Reporting Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others

Introduction

This policy details the Institutional Review Board (IRB) requirements for reporting adverse events and unanticipated problems that occur during the course of a research project. Department of Health and Human Services Regulations (DHHS) and Federal and Drug Administration (FDA) regulations require investigators to promptly report “to the IRB … all unanticipated problems involving risks to human subjects or others” (45CFR56.108(b)(1), 21 CFR 312.53(c)(1)(vii), and 21 CFR 312.66). In addition, federal regulations (45 CFR 46.109(e) and 21 CFR 56.109(f)) require the IRB to conduct continuing review of a study at intervals appropriate to the degree of risk presented by the study, but at least annually. To ensure that the risk/benefit ratio remains acceptable, the IRB must consider the occurrence of unanticipated problems.

Department of Health and Human Services (DHHS) and Food and Drug Administration Regulations (FDA) do not consistently define or use the term adverse event, nor is there a common definition of this term across public or private, government and non-government entities. The definition used in this guidance is modified from the definition of an adverse event from the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice.

Definitions

Adverse event: Any untoward or physical or psychological occurrence or undesirable and unintended effect for a participant that may present during interventions and interactions used in the research or from the collection of identifiable private information under the research, whether or not there may be a relationship to the individual’s participation in the research.

Anticipated problem/adverse event: Any foreseen or expected problem or event which was described in the general investigational plan, the current application, the current investigator brochure, or in the informed consent document submitted to the IRB.

Related to the research: An event is related to the research if, in the opinion of the investigator, it was, more likely than not, the result of the interventions or interactions used in the research or the result of the collection of identifiable private information in the research (i.e., there is a reasonable possibility that the event may have been caused by participation in the research).

Serious adverse event: Any adverse event temporally associated with the individual’s participation in research that meets any of the following criteria:

- Results in death
- Is life threatening (places the subject at immediate risk of death from the event as it occurs)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
• Based upon appropriate medical judgment, may jeopardize the individual’s health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

• Results in a breach of confidentiality that is damaging to the participant’s rights, employment, financial standing or reputation

**Unanticipated problems involving risks to subjects or others:** Any incident, experience, or outcome that meets **all** of the following criteria:

• Is 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.

• Is related or possibly related to an individual’s participation in the research.

• Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known.

**Unexpected adverse event:** Any adverse event occurring in one or more participants in a protocol when the nature, severity, or frequency is not consistent with either

• the known or foreseeable risk of adverse events associated with the research procedures that are described in (a) the protocol-related documents (i.e., the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document) and (b) other relevant sources of information (i.e., product labeling and package inserts); or

• the expected natural progression of any underlying disease, disorder, or condition of the individuals(s) experiencing the adverse event and the individual’s predisposing risk factor profile for the adverse event.

**Unanticipated adverse device effect (UADE):** For studies of medical devices, the investigational device exemption regulations define an unanticipated adverse device effect as “any serious effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects” (21 CFR 812.3(s)).

**Investigator Reporting Requirements**

Investigators must promptly report to the IRB

1. any serious adverse event that is related to the research; or

2. any event that meets the definition of an unanticipated problem.

In general, a [Report of Adverse Events or Unanticipated Problems](#) should be submitted to the Office for Responsible Research within one week of an occurrence or within one week of the principal investigator becoming aware of an occurrence. If the problem poses an immediate risk of serious harm to any human subject, it should be reported immediately. If applicable, reporting must also follow the requirements set forth in any data safety and monitoring plans that are part of the approved IRB application.

For research on medical devices, an unanticipated adverse device effect (UADE) must be reported to the IRB and the sponsor as follows:
• A report of a UADE must be submitted to the sponsor and the reviewing IRB as soon as possible but in no event later than 10 working days after the investigator first learns of the event (21 CFR 812.150(a)(1)).
• Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to the FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (21 CFR 812.46(b), 21 CFR 812.150 (b)(1)).

Relationship between Adverse Events and Unanticipated Problems

An unanticipated problem is by definition unexpected, whereas an adverse event may be expected or unexpected. Adverse events relate to harm to participants; unanticipated problems may involve an increased risk of harm even if no actual harm occurred.

