**Title:** Unanticipated Events and Adverse Events
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**Standard Operating Practice**: 25

## 25.1. Executive Summary

This document provides information regarding NC State University IRB's unit standard for unanticipated problems and adverse events. This document outlines processes and expectations for reporting and addressing unanticipated problems and adverse events.

## 25.2. Standard Operating Practice

NC State University investigators and Institutional Review Board (IRB) staff have an obligation to report unanticipated problems involving risks to subjects or others, and certain types of adverse events. Investigators must report applicable unanticipated problems and adverse events to the IRB as outlined in this unit standard. The IRB will then review the report and consider corrective actions or substantive changes, as necessary, in order to protect the safety, welfare, and rights of subjects or others. The IRB also has an obligation to report identified unanticipated problems to the Office for Human Research Protections (OHRP). These policies and procedures apply to all human subject research under the jurisdiction of the NC State University IRB office.

## 25.3. Operational Procedures

### 25.3.a. Definition of Terms

#### 25.3.a.i. Adverse Event

1. 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.
2. Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.
3. A serious adverse event is one that:
    a. results in death;
    b. is life-threatening (i.e., places the subject at immediate risk of death from the event occurrence);
    c. results in inpatient hospitalization or prolongation of existing hospitalization;
    d. results in a persistent or significant disability/incapability;
    e. results in a congenital anomaly or birth defect;
    f. based on appropriate medical judgment, may jeopardize the subject's health or require medical or surgical intervention

#### 25.3.a.ii. Unanticipated Problem

1. An unanticipated problem is an incident, experience, or outcome that meets all of the following criteria:
    a. unexpected (in terms of nature, severity, or frequency) given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, and the characteristics of the subject population being studied;
    b. related or possibly related to a subject's participation in the research; and

c. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

#### 25.3.a.iii. Possibly Related

There is a reasonable possibility that the problem, event, incident, experience, or outcome may have been caused by the procedures involved in the research. Adverse events may be caused by one or more of the following:

1. the procedures involved in the research;
2. an underlying disease, disorder, or condition of the subject; or
3. other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

In general, adverse events that are determined to be at least partially caused by (1) would be considered related to participation in the research, whereas adverse events determined to be solely caused by (2) or (3) would be considered unrelated to participation in the research.

### 25.3.b. Reporting Process

#### 25.3.b.i. When to Report a Problem or Event

1. Investigators must report all unanticipated problems, including unanticipated problems that are also adverse events to the IRB.
2. The vast majority of adverse events occurring in human subjects research are not unanticipated problems
3. Most adverse events do not meet the first criterion for an unanticipated problem and do not need to be reported.

#### 25.3.b.ii. Reporting Timeline Requirements

1. The investigator must promptly report any unanticipated problems and adverse events to the NC State University IRB by:
    a. completing the Report Unanticipated or Adverse Events online form (opens in a new window); or
    b. emailing the IRB Director at irb-director@ncsu.edu.
2. The NC State University IRB requires investigators to report in accordance with the following guidelines in order to satisfy the prompt reporting requirement:
    a. Unanticipated problems and adverse events must be reported to the IRB within five business days of the investigator becoming aware of the event.
        i. The IRB strongly recommends that a preliminary report be submitted by the researcher within 48 hours of learning of the serious adverse event with a formal follow-up report submitted within the above timeline.
        ii. Investigators should not include identifiable information about research subjects in the report.
    b. The IRB chair or their designee will report all unanticipated problems or adverse events as appropriate to the institutional official (IO), the supporting agency head (or designee), and to OHRP (for federally funded research) within one month of the IRB's receipt of the report of the problem from the Investigator.
    c. In some cases, the requirements for prompt reporting may be met by submitting a preliminary report to the IRB, the IO, the supporting HHS agency head (or designee), and OHRP, with a follow-up report submitted at

a later date when more information is available. Determining the appropriate time frame for reporting a particular unanticipated problem requires careful judgment by persons knowledgeable about human subject protections. The primary consideration in making these judgments is the need to take timely action to prevent avoidable harms to other subjects

**25.3.b.iii. Making a Report**

1. When making a report to the NC State University IRB, an investigator should include the following information:
    a. appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
    b. a detailed description of the adverse event, incident, experience, or outcome. Subject names and identifiable information should not be included in the report;
    c. an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem; and
    d. a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

