

Cornell University
Office of Research Integrity and Assurance
Human Research Participant Protection Program

SOP 4: UNANTICIPATED PROBLEMS INVOLVING RISK TO HUMAN RESEARCH PARTICIPANTS OR OTHERS:
PROCEDURES FOR REPORTING TO, AND REVIEW BY, THE IRB

1. Subject of Policy & Procedure

Cornell's Federalwide Assurance of Compliance with DHHS Regulations for the Protection of Human Subjects states that: "Research investigators will promptly report to Cornell's Institutional Review Board (IRB) any injuries or other unanticipated problems involving risks to human subjects and others" (Section IV.A.). The IRB, in turn, is required to report promptly such unanticipated problems to the appropriate Institutional Official and federal regulatory authority — generally, the Office of Human Research Protections (OHRP) or the Food and Drug Administration (FDA). An unanticipated problem involving risk to human participants or others, in short, is one that (1) was unforeseen at the time of its occurrence, and (2) indicates that participants or others are at an increased risk of harm. This policy sets forth what types of experiences in the course of a research study qualify as unanticipated problems involving risk to participants or others and what constitutes prompt reporting. This policy also outlines procedures for the reporting and review of such unanticipated problems.

2. Scope of Policy & Procedure

This Policy & Procedure applies to all on-going and future human participant research projects conducted by Cornell faculty, staff, or students or by anyone conducting a research activity supported by Cornell or on property maintained by Cornell.

3. Terms and Definitions

Employees (faculty and staff) and students should consult the IRB Glossary at <http://www.irb.cornell.edu/glossary/>.

4. See Also

Affected researchers and employees should also consult:

1. Cornell University Federal Wide Assurance Registration: <http://www.irb.cornell.edu/regulations/fwa.htm>
2. Unanticipated Problem Report Form: <http://www.irb.cornell.edu/forms/>

5. Regulations and Guidance Applicable to Reporting and IRB Review of Unanticipated Problems

5.1. Federal Regulations

- 5.1.1. 45 CFR 46.103: Requirement for written assurance of compliance with 45 CFR 46; in particular, 45 CFR 46.103(5): Requirement for written procedures for ensuring, in part,

“prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of any unanticipated problems involving risks to subjects or others.”

- 5.1.2.** 21 CFR 56.108: IRB Functions and Operations; in particular 21 CFR 56.108(b): Requirement for written procedures for ensuring “prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of any unanticipated problems involving risks to human subjects or others.”

6. Procedures for Prompt Reporting and Review of Unanticipated Problems within Cornell:

6.1. Unanticipated Problems Defined:

- 6.1.1.** An unanticipated problem involving risk to human participants or others is one that (1) was unforeseen at the time of its occurrence, and (2) indicates that participants or others are at an increased risk of harm. The Protocol Principal Investigator (Protocol PI) should promptly report to the IRB any harm experienced by a participant or another person, which in the Protocol PI’s opinion, is both unanticipated and related to the research, regardless of whether the harm was an onsite or offsite event, and regardless of whether the harm was serious or non-serious. An unanticipated problem is related to the research if in the opinion of the Protocol PI, the problem was more likely than not caused by the research procedures or if it is more likely than not that the problem affects the rights and welfare of current research participants.

One type of unanticipated problem is the adverse event, which is any harm experienced by a participant regardless of whether the occurrence was on-site or off-site and which, in the opinion of the Protocol PI is both unexpected and related to the research. An adverse event is unexpected when its specificity and severity are not accurately reflected in the informed consent document.

