to the research procedures. Those serious, unanticipated problems/events that the Principal Investigator deems unlikely or not related do NOT meet the IRB’s definition of UPRs; however, these events must be reported to the IRB at least annually at the time of 10-year “re-submission” or Continuing Review submission.

Examples

The following types of events are examples of unanticipated problems involving risks to participants or others that should be reported to the IRB:

1. Any serious accidental or unintentional change to the IRB-approved protocol that involves risk or has the potential to recur.

2. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
3. Any publication in the literature, data and safety monitoring report, interim result (e.g., suspension of enrollment due to new risk information) or other finding that indicates an unexpected change to the risk/benefit ratio of the research.
4. Any breach in confidentiality or privacy that may involve risk to a participant or others.
5. Any complaint of a subject that indicates an unanticipated risk (e.g., unexpected side effect) or that cannot be resolved by the research staff.
6. In FDA clinical trials, adverse events that involve participants enrolled at sites under the direct purview of the UC San Diego IRB that are serious, unexpected, and reasonably related to the study treatment or intervention and that are expected to result in a change to the protocol or consent documents and/or dissemination of new information to subjects and any unanticipated adverse device effect occurring during the trial.
7. Any other event that indicates participants or others might be at risk of serious, unanticipated harms that are reasonably related to the research.

IRB Review of Reports of Unanticipated Problems Involving Risks to Participants

The IRB evaluates the report and determines whether the event constitutes an unanticipated problem. The IRB will also make a decision as to what the appropriate remedies should be, including whether research should be suspended or terminated, and whether the event needs to be reported to federal departments or agencies, such as Office of Human Research Protection (OHRP) or the Food and Drug Administration (FDA), and the UCSD Institutional Official.

Procedures

1. Principal investigator submits AE and UPR reports in a timely fashion to the HRPP and develops a Research Plan describing data and safety monitoring.
2. IRB Administrator reports UPRs, instance of serious or continuing noncompliance with regulations or committee requirements, to the FDA, OHRP, and other appropriate institutional officials in compliance with federal regulations and institutional policies.

Applicable Regulations, Forms and Links

[FDA Guidance for Reporting Adverse Events](#)

[Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events](#)

[Reporting Unanticipated Problems Involving Risk to Participants or Others \(UPRs\) to the IRB fact sheet](#)

[Decision Tree for Reporting Unanticipated Problems and Adverse Events in Research to the IRB and RCP](#)

[Report Of Unanticipated Problem Involving Risk To Subject Or Others form](#)