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Procedure for Reporting of Adverse Events and Unanticipated Problems Involving Risks to Human Research Participants or Other Individuals

A. Background

Regulations promulgated by the Department for Health and Human Services (HHS) and the Food and Drug Administration (FDA) provide the basis for the Human Research Protection Program's guidance regarding reporting adverse events and unanticipated problems.

HHS regulations:

- Require UT administrators to promptly report any unanticipated problems involving human research subjects to OHRP, institutional officials, and the sponsoring agency [45 CFR 46.103(a)];
- Require the responsible IRB to make certain determinations regarding risks to participants prior to approving research and at least once per year unless continuing review is not required [45 CFR 46.111(a); 45 CFR 46.109(e)-(f)];
- Require institutions engaged in research to have written procedures for ensuring prompt reporting of unanticipated problems involving risks to subjects or others [45 CFR 46.108(a)(4)]; *AND*
- Give the responsible IRB the authority to terminate IRB approval of research that is associated with unexpected serious harm to subjects [45 CFR 46.113]

FDA regulations:

- Require investigators to promptly report to the IRB all unanticipated problems [21 CFR Parts 56, 312 and 812].
- Require investigators to submit to the IRB and the sponsor a report of an unanticipated adverse device event (UADE) no later than 10 working days after the investigator learns of the event [21 CFR 812.150(a)(1)].

The information contained in this guidance document will:

- Provide a framework to ensure that the reporting and review of adverse events and unanticipated problems occur in a timely, meaningful way so that participants in human subject research are better protected from avoidable harms, while minimizing unnecessary burden on investigators and IRB members, **and**
- Clarify the need to report unanticipated problems that increase the risk of harm; document responsibilities of investigators and the Institutional Review Board with respect to adverse events and unanticipated problems; assure compliance with federal regulations for prompt reporting of unanticipated problems to institutional officials, supporting agencies, sponsors and the Office for

Human Research Protections (OHRP); and provide reference links to OHRP and FDA regulatory guidance related to this topic.

B. Definitions

1. What are adverse events?

The HHS regulations at 45 CFR 46 do not define or use the term adverse event, nor is there a common definition of this term across government and non-government entities. For purposes of this guidance document, the term adverse event is used broadly and includes any event meeting the following definition:

Adverse Event - 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.

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.

Serious Adverse Events as defined by the FDA are any of the following undesirable experiences associated with the use of a medical product. Serious adverse events include:

- **death** as a result of the adverse event
- **life-threatening**, substantial risk of dying at the time of the adverse event
- **inpatient hospitalization**, initial or prolonged as a result of the adverse event
- an event that caused **disability, permanent damage** or was incapacitating
- **congenital anomaly or birth defect**
- **an incident requiring surgical or medical intervention** to prevent permanent damage (devices).
- **Other serious events** that do not fit the above but may jeopardize the patient

In the context of multicenter clinical trials, adverse events can be characterized as either ***internal*** adverse events or ***external*** *adverse events.*

For an institution engaged in a multicenter clinical trial;

- ***internal adverse events*** are those adverse events experienced by subjects enrolled by the institutional investigator(s), whereas

- ***external adverse events*** are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial. In the case of *external adverse events*, the investigators at all participating institutions learn of such events via reports that are distributed by the sponsor or coordinating center of the multicenter clinical trials. At many institutions, reports of external adverse events represent the majority of adverse event reports currently being submitted by investigators to IRBs.

For an institution engaged in a single-center clinical trial, <u>all</u> adverse events would be considered *internal adverse events.*

- In the case of an ***internal adverse event***, an investigator at that institution typically becomes aware of the event directly from the subject, another collaborating investigator at the same institution or the subject's healthcare provider either directly or through reports sent to the investigator. This may include Emergency Room visits or other hospitalizations at other facilities.

2. What are unanticipated problems?

The phrase "**unanticipated problems involving risks to subjects or others**" is found but not defined in the HHS regulations at 45 CFR part 46. OHRP considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

- **unexpected** (in terms of nature, severity, or frequency) given (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;
- **related or possibly related** to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- **serious** 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.

C. How do you determine which adverse events are unanticipated problems?

In OHRP's experience, most IRB members, investigators, and institutional officials understand the scope and meaning of the term *adverse event* in the research context but lack a clear understanding of OHRP's expectations for what, when, and to whom, adverse events need to be reported as unanticipated problems, given the requirements of the HHS regulations at 45 CFR part 46 (*i.e., adverse events that are unanticipated problems must be reported promptly to the IRB*).

The key question regarding a particular adverse event is whether it meets the three criteria for being defined as an unanticipated problem: (1) the adverse event is unexpected, (2) the adverse event is related or possibly related, **AND** (3) the adverse event suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

Appendix A of this document contains a flowchart for reporting adverse events.

D. The Procedure for Reporting Adverse Events and Unanticipated Problems

1. Time frame for reporting

Report within 48 hours of discovery or notification:

- An internal death the Investigator determines to be directly related/possibly related to a study intervention *(not natural causes or underlying disease progression)*
- Events resulting in temporary or permanent interruption of study activities by the investigator, sponsor, or DSMB to avoid potential harm to subjects

Report within 10 working days of discovery or notification:

- Internal unanticipated problems (i.e., related/possibly related, serious, AND unexpected)
- Any internal incident, experience or outcome that is related/possibly related, serious AND is unexpected.
- Any internal adverse event that an Investigator believes could influence the safe conduct of the research

Report at the time of continuing review:

- Internal adverse events that are related/possibly related but are not deemed to be anticipated problems (i.e., related/possibly related, unanticipated, not serious)
- A summary of external adverse events that increased risk to subjects or others

Do NOT report:

- Internal Adverse Events that are unrelated to the study
- Internal Adverse Events that pose no more than minimal risk to subjects
- Individual External Adverse Events

2. The investigator will include the following information:

(A) a clear explanation of why the adverse event or series of adverse events has been determined to be an unanticipated problem; and

(B) a description of any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem.

Flowchart for Reporting Internal Adverse Events and Unanticipated Problems to UT IRBs