Examples of unanticipated problems that should be reported include the following:
• A breach in confidentiality resulting from disclosure of confidential information or from lost or stolen confidential information that may involve risk to the subjects or others
• Complaint of a participant or family member that indicates an unanticipated risk
• Laboratory or medication errors that may involve potential risk to the individual or others
• Disqualification or suspension of investigators
• Accidental or unintentional change to the IRB-approved protocol that involves risks or has the potential to recur
• Deviation from the IRB-approved protocol without prior IRB review to eliminate apparent immediate hazard to a research participant
• Any deviation from the IRB-approved protocol that increases risk or affects the participants’ rights, safety, or welfare
• Publication in literature, a safety monitoring report, interim results, or other finding that indicates an unexpected change in the risk/benefit ratio of the research

Any adverse event (AE) must be reported (whether or not it is serious) if it meets the definition of an unanticipated problem (i.e., unexpected, related to the research, suggests increased risk of harm to subjects or others). In general, the following types of adverse events should be considered as unanticipated problems that must be reported to the IRB:
• Single occurrence of a serious, unexpected, and uncommon event that is strongly associated with the research
• A single or small number of a serious, unexpected event that is not commonly associated with the research procedures but is unusual given the study population
• Multiple occurrences of an AE that, based on aggregate analysis, is determined to be an unanticipated problem (There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects [e.g., a comparison of rates across treatment groups in the drug treatment arm versus a control].)
• An AE that is described in the investigator’s brochure, protocol, or informed consent documents but occurs at a specificity or severity that is inconsistent with prior observations
• A serious AE that is described in the investigator’s brochure, protocol, or informed consent documents but for which there is a significant increase in the expected rate of occurrence (Ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison.)
• Any other AE or safety finding, including those based on animal or epidemiologic data, that would cause the sponsor to modify the investigator’s brochure, protocol, or informed consent documents or would prompt other action by the IRB to ensure the protection of human subjects

**IRB Process for Handling Reported Problems**

1. Upon review of the form, the IRB Co-chair(s) will (a) determine if the report includes the necessary information, (b) perform an initial evaluation, and (c) consult with appropriate individuals (e.g., physician on the IRB) if necessary.

2. If, in the judgment of the IRB Co-chair or the Director of the Office for Responsible Research, participants may be at immediate risk of harm and there is insufficient time to wait for review by the convened IRB, an IRB Chair, Co-Chair, or the Director of the Office for Responsible Research will require the principal investigator to suspend the study in accordance with the IRB policy for suspension or termination of research. (See the SOP for “Suspension or Termination of IRB Approved Research.”)

3. If participants are not at immediate risk, the report will be scheduled for review at the next meeting of the convened IRB.

4. Accidental or unintentional deviations to the IRB-approved protocol that do not involve risks are reviewed by the IRB Co-chair(s) and forwarded to the Director of the Office for Responsible Research for review for potential noncompliance.

5. For all unanticipated problems/serious adverse events submitted under the IRB’s prompt reporting policy, the convened IRB determines whether the problem/event involves risk to research participants or others and specifies any corrective actions. If the problem/event involves risk to subjects or others, the IRB will follow the regulatory reporting requirements. The IRB actions may include the following:
   - Acknowledgement/acceptance without further recommendation
   - A request for further clarification from the investigator
   - Changes in the protocol (e.g., additional tests or visits to detect similar events in a timely fashion; changes to the confidentiality measures employed in the study)
   - A requirement to inform subjects already enrolled about additional risks
   - A change in frequency of continuing review
   - Further inquiry into other protocols utilizing particular dietary supplements, devices, or procedures in question
   - Requirements for additional training for investigators and/or research staff
   - Monitoring of the research procedures or informed consent process
   - Referral to other organizational entities (e.g., University Counsel)
   - Suspension or termination of the study
   - Request for quality improvement review or other actions deemed appropriate by the IRB

6. If the IRB acknowledges/accepts the report and deems that no further follow-up is required, ORR staff will send a letter to the PI indicating the review outcome.

7. If the committee requests clarification(s) or addition, information or revisions, ORR staff will notify the PI in writing of the need for additional information and/or changes.

8. The Director of the Office for Responsible Research will draft and submit reports related to IRB determinations to federal agencies or sponsors, as required under federal regulations.
Resources

1. 45 CFR part 46 – Protection of Human Subjects
2. 21 CFR part 50 – Protection of Human Subjects
3. 21 CFR part 56 – Institutional Review Board
4. 21 CFR part 312 – Investigational New Drug Application
5. 21 CFR part 812 – Investigational Device Exemptions