UNIVERSITY OF SOUTH ALABAMA

IRB SOP 601
Unanticipated Problems and Adverse Event Reporting

Purpose

The purpose of this standard operating procedure (SOP) is to ensure that adverse and serious adverse events are defined, recorded, reported, and evaluated as required by the USA Institutional Review Board (IRB).

Scope

This SOP applies to all research involving human subjects that is conducted at USA or any of its affiliate institutions. Application of this SOP starts at the time the participant signs the initial Informed Consent Form and continues through 30 days after the participant completes the active part of the study, unless otherwise stated.

Policy

Investigators are responsible for prompt reporting to the IRB of "any unanticipated problems involving risks to participants or others…" (45CFR46.103.b (5)). The IRB maintains responsibility for initial assessment of the risk/ benefit ratio in a research activity involving human participants. During the course of the project, investigators are required to promptly inform the IRB of any unanticipated negative effect or undesirable experience that is possibly, probably or definitely related to study procedure(s).

Adverse events are not necessarily physical in nature; attention must be paid to psychological harm (such as depression, thoughts of suicide, etc.), threats to privacy, or participant safety. An event is considered serious and must be reported when the participant experiences an unusually strong response, recurring problems, and/or death.

Definitions

Adverse Event: Any unfavorable or unintended disease, sign, or symptom (including abnormal laboratory finding) that is temporally associated with the use of a medical therapy or procedure. An adverse event may or may not be considered related to the medical therapy or procedure.

Observational Studies: A type of research in which investigators assess outcomes in participants without the investigator or study team changing the participants' routine medical care or lifestyle.

Serious Adverse Event (SAE): A serious adverse event is defined as an adverse experience that results in any of the following outcomes:

a. death;
b. a life-threatening adverse experience;
c. inpatient hospitalization or prolongation of existing hospitalization;
d. a persistent or significant disability such to disrupt a person's ability to conduct normal life functions;
e. a congenital anomaly/birth defect;
f. causes cancer;
g. significant overdose or protocol error; or
h. certain medical events that may not result in death, be life-threatening, or require hospitalization, may also be considered a serious adverse event when appropriate medical or surgical intervention is necessary to prevent one of the outcomes listed above.

Unexpected Adverse Event: An **unexpected** adverse event is any adverse experience whose nature, severity, and frequency of risk are not described in the information provided for IRB review, including the protocol and consent form.

Unanticipated Problems (Non-Adverse Event): *Unanticipated problems* is a broad term that includes not only unfavorable outcomes that have occurred that were not expected, but also the development of potentially increased risks of harm occurring in the future. According to guidance developed by the Office for Human Research Protections (OHRP), an unanticipated problem is an incidence, experience, or outcome that meets all 3 of the following criteria:

1. The incidence, experience, or outcome is unexpected given the research procedures described in protocol-related documents (e.g., the study protocol, the consent documents, the Investigator's Drug Brochure) and the characteristics of the population being studied. An event may be considered unexpected if it exceeds the nature,

severity, or frequency described in the study-related documents, Investigator's Drug Brochure, product labeling, or package insert.
2. The incidence, experience, or outcome is related or probably related to participation in the research study. Probably related means the incidence, experience, or outcome is more likely than not to be caused by the research study procedures.
3. The occurrence of the incidence, experience, or outcome suggests that the research places the participant or others at a greater risk of harm (physical, psychological, economic, or social) than was previously known or recognized.

Procedures

1.0 Special Reporting Requirements

1.1 Reporting Adverse Events to the FDA

In addition to IRB requirements, Physician Investigators who have obtained their own IND or IDE are required to notify the FDA of any adverse experience that is serious, unexpected, and related to the investigational product. See Guidance for Investigators Using an FDA Regulated Product-Adhering to Federal Regulations, Guidance for Investigators-Investigators Acting as the Sponsor of an Investigations

2.0 Non- Serious Adverse Event Reporting

Non-serious adverse events that are unexpected and related, possibly related, or probably related to the study product or procedures must be reported to the IRB no later than 14 working days upon learning of the event using the USA Adverse Event Report Form. If the research is sponsored by an outside entity, a copy of the adverse event form reported to the sponsor must be included with the IRB submission. Relationship to the study product or procedures must be determined by the Principal Investigator or Sub-Investigator.

Non-serious adverse events should be reported from the time of informed consent through 30 days after the end of *active* study participation.

Non-Serious Adverse Event Reporting	
TYPE OF EVENT	**Report to IRB**
Unexpected AND related, possibly related, or probably related	14 working days

Updates or follow-up reports are not required unless the non-serious event becomes a serious adverse event or unless otherwise stated by the Board. If this upgrade in severity occurs then procedures in section 3.0 should be followed.

