UNIVERSITY OF SOUTHERN MAINE
Office of Research Integrity & Outreach

Procedure #:	HRPP-006
AAHRPP:	Standard I-9, Element II.2.G., Element II.2.I., Element II.5.B. & Element III.2.D.
Date Adopted:	03/27/2017
Last Updated:	2/5/2025
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Procedure Title:	Unanticipated Problems and Adverse Events

1.0 Objective

1.1. The objective of this Standard Operating Procedure (SOP) is to describe the policies and procedures for prompt investigator reporting of unanticipated problems or adverse events and the procedures for the Institutional Review Board (IRB) review of investigator reports.

2.0 General Description

2.1. The primary responsibility of the IRB is to ensure the protection of the rights and welfare of research subjects. In performing that responsibility, the IRB must maintain written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and any supporting department or agency head of any unanticipated problems involving risks to subjects or others.

3.0 Definitions

3.1. **Unanticipated problems involving risks to subjects or others (UPIRSO)** refer to any incident, experience, or outcome that meets **all** of the following criteria:

3.1.1. is unexpected (in terms of nature, severity, or frequency) given that (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;

3.1.2. is related or possibly related to participation in the research; and

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

3.1.4 Events that satisfy all three criteria are reportable to the IRB.

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

3.3. 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.

3.4. Adverse Events (AE) are any untoward or unfavorable 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. AEs encompass both physical and psychological harm and occur most frequently in the context of biomedical research, although they can occur in the context of social and behavioral research.

3.4.1. AEs that are a UPIRSO are reportable to the IRB. If investigators are unsure whether an AE is a UPIRSO, the event should be reported. The IRB will review the report and make a final determination as to whether the event constitutes a UPIRSO.

3.5. Serious AEs (SAE) is any AEs temporarily associated with the subject's participation in research that meets **any** of the following criteria:

3.5.1. results in death;

3.5.2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);

3.5.3. requires inpatient hospitalization or prolongation of existing hospitalization;

3.5.4. results in a persistent or significant disability/incapacity;

3.5.5. results in a congenital anomaly/birth defect; or

3.5.6. any other AE 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.

3.5.7. Serious AEs that are a UPIRSO are reportable to the IRB. If the investigator is unsure whether an SAE is a UPIRSO, the event should be reported. The IRB will review the report and make a final determination as to whether the event constitutes a UPIRSO.

3.6. **Unexpected AEs** are any AEs occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either:

3.6.1. the known or foreseeable risk of AEs associated with the procedure involved in the research that is described in (a) the protocol-related documents and (b) other relevant sources of information; or

3.6.2. the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the AE and the subject's predisposing risk factor profile for the AE.

3.7. **External events** are events occurring at sites for which the University of Southern Maine (USM) IRB does not have oversight.

4.0 Responsibility

4.1. Execution of SOP: IRB Chair, IRB Members, Office of Research Integrity and Outreach (ORIO) Staff, Research Compliance Administrator (RCA), Principal Investigator (PI), and Study Personnel (SP).

5.0 Procedure

5.1. Deciding if an AE meets the criteria for a UPIRSO

5.1.1. Is AE unexpected?

5.1.1.1. An AE 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:

5.1.1.1.1. The known or foreseeable risk of AEs associated with the procedures involved in the research that is described in

5.1.1.1.1.1. the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and

5.1.1.1.1.2. other relevant sources of information, such as product labeling and package inserts; or

5.1.1.1.2. The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the AE and the subject's predisposing risk factor profile for the AE.

5.1.2. Is the AE related or possibly related to a subject's participation in the research (as defined above)?

5.1.2.1. AEs that are related or possibly related to participation in the research may be caused by one or more of the following:

5.1.2.1.1. The procedures involved in the research;
5.1.2.1.2. An underlying disease, disorder, or condition of the subject;
5.1.2.1.3. Other circumstances unrelated to either the research, or any underlying disease, disorder, or condition of the subject.

5.1.2.2. In general, AEs 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 AEs determined to be solely caused by the subject's underlying condition or state of illness or other circumstances clearly outside of the study would be considered unrelated to participation in the research.

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

5.1.3.1. AEs that are unexpected, related or possibly related to participation in research, and serious, are the most important subset of AEs representing UPIRSOs 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 to the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects.

5.1.3.2. Other AEs that are unexpected and related or possibly related to participation in the research, but not serious, would also be UPIRSOs 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 AEs should also be reported, for consideration of changes or corrective actions.

5.1.3.3. For any AE that places the subjects or others at greater risk of harm, the IRB or IRB Chair will, if warranted, take steps to protect subjects.

5.2. Differentiating between a UPIRSO and an AE

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

5.2.1.1. Not all AEs are UPIRSOs. Only a small subset of AEs occurring in FDA-regulated clinical trials and other types of studies constitute UPIRSOs. Many events that are required to be reported to the sponsor or federal agency are not UPIRSOs.

5.2.1.2. A UPIRSO may not be an AE. 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 a UPIRSO

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.

