

8. Unanticipated Problems Involving Risks to Subjects or Others

8.1. Policy

DHHS and FDA regulations state that institutions must have written policies on reporting Unanticipated Problems involving risks to subjects or others (as defined below) to the IRB, institutional officials and relevant Federal agencies and departments.

The following procedures describe how Unanticipated Problems involving risk to subjects or others are handled in research under the auspices of the University. Refer to the UMKC website for FAQs on reporting to facilitate determining whether an Unanticipated Problem exists.

8.2. Definitions

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 (modified from the definition of Adverse Events in the 1996 international conference on harmonization e-6 guidelines for good clinical practice).

External Adverse Event: Adverse Events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial.

Internal Adverse Event: Adverse Events experienced by subjects enrolled by the investigator(s) at that institution. In the context of a single-center clinical trial, all Adverse Events would be considered *internal Adverse Events*.

Possibly related to the research: there is a reasonable possibility that the Adverse Event, incident, experience or outcome may have been caused by the procedures involved in the research (modified from the definition of *associated with use of the drug* in FDA regulations at 21 CFR 312.32(a)).

Serious Adverse Event: (SAE) any Adverse Event temporally associated with the subject's participation in research that meets any of the following criteria:

- Results in death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect; or
- Any other Adverse Event 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 (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Others: means Individuals other than research participants (e.g., investigators, research assistants, students, the public, research subjects' partners, etc.).

Unexpected: means the incident, experience or outcome is not expected (in terms of nature, severity, or frequency) given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent documents; and the characteristics of the subject population being studied.

Unanticipated Problem involving risks to participants or others (or Unanticipated Problem): means any incident, experience, outcome, or new information where all three elements exist:

- Is unexpected;
- Is related or possibly related to participation in the research, and
- Indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.3. Procedures

8.3.1. Reporting

Investigators must report the following to the IRB:

- Any event which in the opinion of the PI meet the criteria for an Unanticipated Problem.
- Information that indicates a change to the risks or potential benefits of the research.
For example:
 - An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB.
 - A paper is published from another study that shows that the risks or potential benefits of the research may be different than initially presented to the IRB.
- A breach of confidentiality, privacy or data security
- Complaint of a participant when the complaint qualifies as an Unanticipated Problem.
- Sponsor imposed suspension for risk.

8.3.2. Submission of Reports

Unanticipated Problems at a UMKC site (or at a non-UMKC site where UMKC is the IRB-of-record), must be reported to the IRB.

8.3.2.1. Unanticipated Problems occurring at Internal Site(s) Reporting

- Reporting to the IRB within 24 hours of notification of occurrence/becoming aware of occurrence
 - Deaths

- Reporting to the IRB within 5 business days of notification of occurrence/becoming aware of occurrence
 - Serious, but non-death Adverse Events (SAEs are defined under 8.2) that meet the definition of an Unanticipated Problems
- Reporting to the IRB within 10 business days of notification of occurrence
 - Non-serious Adverse Events that meet the definition of an Unanticipated Problem.

8.3.2.2. Unanticipated Problems occurring at External Sites

The UMKC IRB does not require the UMKC PI to report Unanticipated Problems occurring at external sites.

However, if the study sponsor requires IRB submission of Unanticipated Problems originating at non-UMKC sites, including all IND safety reports, these may be submitted with a cover letter, which includes reference number(s) that link the Adverse Event to a safety report, the type of report(s) being submitted, a statement that these events are not considered reportable by the above UMKC IRB requirements and signed by the site PI/Sub-I. Receipt of such reports will be acknowledged by the IRB but will not be reviewed.

For Unanticipated Problems not at a UMKC site (i.e., external), UMKC's IRB will accept event reports from a non-UMKC site submitted by investigators, study sponsors or the FDA on behalf of investigators.

UMKC's IRB recognizes that for multi-center studies, the sponsor is in a better position to process and analyze unanticipated event information for the entire study, and to assess whether an occurrence is an Unanticipated Problem for the study. Accordingly, investigators may rely on the sponsor's assessment and provide the sponsor's assessment to the IRB.

8.3.3. IRB Procedures for Handling Adverse Events and Possible Unanticipated Problems

8.3.3.1. Review by IRB Staff and Chair

Upon receipt of an **Adverse Event Form** from a PI, the IRB staff checks the form for completeness. If any applicable sections of the form are incomplete or have been answered unsatisfactorily, the IRB staff will contact the PI or the designated contact person to obtain additional information.

The IRB Chair and/or other experienced member(s) designated by the IRB Chair receives and reviews the report of the event(s) considered to be an Adverse Event and/or Unanticipated Problem and comments and/or acknowledges as applicable.

Based on the information received from the investigator, the IRB Chair (or designee) may suspend research to ensure protection of the rights and welfare of participants. Suspension

directives made by the IRB Chair (or designee) must be reported to a meeting of the convened IRB, IO and all applicable Federal reporting agencies.

The IRB or the IRB Chair (or designee) has authority to require submission of more detailed information by the PI, the sponsor, the study coordinating center, or DSMB/data monitoring committee about any AE or Unanticipated Problem occurring in a research protocol as a condition of the continuation of the IRB's approval of the research.

If the reviewer considers that either (1) the problem was foreseen; or (2) no participants or others were harmed and participants or others are not at increased risk of harm, the reviewer should indicate this finding and the determination is communicated to the PI and no further action is taken.

The reviewer may consult all study related materials in order to appropriately review the Adverse Event or Unanticipated Problem. If the reviewer determines the Adverse Event or Unanticipated Problem poses no more than minimal risk, the reviewer will take appropriate action depending on the nature of the risk involved, including requesting modification of the protocol or the consent form, if applicable. The results of the review will be recorded, communicated to the PI, and reported to the IRB.

All reported Unanticipated Problems where the risk is more than minimal will be reviewed at a convened IRB meeting. All events determined to be Unanticipated Problems will be reported to the IRB (see section 8) and to relevant Regulatory Agencies and Institutional Officials according to the procedures in section 11.

8.3.3.2. IRB Review

The committee will have access to all study related materials, the event report, and recommendations from the IRB Chair (or designee), when appropriate.

After review of the protocol and event report, the convened IRB will make findings and recommendations based on the following considerations:

- Whether the reported event is a serious Adverse Event and/or Unanticipated Problem according to the definition in this policy.
- What action in response to the report is appropriate?
- Whether suspension or termination of approval is warranted.
- Whether further reporting to institutional and/or Federal officials is required.

As a part of the resolution of the reported serious Adverse Event or Unanticipated Problem the IRB may recommend any of the following actions:

- No action
- Requiring modifications to the protocol
- Revising the continuing review timetable