- 6.1.2.** Serious adverse events requiring immediate reporting to the IRB within 24 hours of the first awareness of their occurrence, whether such awareness is first attained by the Protocol PI or another researcher, the Office of Research Integrity & Assurance (ORIA), or a member of the IRB:

- 6.1.2.1. Death of a research participant
- 6.1.2.2. Serious injury to a research participant

- 6.1.3.** Examples of non-serious unanticipated problems, including non-serious adverse events, requiring reporting within 2 weeks of the first awareness of their occurrence, whether such awareness is first attained by the Protocol PI or another researcher, ORIA, or a member of the IRB:

- 6.1.3.1. Negative, non-life threatening physical reactions in a research participant to drugs administered in a study
- 6.1.3.2. Physical consequences to a research participant from dietary manipulations (*e.g.*, fainting)
- 6.1.3.3. Negative, non-life threatening physical reactions in a research participant who has a chronic disease (*e.g.*, diabetes, heart condition)
- 6.1.3.4. Unanticipated accident to a research participant (*e.g.*, participant’s falling off a treadmill during an exercise study)

- 6.1.3.5. Display of unanticipated emotional upset or degree of emotional upset by a research participant
- 6.1.3.6. Accidental or unintentional change to the IRB-approved protocol that harmed research participants or others or that indicates that such persons may be at an increased risk of harm
- 6.1.3.7. Release, including inadvertent release, of personal information of a research participant, or some other breach of confidentiality
- 6.1.3.8. Occurrence that the sponsor requires be reported to it promptly
- 6.1.3.9. Sponsor-imposed suspension for risk
- 6.1.3.10. Acquisition of information that indicates a change to the risk-benefit analysis of the research, such as (1) an interim analysis or safety monitoring report indicating that frequency or magnitude of harms or benefits may be different from what was presented to the IRB; or (2) publication of a paper from another study showing that risks or potential benefits of the Cornell research study may be different from what was presented to the IRB.
- 6.1.3.11. Failure of equipment during a study if such failure did *or* could have resulted in harm to a research participant
- 6.1.3.12. Change to the protocol taken to eliminate an apparent immediate hazard to a research participant, without prior IRB review
- 6.1.3.13. Complaint of a participant which indicates unanticipated risks or which cannot be resolved by the research team

6.1.4. The IRB has the authority to conduct site visits to promote research integrity if the IRB receives an excessive number of unanticipated problems, or if the IRB independently suspects non-compliance or risks generated by the Protocol PI and/or the research team.

6.2. Prompt Reporting Defined:

Serious adverse events must be reported to the IRB immediately, with a written report by the PI following within 24 hours of the PI's becoming aware of the event. Serious adverse events are (1) death of a research participant; or (2) serious injury to a research participant. Even if such events are not related to the conduct of the research study, and, thus, are not required to be reported to OHRP, a Protocol PI should obtain documentation from the hospital or another appropriate source tending to show that the death or serious injury is not related to the research, and should provide this information to ORIA.

All other non-serious unanticipated problems should be reported to the IRB within 2 weeks of the first awareness of the problem by the Protocol PI or another researcher, ORIA, or a member of the IRB. Prompt reporting is important, as unanticipated problems often require some modification of study procedures, protocols, and/or informed consent processes. Such modifications require the review and approval of the IRB.

A Protocol PI should report an unanticipated problem to the IRB by completing and submitting to ORIA three hard copies of the Unanticipated Problem Report Form.

6.3. IRB Review of Unanticipated Problem Report Forms:

6.3.1. Upon receipt of the three hard copies of the Unanticipated Problem Report Form ("UP Report Form"), ORIA, in consultation with the Chair of the IRB and the Assistant Vice

President for Research Compliance, as appropriate, will review it to determine first whether the reported occurrence qualifies as an unanticipated problem, as defined above in Section 6.1.