5.2.2. There are other types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represents UPIRSOs but is not considered AEs. Some UPIRSOs involve social or economic harm instead of the physical or psychological harm associated with AEs. In other cases, UPIRSOs 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. This is a UPIRSO and must be reported because the incident was

5.2.2.1. unexpected (i.e., the investigators did not anticipate the theft);
5.2.2.2. related to participation in the research; and
5.2.2.3. 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.

5.2.3. Other examples of UPIRSOs that should be reported to the IRB, even though they are not AEs, include:

5.2.3.1. 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;
5.2.3.2. Breach in confidentiality resulting from the disclosure of confidential information or from lost or stolen confidential information;
5.2.3.3. An unresolved complaint of a participant, family member or another individual;
5.2.3.4. Laboratory or medication errors that may involve potential risk to that individual or others;
5.2.3.5. Change in FDA labeling because of adverse consequences or withdrawal from the marketing of a drug, device, or biologic used in a research protocol;
5.2.3.6. Disqualification or suspension of investigators;
5.2.3.7. Accidental or unintentional change to the IRB-approved protocol that involves risks or has the potential to recur;
5.2.3.8. Deviation from the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant;
5.2.3.9. Any deviation from the IRB-approved protocol that increases the risk or affects the participant's rights, safety, or welfare.

5.3. Required reporting of UPIRSOs

5.3.1. Reporting is required of all UPIRSOs, including those which may occur after the participant has completed or is withdrawn from the study, or following study closure. Reporting is submitted through an online platform..

5.3.2. Expectations for reporting include:

5.3.2.1. Any event occurring at a site for which the USM IRB has direct oversight responsibility and in which UPIRSO is reportable.

5.3.2.1.1. Upon review of the unexpected and related/possibly related event, the IRB will make the final determination as to whether the event constitutes a UPIRSO.

5.3.2.2. Any event occurring at USM or other location, whether or not USM IRB has direct oversight responsibility, in which a determination has been made by the U.S. Food and Drug Administration (FDA), research sponsor, coordinating center, Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC) or another centralized monitoring group that the event is a UPIRSO.

5.3.2.2.1. Only the following reports should be submitted to the IRB:

5.3.2.2.1.1. Summary safety information or analyses of AEs provided by the sponsor that describe significant changes in a product's safety profile;

5.3.2.2.1.2. Reports of individual AEs only if they have significant implications for human subject safety (e.g., a report of acute hepatic necrosis);

5.3.2.2.1.3. Reports of aggregate data (e.g., analyses and line listings of AEs) identifying serious unexpected AEs;

5.3.2.2.1.4. Reports from a DMC, whether these describe concerns or identify no problem.

5.3.3. For AEs that were determined to be UPIRSOs since the last renewal, a summary should also be submitted to the IRB at the time of continuing review.

5.3.3.1. This summary should reflect the aggregate analysis described above with a commentary on a risk-benefit analysis. Do not simply list events.

5.4. Timing of reports

5.4.1. Events that meet the criteria for a UPIRSO and are also serious AEs should be reported to the IRB within one (1) week of the investigator becoming aware of the event.

5.4.2. Any other events that meet the criteria for a UPIRSO should be reported to the IRB within two (2) weeks of the investigator becoming aware of the problem.

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

5.5. Handling non-reportable AEs

5.5.1. External events should not be reported to the IRB unless accompanied by an aggregate analysis that establishes their significance and a corrective action plan that addresses the problem. Individual AE reports shall be maintained by the investigator.

5.5.2. 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 AE reports and recommendations derived from data and safety monitoring.

5.6. Additional reporting responsibilities

5.6.1. Apart from institutional reporting obligations, it is the investigator's responsibility to make reports of AEs and unanticipated problems to the sponsor and/or FDA, where required.

5.7. IRB and USM responsibilities

5.7.1. The Chair or designee(s) of the USM IRB will review all reports of unanticipated problems. If a reported event poses a 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 provided by the PI to ensure the resolution of the immediate scenario and prevent future occurrences.

5.7.2. 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 convened IRB should make a final determination as to whether the event constitutes a UPIRSO.

5.7.3. The IRB has the authority to suspend or terminate IRB approval of protocols that are found to pose an unanticipated or heightened risk. Other actions taken by the IRB may include but are not limited to:

5.7.3.1. modification of the research protocol;
5.7.3.2. modification of the information disclosed during the consent process;
5.7.3.3. additional information provided to past participants;

5.7.3.4. notification of current participants, which is required when such information might relate to participants' willingness to continue to take part in the research;
5.7.3.5. the requirement that current participants re-consent to participation;
5.7.3.6. modification of the continuing review schedule;
5.7.3.7. monitoring of the research;
5.7.3.8. monitoring of the consent;
5.7.3.9. obtaining more information pending a final decision;
5.7.3.10. referral to other organizational entities; and/or
5.7.3.11. requirements for additional training for investigators and/or research staff.

5.7.4. Determinations from the convened IRB meeting are documented in the minutes.

5.7.5. The Institutional Official is responsible for all required reporting of UPIRSO and the resulting IRB actions to the appropriate federal agencies, according to policy *HRPP-034 Mandated Reporting to External Agencies.*

6.0 References

6.1. 45 CFR 46.103;

6.2. 21 CFR 56.108;

6.3. 45 CFR 46.113;

6.4. 21 CFR 56.113;

6.5. OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and AEs.