3.0 Serious Adverse Event Reporting

All serious adverse events that are unexpected and related, possibly related, or probably related to the study product or procedures must be reported to the sponsor and the IRB immediately, but no later than five working days upon learning of the event using the USA Adverse Event Report Form. If the research is sponsored by an outside entity, a copy of the adverse event form reported to the sponsor must be included with the IRB submission. Relationship to the study product or procedures must be determined by the Principal Investigator or Sub-Investigator.

Serious adverse events, unless otherwise stated in this policy, should be reported from the time of informed consent through 30 days after the end of *active* study participation.

Serious Adverse Event Reporting	
TYPE OF EVENT	**Report to IRB**
Serious AND unexpected AND related, possibly related, or probably related	5 working days

Updates or follow-up reports are not required unless the serious adverse event ends with a death or unless otherwise stated by the Board. If this upgrade in severity occurs than procedures in section 3.1 should be followed.

3.1 **Death**

Deaths judged to be the result of study disease progression do not need to be reported. All other deaths, whether or not they are directly related to study procedures, must be reported. Deaths must be submitted to the IRB within three working days from the time the first member of the study team is aware of the event.

Deaths must be reported throughout the subject's participation on a study including the active and follow-up period.

Death Reporting	
TYPE OF EVENT	**Report to IRB**
Death outside of study disease progression	3 working days

4.0 Non-Adverse Event Unanticipated Problems

Unanticipated problems not deemed to be an adverse event in a study which might affect participant risk benefit analysis, confidentiality, or participants' willingness to continue in a project are to be reported to the IRB. The IRB will consider the effect of the problem on the study and on the participants already enrolled.

In some instances, revisiting the consent process with previously enrolled participants may be necessary. If the problem prompts a change in the study, the consent process and documentation may require alteration for future study participants. The investigator should use their own judgment when determining if an event is considered reportable beyond the scope of this policy.

Examples of non-adverse event unanticipated problems include:

- An accidental or unintentional change to the IRB approved protocol that placed one or more participants at increased risk, or has the potential to occur again.
- A change to the protocol made without prior IRB review to eliminate an apparent immediate hazard to a research participant.
- Interim findings and/or a safety monitoring report that indicate an unexpected change to the risks or potential benefits of the research in terms of severity or frequency.
- Publication in the literature that indicates an unexpected change to the risks or potential benefits of the research.
- A complaint of a participant that indicates unexpected risks or that cannot be resolved by the research team.
- Incarceration of a participant in the course of a study.
- A change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- A breach of a participant's confidentiality or privacy that involves potential risk to that participant or others.

Unanticipated Problem Reporting	
TYPE OF EVENT	**Report to IRB**
Unanticipated Problem, non-adverse event	7 working days

5.0 Observational Studies

Adverse events noted in observational studies do not require reporting to the IRB.

6.0 IRB responsibilities following receipt of SAE/Follow-up Report

Adverse Events and Unanticipated problems are assigned to a member of the IRB to re-evaluate the risks/benefits of the study and/or the appropriateness of the recruitment/consent process to determine if any changes should be made in the protocol or consent form. If the investigator has already modified the protocol or consent form in response to these events, the appropriateness of these changes is also reviewed. The Adverse Events reviewer may

recommend additional review by the full IRB. The IRB office will provide acknowledgement of receipt of this information and request additional information if follow-up or clarification is needed. The full committee has the right to request additional information from the investigator, note the occurrence of the adverse event but take no action, ask the investigator to modify the protocol or the informed consent or suspend or terminate the project.

The IRB is responsible for continuing review of all human subjects research. This is done through the annual renewal process required for any ongoing study. Thus, all reported adverse events should also be noted in the Annual Renewal Report Form when a renewal application is submitted for the study, so that the IRB may consider renewal of the protocol in light of such information.

7.0 Safety Alerts, IND Safety Reports, MED Watch Reports

During the course of a study, IND Safety Reports or other adverse event reports are provided from the sponsor. The IRB does not require submission of these reports. The reported information will be inserted into an updated investigator's brochure. The investigator's responsibility is to ensure that the risk/benefit relationship of the research remains acceptable.

Related Federal Regulations

45 CFR 46.130(b)(5); 21 CFR 56.108(b); 21 CFR 812.3(s)

Related Guidelines

FDA – Adverse Event Reporting to IRBs – Improving Human Subject Protection

OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks & Adverse Events Guidance, 2007

HISTORY

Revisions: October 2018; March 2025