



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 subject signs the initial Informed Consent Form and continues through 30 days after the subject 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:** The University's policies on adverse events are based on Food and Drug Administration regulations. According to the FDA, a "**serious** adverse drug experience" with respect to human clinical experience includes "any experience that suggests a significant hazard, contraindication, side effect, or precaution," including "any experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose."

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

**Unanticipated Problems:** *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 subject 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 subjects or others at a greater risk of harm (physical, psychological, economic, or social) than was previously known or recognized.

**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.

**Observational Studies:** Submission of adverse events on observational studies, which is research on materials collected for non-research purposes: These studies do not involve intervention from the study physician, and the subject only provides authorization for the use and disclosure of their personal health information, assessment, treatment and outcomes of the principal investigators' routine practice of providing care.

## Procedures

### 1.0 Special Reporting Requirements

#### 1.1 - Gene Therapy Studies

Investigators who have received approval from FDA to initiate a human gene transfer protocol must submit a written report of serious adverse events that are unexpected and associated with the use of the gene transfer product to the NIH Office of Biotechnology Activities (NIH/OBA), the USA Institutional Biosafety Committee, the USA IRB, and the FDA or study sponsor within specified timeframes as found in Appendix M-1-C-4 in the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines). Gene therapy investigators must submit annual reports to OBA as set forth in Appendix M-1-C-3 of the NIH Guidelines.

#### 1.2 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 need to be reported to the IRB. Relationship to the study product should be determined by the Principal Investigator or Sub-Investigator.

NOTE: An adverse event for an observational study must be reported to the sponsor, and does not need to be reported to the IRB.

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

<b>Adverse Event Reporting</b>	
<b>TYPE OF EVENT</b>	<b>Report to IRB</b>
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 unexpectedly associated with the study procedures must be reported to the sponsor and the IRB immediately, but no later than 7 working days upon learning of the event using the USA Adverse Event Report Form.

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.

<b>Serious Adverse Event Reporting</b>	
<b>TYPE OF EVENT</b>	<b>Report to IRB</b>
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 then procedures in section 3.1 should be followed.

#### **3.1 Death**

Deaths judged to be the result of progressive cancer disease 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.

<b>Death Reporting</b>	
<b>TYPE OF EVENT</b>	<b>Report to IRB</b>
Death	3 working days

#### 4.0 Unanticipated Problems

Unanticipated problems in a study which might affect subject risk benefit analysis, confidentiality, or subjects' 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 subjects already enrolled.

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

Examples of 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.

<b>Unanticipated Problem Reporting</b>	
<b>TYPE OF EVENT</b>	<b>Report to IRB</b>
Unanticipated Problem	7 working days

#### 5.0 IRB responsibilities following receipt of SAE/Follow-up Report

The Adverse Events designated member of the IRB reviews all adverse event reports and/or incident reports in order 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 subject research. This is done through the annual renewal process required for any ongoing study. Thus, all reported adverse events should also be described in detail 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.

#### **5.0 Safety Alerts, IND Safety Reports, MED Watch Reports**

During the course of a study, the IRB may receive IND Safety Reports or other adverse event reports from the sponsor. The IRB does not require submission of these reports, but will acknowledge reports if required by the sponsor. 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

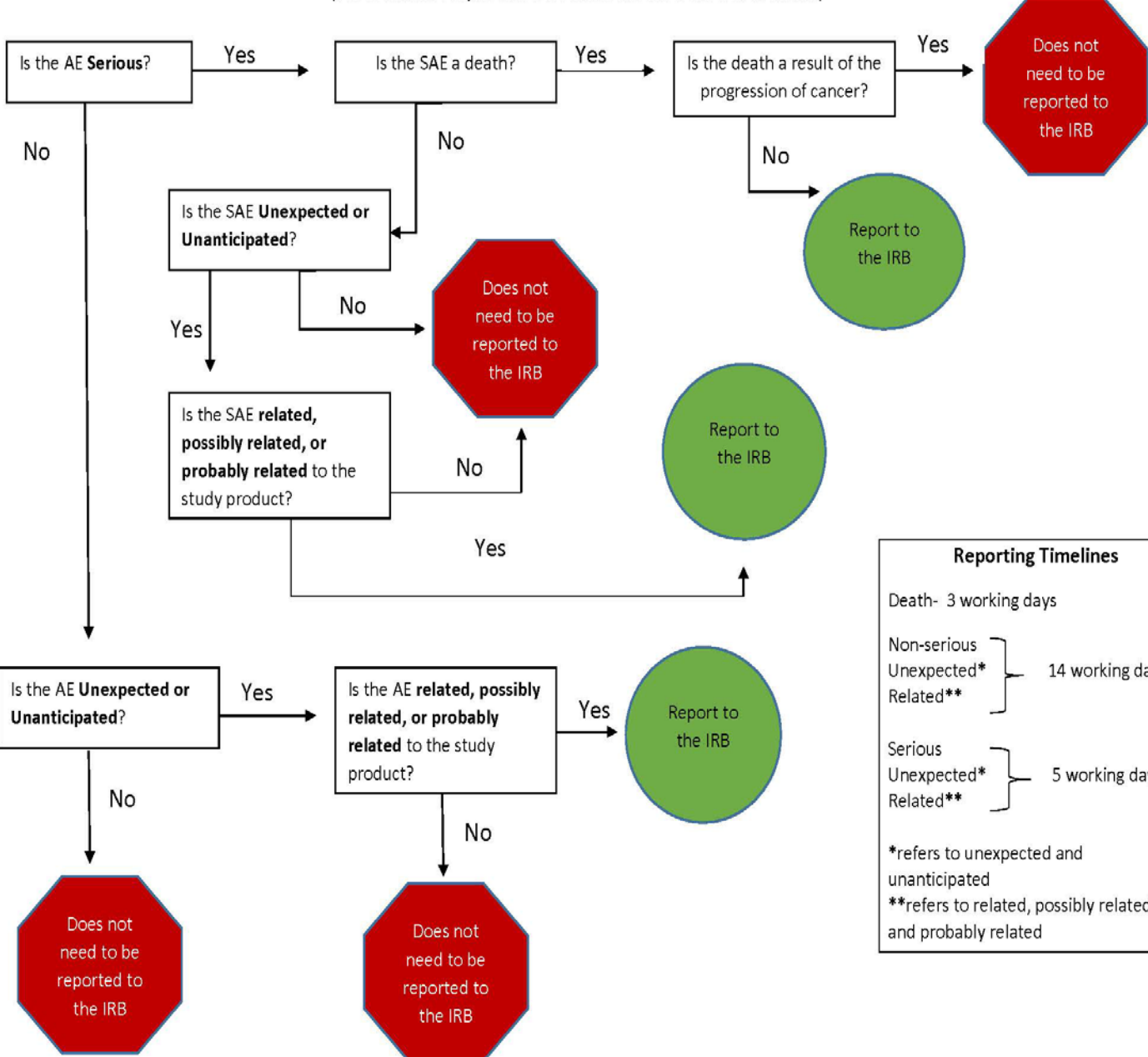
#### **HISTORY**

Effective Date:

Revisions: October, 2018

### Adverse Event Reporting

(For all human subject research that is not observational in nature)



Reporting Timelines	
Death-	3 working days
Non-serious Unexpected* Related**	14 working days
Serious Unexpected* Related**	
*refers to unexpected and unanticipated	
**refers to related, possibly related, and probably related	