- 6.3.1.1.** If the occurrence does not qualify as an unanticipated problem, no further action will be taken unless it is determined that serious or continuing non-compliance has occurred. *See* SOP 5: Managing Non-Compliance in Human Research Protection Program. ORIA will document this determination on the three hard copies of the UP Report Form; one copy will be retained by ORIA in accordance with SOP __: Document Management, and the other two copies will be forwarded to the Protocol PI and the Chair of the IRB.
- 6.3.1.2.** If the occurrence does qualify as an unanticipated problem, ORIA will determine next (1) whether the reported occurrence is a serious adverse event requiring review and modifications by the convened IRB; or (2) whether the reported occurrence is a non-serious unanticipated problem that can receive expedited review by the IRB Chair or the Chair's designated reviewer(s). Furthermore, ORIA will consult with the Chair of the IRB and the Assistant Vice President for Research Compliance to ensure prompt and appropriate reporting of the occurrence to the Institutional Official, OHRP, FDA, and other regulatory agencies, as appropriate, in accordance with SOP 7: Reporting Unanticipated Problems, Noncompliance, Suspensions and Terminations to Regulatory Agencies and Sponsors.
- 6.3.2.** If the reported occurrence is determined to be a serious adverse event, as defined above in Section 6.1.2, the Chair of the IRB will suspend the protocol until the convened IRB reviews and acts on the protocol. *See* SOP 6: Suspensions and Terminations of IRB Approval of Research Protocols. ORIA will place the UP Report Form on the agenda for the next meeting of the convened IRB for their discussion and resolution. The review of the UP Report Form will take place in accordance with the procedures set forth in SOP 3: Initial and Continuing Review by the IRB, Section 9.2 (Procedures for Convened Committee Review).
- 6.3.3.** If the reported occurrence is determined to be an unanticipated problem, as defined above in Section 6.1.3, the UP Report Form will be assigned for Expedited Review. An IRB member with relevant expertise will be selected by ORIA or the Chair of the IRB as the Expedited Reviewer. The IRB Chair may assign the UP Report Form to himself or herself for review or to an Expedited Reviewer with the relevant expertise, or may obtain consultation to obtain that expertise. The Expedited Reviewer may require any action with respect to the protocol at issue, except that the following recommended actions require ORIA's placing the UP Report Form on the agenda of the next meeting of the convened IRB for their discussion and resolution: (1) modification of a protocol that was previously approved by the convened IRB; and (2) termination of a previously approved protocol. The Expedited Reviewer may, however, request the Chair of the IRB to suspend a protocol until the convened IRB reviews and acts on the protocol. ORIA will email the Expedited Reviewer's comments, questions, and/or decisions (*see below*, 6.3.4) to the Protocol PI. The Protocol PI will respond in writing to ORIA, and this response will be reviewed by the Expedited Reviewer and/or the Chair of the IRB. The Protocol PI, the Expedited Reviewer, or the Chair of the IRB may request that the UP Report Form be referred to the convened IRB for a decision. If the UP Report Form is not so referred, the

IRB agenda will notify the other IRB members of the decision(s) made by the Expedited Reviewer with respect to the UP Report Form.

6.3.4. The range of possible actions that could be taken by the IRB with respect to the UP Report Form include:

- 6.3.4.1. Modification of the protocol
- 6.3.4.2. Modification of the information disclosed during the consent process
- 6.3.4.3. Providing additional information to past participants
- 6.3.4.4. Notification to current participants when such information might relate to participants' willingness to continue to take part in the research
- 6.3.4.5. Requirement that the current participants re-consent to participation
- 6.3.4.6. Modification of the continuing review schedule
- 6.3.4.7. Monitoring of the research
- 6.3.4.8. Monitoring of any modified informed consent process
- 6.3.4.9. Suspension of the research
- 6.3.4.10. Termination of the research
- 6.3.4.11. Referral to other organizational entities (*e.g.*, Institutional Biosafety Committee)
- 6.3.4.12. Obtaining additional information
- 6.3.4.13. Termination of a previously approved protocol, which occurs when the IRB permanently withdraws approval for all research activity

6.3.5. Following a final determination of an action with respect to the UP Report Form, ORIA will draft and email a letter to the Protocol PI on behalf of the Chair of the IRB, setting forth the IRB actions and any required modifications. Suspensions or terminations of research will be carried out in accordance with SOP 6: Suspensions and Terminations of IRB Approval of Research Protocols. The Protocol PI will provide written notification to ORIA when he or she has made the required modifications.