Adverse Events and Unanticipated Problems
Involving Risks to Human Research Participants or Other Individuals:
Responsibilities of the Investigator and the Institutional Review Board

The purpose of this policy and procedure is to:

- 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;
- 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; and
- Assure compliance with federal regulations for prompt reporting of unanticipated problems to institutional officials, supporting agencies and the federal Office for Human Research Protections (OHRP).

Definitions and clarifications of terms (defined terms appear in bold, italicized text throughout this document):

Adverse Event – Any abnormal, untoward or unfavorable physical, psychological, social, legal or economic occurrence in a human subject, including any abnormal exam or test result, symptom, or disease, occurring during or in close proximity to the end of the subject’s participation in the research, whether or not considered related to the subject’s participation in the research. Whether an event is deemed to be in close proximity should be based on the principal investigator’s reasonable professional judgment considering the protocol procedures. For example, psychological distress that occurs one year after taking a survey containing sensitive topics would not be considered “in close proximity” whereas developing cancer within one year of receiving chemotherapy may reasonably be considered “in close proximity” to the end of the subject’s participation in the research.

External adverse events. When a researcher is engaged in a multicenter clinical trial, external adverse events are those adverse events experienced by subjects enrolled by non-UT investigators at other institutions engaged in the clinical trial.

Internal adverse events – When a researcher is involved in a multicenter clinical trial, internal adverse events are those adverse events experienced by subjects enrolled by a UT investigator. In the context of a research involving only subjects enrolled through UT investigators, all adverse events are considered internal adverse events.

Possibly Related – there is a reasonable possibility that the incident, experience, or outcome may have been caused by the research procedures, investigational drug, or investigational device involved in the research.

In research covered by Food and Drug Administration (FDA) regulations – events that are “associated with the use of the drug” as defined in FDA regulations at 21 CFR 312.32(a) are considered possibly related.
Serious adverse event: Any adverse event temporally associated with the subject’s participation in research that meets any of the following criteria:

1) results in death;
2) is life-threatening (places the subject at immediate risk of death from the event);
3) requires inpatient hospitalization or prolongation of existing hospitalization;
4) results in a persistent or significant disability or incapacity;
5) results in a congenital anomaly or birth defect; or
6) 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).

In research covered by FDA regulations – a “Serious Adverse Drug Experience” as defined by FDA regulations at 21 CFR 312.32(a) is considered a Serious Adverse Event for purposes of this policy.

Unanticipated Problem – refers to an unexpected problem, incident, experience, or outcome that does not cause harm, but causes a greater risk of harm and meets all of the following criteria:

(1) Is 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;

(2) Is related or possibly related to participation in the research; and

(3) Event 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.

Unexpected Adverse Event: Any adverse event occurring in one or more subjects in a research protocol when the nature, severity, or frequency is not consistent with either:

(1) the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or

(2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject’s predisposing risk factor profile for the adverse event.

In research covered by FDA regulations – an “unexpected adverse drug experience” as defined by FDA regulations at 21 CFR 312.32(a) is an unexpected adverse event.

Regulatory Background:

Regulations promulgated by the Department for Health and Human Services (HHS) and the Food and Drug Administration (FDA) regulations provide the basis for the DHRP’s policy 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)-(b)];
- Require the responsible IRB to make certain determinations regarding risks to participants prior to approving research and at least once per year [45 CFR 46.111(a); 45 CFR 46.109(e)];
- 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]; and
- Require institutions engaged in research to have written procedures for ensuring prompt reporting of unanticipated problems involving risks to subjects or others [45 CFR 46 103(b)(5)].

FDA regulations:

- Require investigators to promptly report to the IRB all unanticipated problems
- Require investigators to submit to the IRB and the sponsor a report of an unanticipated adverse device effect (UADE) no later than 10 working days after the investigator learns of the effect

Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events must be classified as (1) expected or unexpected; (2) related, possibly related, or unrelated to the research; and (3) serious or not serious. In multi-center clinical trials, adverse events have a fourth classification of either internal or external.

Unanticipated problems include certain types of incidents, experiences, and outcomes that occur during the conduct of human subject research that are not known or foreseeable events. Such unanticipated problems could involve social or economic harm, or problems that place the participant at an increased risk of harm, but no actual harm occurs. For example, a stolen laptop with research data regarding illicit drug use, or a dosing error that does not cause actual harm are both unanticipated problems.

For some research supported by the Department for Health and Human Services (HHS), the FDA and the HHS agency supporting the research (e.g. the National Institutes of Health [NIH]) may have separate regulatory and policy requirements regarding the reporting of unanticipated problems and adverse events. Guidance can be obtained directly from the supporting agency and the UT Department for Human Research Protections.

