

19.0 Reporting of Unanticipated Problems and Adverse Events to the IRB

Federal regulations require investigators to report to the IRB any unanticipated problems involving risks to subjects or others. There has historically been confusion about what needs to be reported. Therefore, it is important to delineate the definitions that inform reporting requirements. In particular, it is important to understand the difference between “adverse events” and “unanticipated problems” because many adverse events are not reportable. OHRP and FDA have issued guidance that clarifies what should be reported to the IRB, and UNC-Chapel Hill policy is based on this guidance. This federal guidance clarifies that investigators need only report unanticipated problems. Adverse events that are not unanticipated problems are not required to be reported to the IRB. (See Appendix U).

19.1 Definitions

19.1.1 According to federal guidance, “unanticipated problems involving risks to subjects or others” or “Unanticipated Problem” (UP) refers to any incident, experience, or outcome that:

- 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 a subject’s participation in the research; and
- 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 or recognized.

Note that for UNC-Chapel Hill reporting purposes an event that satisfies the first two criteria will be considered reportable. See SOP 19.4 for additional information.

19.1.2 “Adverse event” or “adverse experience” (AE) is any untoward or 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. Adverse events encompass both physical and psychological harms and occur most frequently in the context of biomedical research, although they can occur in the context of social and behavioral research.

19.1.2.1 “Internal adverse event” is an adverse event experienced by subjects enrolled by the investigator(s) at UNC-Chapel Hill or UNC Health Care System or at a site

for which a UNC-Chapel Hill IRB has oversight. In the context of a single-center clinical trial, all adverse events would be considered internal adverse events.

19.1.2.2 “External adverse event” is an adverse event experienced by subjects enrolled by investigators at other (“outside”) institutions engaged in a multi-site clinical trial.

19.1.3 “Serious Adverse Event” (SAE) is any adverse event temporally associated with the subject’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 occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- any other adverse event that, 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 (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

19.1.4 “Unexpected Adverse Event” as defined by the FDA, is any adverse event, the specificity or severity of which is not consistent with the current Investigator Brochure; or, if an Investigator Brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

19.1.5 “Possibly related to the research” refers to the reasonable possibility that the adverse event, incident, experience or outcome may have been associated with the procedures involved in the research (modified from the definition of associated with use of the drug in FDA regulations at 21 CFR 312.32(a)).

19.1.6 “Related to the research” refers to an incident, experience or outcome that is likely to have resulted from participation in the research study.

19.1.7 “Data Safety Monitoring Plan” (DSMP) is a plan written to ensure that the relevant data are collected and assessed to monitor subject safety within a study. Part of the DSMP may be the

establishment of a Data and Safety Monitoring Board (DSMB), also called a “Data Monitoring Committee” (DMC), but this is not necessarily required for every DSMP. Ongoing review of the data by an independent individual or committee assures the investigator(s) that the trial can continue without jeopardizing patient safety. Monitoring activities should be conducted by experts in the disciplines needed to interpret the data and ensure patient safety and should be external to (independent from) the study.

The IRB’s evaluation of the DSMP should include:

- Reporting mechanisms
- Frequency of monitoring regarding time or number of subjects
- Specific data to be monitored
- Procedures for analysis and interpretation of the data
- Actions at defined events or end points
- Procedures for communication from the data monitor to the IRB and sites

DSMBs for multi-site studies are responsible for forwarding summary reports of adverse events to each IRB involved in the study.

19.2 Deciding if an event meets the criteria for Unanticipated Problem

19.2.1 Is it unexpected?

An event is unexpected if it occurs in one or more subjects or others participating in a research protocol, and the event’s nature, severity, or frequency is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject’s predisposing risk factor profile for the adverse event.

19.2.2 Is it related or possibly related to a subject’s participation in the research?

Events that related or possibly related to participation the in the research may be caused by one or more of the following:

- The procedures involved in the research;

- An underlying disease, disorder, or condition of the subject;
- Other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

In general, events that are determined to be at least partially caused by the procedures in a study would be considered related to participation in the research, whereas events determined to be solely caused by the subject's condition or state of illness or other circumstances clearly outside of the study would be considered unrelated to participation in the research.

19.2.3 Does it suggest that the research places subjects or others at greater risk of harm than was previously known or recognized?

Adverse events that are unexpected, related or possibly related to participation in research, and serious are the most important subset of adverse events representing unanticipated problems, because such events always suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. These events warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects.

Other adverse events that are unexpected and related or possibly related to participation in the research, but not serious, would also be unanticipated problems if they suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. These events should also be reported, for consideration of changes or corrective actions.

19.3 Differentiating between an Unanticipated Problem and an Adverse Event

By definition, an "unanticipated problem" is unexpected, whereas an "adverse event" may be anticipated or unanticipated. Additionally, an unanticipated problem may involve the increased risk of harm—whether or not any actual harm occurred. In order to decide which events or circumstances constitute an unanticipated problem, it is important to bear in mind the following:

- Not all Adverse Events are Unanticipated Problems. Only a small subset of "adverse events" occurring in FDA-regulated clinical trials and other types of studies constitute unanticipated problems and therefore must be reported promptly to the IRB. Many events that are required to be reported to the sponsor or federal agency are not unanticipated problems.

- An unanticipated problem may not be an Adverse Event. It is possible for an event that does not involve actual physical, psychological, social, or economic harm to a research subject or another person nevertheless to constitute an unanticipated problem that must be reported to the IRB. This is the case if the event places subjects or others at increased or different risk of harm, regardless of whether actual harm has occurred.