**25.3.b.iv. Researcher Reporting Responsibilities**

1. The investigator is responsible for assessing and documenting unanticipated problems and adverse events and reporting to the IRB, as required by this policy, regardless of who observed or became aware of the event.
2. The investigator should use their judgment when determining if an event or problem is considered reportable. When in doubt, the investigator should contact the IRB for guidance.
3. In the absence of the investigator, a co-investigator can fulfill these requirements to meet the reporting timeline.
4. In the absence of either the investigator or a co-investigator, any other research personnel must contact the IRB for direction.
5. For collaborative research, unanticipated problems and adverse events should be reported to the IRB of Record.
    a. When NC State University IRB is the IRB of Record
        i. Unanticipated problems and adverse events must be reported in accordance with this unit standard regardless of where the unanticipated problem or adverse event occurred.
        ii. The NC State investigator is responsible for coordinating the reporting.
    b. When NC State University IRB is the Relying IRB
        i. Unanticipated problems and adverse events must be reported in accordance with the policies and procedures of the reviewing IRB including informing the NC State IRB of the issue.
6. The investigator must fulfill the reporting requirements of other organizations (e.g., sponsor) that are not satisfied nor precluded by submitting an unanticipated problem and adverse events report to the IRB. Likewise, submitting unanticipated problem or adverse event reports to other organizations (e.g., sponsor) does not satisfy the reporting requirement to the IRB.

### 25.3.c. IRB Review and Response

#### 25.3.c.i. Initial Review

1. Initial review of unanticipated problems and adverse events will be conducted by the IRB director, IRB chair, or designee unless another IRB member is specifically named by the IRB director or institutional official or a conflict of interest prevents this duty.
2. The IRB director (or designee) is authorized to take the following actions in response to any incident report:
    a. Conduct an administrative review of the report, including assessing whether the incident constitutes an unanticipated problem and by whom it should be reviewed (e.g., the IRB director only, IRB chair only, an IRB subcommittee, or the convened full board IRB).
    b. If convened full board IRB review is needed, the IRB director or designee assigns the incident report for review at the next available regularly scheduled IRB meeting. Alternatively, the IRB director may convene an emergency meeting of the IRB to review the report.
    c. If the IRB director (or designee) finds that the rights, safety, and welfare of subjects are jeopardized by the research, the IRB director may suspend research until such time that the full IRB can convene to review the report.
3. When reviewing a report of an unanticipated problem or adverse event, the IRB should consider whether the affected research protocol still satisfies the criteria for IRB approval under regulations at 45 CFR 46.111. The IRB should consider whether risks to subjects are still minimized and reasonable in relation to the anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result.
4. When reviewing a particular incident, experience, or outcome reported as an unanticipated problem by the investigator, the IRB may determine that the incident, experience, or outcome does not meet all three criteria for an unanticipated problem. In such cases, further reporting to appropriate institutional officials, the department or agency head (or designee), and OHRP would not be required.
5. The IRB chair or their designee is responsible for reporting unanticipated problems to OHRP and/or the Food and Drug Administration (FDA), as required.

#### 25.3.c.ii. Possible Post-Review Required Actions

1. After reviewing the unanticipated problem or adverse event report, the IRB may require the following actions in order to protect the ongoing safety of research subjects:
    a. modification of subject inclusion or exclusion criteria to mitigate the newly identified risks;
    b. implementation of additional procedures for monitoring subjects;
    c. modification of informed consent documents to include a description of newly recognized risks
    d. provision of additional information about newly recognized risks to previously enrolled subjects;
    e. suspension of enrollment of new subjects;
    f. suspension of research procedures for currently enrolled subjects;
    g. suspension of the entire study; and/or
    h. termination of approval for the entire study.

2. If the response to an unanticipated problem or adverse event requires an amendment of the research protocol and/or informed consent forms, an amendment request must be submitted to the IRB.
    a. If the changes are minor, they may be reviewed by expedited review procedures.
    b. If the changes are more than minor, they must be reviewed and approved by the convened full board.
    c. Any such proposed changes in response to an unanticipated problem must be reviewed and approved by the IRB before being implemented, except when implementation is necessary to eliminate apparent immediate hazards to subjects.