Event Reporting Requirements - Determining What to Report and When

Adverse events and unanticipated problems must be reported to the responsible IRB according to the time table below. OHRP provides additional guidance on determining whether an adverse event is unexpected, related or possibly related, or an unanticipated problem.

http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm

At the time of publication of this policy, the FDA has not issued final guidance on adverse event reporting. FDA draft guidance (for comment purposes only) is available at http://www.fda.gov/OHRMS/DOCKETS/98fr/07d-0106-gdl0001.pdf.

Investigators should refer to the definitions given above when using the time table. Questions may be directed to the Director of Regulatory Compliance for the Department for Human Research Protections at 419-383-6903 or IRB.Biomed@utoledo.edu.
<table>
<thead>
<tr>
<th>Type of Event or Problem</th>
<th>Expected or Unexpected (Nature, Severity or Frequency)</th>
<th>Relatedness to Participation in Research</th>
<th>Example</th>
<th>P.I.’s Report to IRB</th>
<th>**IRB’s Report to Institutional Official, OHRP &amp; Sponsoring Agency</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERNAL Adverse Event</td>
<td>Expected</td>
<td>Related or Possibly Related</td>
<td>Severe abdominal pain and moderate gastritis after 1 month on osteoarthritis study drug; P.I. concludes related; consent stated 2% occurrence; ≤ 2% of subjects experienced the side effect</td>
<td>Serious: If death or unscheduled hospitalization, report within 30 days. Report all others at *continuing review. Not Serious: *At continuing review</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>INTERNAL Adverse Event</td>
<td>Unexpected</td>
<td>Related or Possibly Related</td>
<td>Severe abdominal pain and moderate gastritis after 1 month on osteoarthritis study drug; P.I. concludes related; consent stated 2% occurrence; 15% of subjects have experienced the side effect</td>
<td>Serious: Within 7 Days of P.I. or Study Team Becoming Aware Note: protocol and ICF modifications likely required</td>
<td>Not Serious: Within 30 Days Not Serious: If greater risk of harm, report within 30 days of 1st convened IRB meeting</td>
</tr>
<tr>
<td>INTERNAL Adverse Event</td>
<td>Unexpected</td>
<td>Not Related</td>
<td>Subject in asthma drug study breaks ankle; P.I. determines not related</td>
<td>Do not report</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>INTERNAL Unanticipated Problem (No Detectable Harm But Greater Risk of Harm)</td>
<td>Unexpected</td>
<td>Related or Possibly Related</td>
<td>Laptop stolen containing unencrypted survey data regarding illicit drug use; or drug dosing error with no detected harm</td>
<td>Within 7 days of P.I. or study team becoming aware of event</td>
<td>Within 30 days of 1st convened IRB meeting following report to IRB staff</td>
</tr>
<tr>
<td>EXTERNAL Adverse Event or Unanticipated Problem (No Detectable Harm But Greater Risk of Harm)</td>
<td>Unexpected</td>
<td>Related or Possibly Related</td>
<td></td>
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<td>EXTERNAL Adverse Event</td>
<td>Expected</td>
<td>Related or Possibly Related</td>
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*If the research does not require continuing review due to study termination, events must be reported on final report.*
Events That Should Not Be Reported to the IRB

- Individual adverse events that are not related to the study
- Normal disease progression
- Adverse events that are expected, previously disclosed to the IRB as a potential risk of the study, and not serious. Note that serious adverse event is defined by this policy and must be reported, even if expected.
- Follow up reports of previously reported events that do not meet the test of serious, related and unanticipated should not be reported unless the follow up event substantiates the need for a change to the informed consent, protocol, IB, or risks of the study.
- Individual external events that are expected and not serious. When there is a DSMB/DMC report available, the DSMB report must be submitted with each continuing review.
- Individual external adverse events that are not serious. Include these events in DSMB/DMC report if a monitoring board exists. If a monitoring board does not exist and is not required by the IRB, then non-serious external events should not be reported.
- Individual external adverse events that are expected. Include these events in DSMB/DMC report if a monitoring board exists. If a monitoring board does not exist and is not required by the IRB, then non-serious external events should not be reported.

Forms for Reporting Adverse Events and Unanticipated Problems


Content of Investigator’s Report To The IRB

Investigators must report internal adverse events and unanticipated problems on the form prescribed by the DHRP. Information requested by the form includes:

1) appropriate identifying information for the research protocol, included the IRB number, investigator’s name, and the protocol title;
2) a detailed description of the adverse event, incident, experience, or outcome;
3) a notation of whether the event, incident, experience or outcome is the initial report or a follow-up report;
4) an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem {or adverse event}; and
5) a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

External events may be reported by submitting documents provided by the sponsor with relevant information highlighted.