There are other types of incidents, experiences and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at risk of harm, but no harm occurs. For example, an investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's car on the way home from work. This is an unanticipated problem that must be reported because the incident was (a) unexpected (i.e., the investigators did not anticipate the theft); (b) related to participation in the research; and (c) placed the subjects at a greater risk of psychological and social harm from the breach in confidentiality of the study data than was previously known or recognized.

Examples of unanticipated problems that should be reported to the IRB, even though they are not adverse events, include:

- Publication in the literature, safety monitoring report (e.g., DSMB report), interim result, or other finding that indicates an unexpected change to the risk/benefit ratio of the research;
- Breach in confidentiality resulting from a disclosure of confidential information or from lost or stolen confidential information, that may involve risk to that individual or others;
- Complaint of a participant or family member that indicates an unanticipated risk;
- Laboratory or medication errors that may involve potential risk to that individual or others;
- Change in FDA labeling because of adverse consequences or withdrawal from marketing of a drug, device, or biologic used in a research protocol;
- 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 protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant
- Any deviation from the IRB-approved protocol that increases the risk or affects the participant's rights, safety, or welfare.

19.4 Required Reporting of Unanticipated Problems

Reporting is required of all unanticipated problems, including those which may occur after the participant has completed or has withdrawn from the study, including after study closure. This reporting is carried out through completion of an online form found at the OHRE website.

Expectations for reporting include:

- Any Unanticipated Problem involving risks to subjects or others which occurred at a site for which a UNC–Chapel Hill IRB has oversight. For UNC–Chapel Hill purposes, a reportable UP is any incident, experience or outcome that is unexpected and related or possibly related to the research (the first two criteria in 19.1). Upon review of the unexpected and related/possibly related event, the IRB will make the final determination as to whether the event places the subjects at greater risk than previously recognized (the third criterion in 19.1).
- Any event occurring at UNC–Chapel Hill or other location, whether or not UNC–Chapel Hill IRB has direct oversight responsibility, in which a determination has been made by the research sponsor, coordinating center, DSMB/DMC or other centralized monitoring group that the event meets the three criteria for an Unanticipated Problem involving risks to subjects or others (see 19.1.1).

19.5 Timing of Unanticipated Problem (UP) Reports

Unanticipated Problems that are serious adverse events should be reported to the IRB within one (1) week of the investigator becoming aware of the event.

Any other Unanticipated Problem should be reported to the IRB within two (2) weeks of the investigator becoming aware of the problem.

If the Unanticipated Problem Report cannot be completed in its entirety within the required time period, a preliminary report should be submitted. The Unanticipated Problem Report should be amended once the event is resolved and/or more information becomes available.

19.6 Handling non-reportable adverse events and IND safety reports

All individual AE and IND Safety Reports shall be maintained by the Investigator. For those events that are not reportable to the IRB under this policy (19.1.1), a summary (i.e., not individual reports) of all adverse events that have occurred within the last approval period should be submitted to the IRB at the time of continuing review.

Reports from a DSMB/DMC or other independent safety monitoring group should be provided to the IRB on a regular basis, generally at least as often as the study undergoes continuing review. Reports should include findings from adverse event reports and recommendations derived from data and safety monitoring.

19.7 Additional Reporting Responsibilities

It is the Investigator's responsibility to make all required reports of unanticipated problems or adverse events to the FDA and/or sponsor. Because the UNC–Chapel Hill IRB does not require the reporting of many adverse events, this does not obviate the investigator's contractual relationships with sponsors or the FDA.

19.8 IRB and Institutional Responsibilities

The chair or designee(s) of the UNC-Chapel Hill IRB will review all reports of unanticipated problems. If a reported event poses serious risk to subject safety, the chair or designated subcommittee may immediately suspend the study. In most cases, the IRB will review a corrective action plan with the PI in order to resolve the immediate scenario and prevent future occurrences.

Any unanticipated problem involving more than minimal risk(s) to participants or others will be reviewed by the convened IRB. For unanticipated problems referred to the convened IRB, all members will receive the application and consent form, where relevant, and materials describing the unanticipated problem as well as any correspondence with the investigator to date.

The IRB has the authority to suspend or terminate IRB approval of protocols that are found to pose unanticipated or heightened risk. Other actions taken by the IRB may include but are not limited to modification of the research protocol; (ii) modification of the information disclosed during the consent process; (iii) additional information provided to past participants; (iv) notification of current participants, which is required when such information might relate to participants' willingness to continue to take part in the research; (v) requirement that current participants re-consent to participation; (vi) modification of the continuing review schedule; (vii) monitoring of the research; (viii) monitoring of the consent; (ix) obtaining more information pending a final decision; (x) referral to other organizational entities (e.g., Office of University Counsel, Office of Research Compliance, Institutional Official); and/or (xi) requirements for additional training for investigators and/or research staff. Determinations from the convened IRB meeting are documented in the minutes.

The Institutional Official is responsible for all required reporting of unanticipated problems involving risks to subjects or others and the resulting IRB actions to the appropriate federal agencies. This reporting would generally be coordinated through the OHRE. (See SOP 36.0)

References:

21 CFR 312.66

45 CFR 46.103(b)(5)

OHRP Guidance Document, "Adverse Event Reporting Requirements," January 15, 2007

FDA Guidance for Clinical Investigators, Sponsors, and IRBs, "Adverse Event Reporting-Improving Human Subject Protection", April 2007

"NIH Policy for Data and Safety Monitoring," June 10, 1998

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