Reporting of Adverse Events and Unanticipated Problems
Involving Human Research Participants

This guidance outlines Chapman IRB’s requirements for reporting adverse events and unanticipated problems that occur during the course of a research project. Unanticipated problems or adverse events can occur in any type of research (e.g., medical, social, behavioral, or educational research). Some events are expected (e.g., lightheadedness during blood collection), while others are unexpected (e.g., theft of devices containing data). Events also vary in seriousness and the extent to which they are related to the research.

Reporting adverse events and unanticipated problems facilitates protection of research participants by allowing investigators and the IRB to determine whether the event or problem indicates changes are necessary to minimize risk, ensure the risk/benefit ratio remains favorable, and ensure participants are fully informed.

Background

The Department for Health and Human Services (HHS) and the Food and Drug Administration (FDA) regulations provide the basis for the IRB’s guidance regarding reporting adverse events and unanticipated problems.

HHS regulations:

- Require researchers to promptly report any unanticipated problems involving human research participants to Office for Human Research Protections (OHRP), institutional officials, and the sponsoring agency [45 CFR 46.103(a)];
- Require the responsible IRB to make certain determinations regarding risks to participants prior to approving research and at least once per year unless continuing review is not required [45 CFR 46.111(a); 45 CFR 46.109(e)-(f)];
- Require institutions engaged in research to have written procedures for ensuring prompt reporting of unanticipated problems involving risks to participants or others [45 CFR 46.108(a)(4)]; AND
- Give the responsible IRB the authority to terminate IRB approval of research that is associated with unexpected serious harm to participants [45 CFR 46.113]

FDA regulations:

- Require investigators to promptly report to the IRB all unanticipated problems [21 CFR Parts 56, 312 and 812].
- Require investigators to submit to the IRB and the sponsor a report of an unanticipated adverse device event (UADE) no later than 10 working days after the investigator learns of the event [21 CFR 812.150(a)(1)].
Definitions

**Unanticipated problems involving risks to participants 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 participant population being studied;
- Is related or possibly related to an individual’s participation in the research; and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, social, economic, legal, or informational harm) than was previously known.

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

**Adverse event:** Any untoward or unfavorable occurrence in a research participant that is temporally associated with the participant’s involvement in the research. An adverse event encompasses physical, psychological, social, economic, legal, or informational harms. It may or may not be directly related to the individual’s 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; or
- Causes significant psychological, social, economic, or legal harm to the participant or others.

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

- the known or foreseeable risk 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 (e.g., 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 participants (21 CFR 812.3(s)).

**Anticipated problem/adverse event:** Any foreseen or expected problem or event that was described in the IRB-approved research protocol, any applicable investigator brochure, and/or the current IRB-approved informed consent document.

**How do researchers determine which adverse events are unanticipated problems?**

The key question regarding a particular adverse event is whether it meets the three criteria for being defined as an unanticipated problem: (1) the adverse event is unexpected, (2) the adverse event is related or possibly related, **AND** (3) the adverse event suggests that the research places participants or others at a greater risk of harm than was previously known or recognized.

**Procedures for reporting adverse events and unanticipated problems**

**Reporting forms are available in Cayuse IRB.** On the main Study Information page for the relevant protocol, select Incident to create an Adverse Event/Unanticipated Problem form.

The investigator shall include a clear explanation of why the adverse event or series of adverse events has been determined to be an unanticipated problem; and a description of any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem.

**Time frame for reporting**

**Report within 48 hours of discovery or notification:**
- An internal death the investigator determines to be directly related/possibly related to a study intervention (*not natural causes or underlying disease progression*)
- Events resulting in temporary or permanent interruption of study activities by the investigator, sponsor, or Data Safety Monitoring Board (DSMB) to avoid potential harm to participants

**Report within 10 working days of discovery or notification:**
- Internal unanticipated problems (i.e., related/possibly related, serious, AND unexpected)
- Any internal adverse event that an investigator believes could influence the safe conduct of the research

**Report at the time of continuing review:**
- Internal adverse events that are related/possibly related but are not deemed to be anticipated problems (i.e., related/possibly related, unanticipated, not serious)
- A summary of external adverse events that increased risk to participants or others
References