The IRB has the authority to require, as a condition of continued approval by the IRB, submission of more detailed information by the principal investigator, the sponsor, the study coordinating center, or DSMB/DMC about any adverse event or unanticipated problem occurring [45 CFR 46.109(a)].
Adverse Events and Unanticipated Problems Requiring Corrective Actions or Substantive Changes to the Research Protocol or Informed Consent

The principal investigator, together with the sponsor when applicable, are responsible for informing the IRB whether an adverse event(s) or unanticipated problem(s) necessitates changes to the protocol or informed consent process. If the event is an *unanticipated problem* as defined by this policy (unexpected, possibly related or related and a greater risk of harm than previously known), then the investigator must either inform the IRB what changes to the protocol and/or consent form are necessary or explain why changes are not required.

If the event is an *unanticipated problem* as defined by this policy (unexpected, possibly related and greater risk of harm that previously known), then the investigator must either inform the IRB what changes to the protocol and consent form are necessary or explain why changes are not required.

In making the determination of whether changes to the protocol or informed consent form are necessary, investigators should keep in mind that:

- Adverse events that are *unexpected, related or possibly related* and *serious* routinely warrant substantive changes in the research protocol and/or informed consent process and document, or other corrective actions to protect the safety, welfare, and rights of subjects. These types of events suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.
- Adverse events must be reported to the IRB within the required timeframe even if changes to the research protocol or informed consent document are required. Amendments can be submitted after the adverse event report if necessary.
- Events that are not serious warrant consideration of whether changes are necessary.
- Proposed changes to a research study in response to an unanticipated problem must be reviewed and approved by the IRB before being implemented, except when necessary to eliminate apparent or immediate hazards to subjects. If the changes are more than minor, and the protocol originally required convened review, the changes must be approved by the convened IRB. [45 CFR 46.103(b)(4) and 46.110(a)]
- The IRB may require changes in addition to or other than those proposed by the investigator or sponsor to maintain IRB approval.

Examples of Corrective Actions or Substantive Changes To Consider in Response to An Unanticipated Problem (As Provided by OHRP Guidance)

- modification of informed consent documents to include a description of newly recognized risks;
- provision of additional information about newly recognized risks to previously enrolled subjects;
- implementation of additional procedures for monitoring subjects;
- emergency changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects (requires immediate notification to IRB and submission of protocol changes for IRB review);
- modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- suspension of enrollment of new subjects;
- suspension of research procedures in currently enrolled subjects;

Suspension or Termination of IRB Approval

The IRB has the authority under federal regulations to suspend or terminate approval of research that is not being conducted in accordance with the IRB’s requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination will be communicated in writing the investigator, appropriate Institutional officials, and any sponsoring agency or department.
Institutional Review Board Responsibilities at Initial and Continuing Review

Initial Review:

The IRB must receive and review sufficient information regarding the risk profile of the proposed research study, including the type, probability, and expected level of severity of the adverse events that may be caused by the procedures involved in the research. The IRB must also review the investigator’s explanation how the risks of the research will be minimized.

Depending upon the risks of the research and the likelihood that the research could involve risks to subjects that are unforeseeable, the IRB must ensure, if appropriate, that the research includes adequate provisions for monitoring the data collected to ensure the safety of subjects.

Continuing Review:

The IRB must determine whether the criteria for IRB approval continue to be met. In addition, the IRB should:

- Review a summary of any adverse events and unanticipated problems included in the continuing review applications. Review the DSMB/DMC report if a report is required by the IRB.
  o Multi-center trials subject to oversight by a monitoring entity (e.g. the research sponsor, a coordinating or statistical center, or a DSMB/DMC): UT investigators must submit a current report from the monitoring entity. The IRB recognizes that local investigators are unable to prepare a meaningful summary of study-wide information due to the unavailability of information. The monitoring entity’s report should include:
    ▪ A statement regarding what information was reviewed by the monitoring agency;
    ▪ The date of the review; and
    ▪ The monitoring entity’s assessment of the information reviewed.
- Determine whether any adverse events or unanticipated problems have occurred that could alter the IRB’s previous determinations with respect to risks to subjects.
- Confirm that any IRB requirements for monitoring study data to ensure safety of subjects have been implemented. This requirement may be met by confirming receipt of the DSMB/DMC report.