REPORTING TO THE IRB: UNANTICIPATED PROBLEMS IN VolVING RISK TO PARTICIPANTS OR OTHERS, ADVERSE EVENTS, AND OTHER PROBLEMS

PURPOSE

It is the purpose of this policy to describe the procedure to ensure prompt reporting to the Institutional Review Board (IRB), appropriate institutional officials, Sponsor, coordinating center and the appropriate regulatory agencies of unanticipated problems involving risks to participants or others.

POLICY

The University of Cincinnati IRB complies with all applicable local, state, and federal regulations that pertain to reporting requirements. Federal regulations require institutions to have written policies and procedures in place that ensure prompt reporting of unanticipated problems involving risk to participants or others and certain adverse events to the IRB, regulatory agencies and institutional officials.

These problems can occur in any type of research (medical or non-medical) and may include occurrences such as adverse events, research participant complaints, protocol deviations, and other untoward events involving risk. Events requiring prompt reporting by Investigators and research staff may involve physical, psychological, social, legal, or economic harms.

DEFINITIONS

Types of Study Events

1. Unanticipated problem involving risk to subjects or others – Any problems which were not contemplated when the research was approved and which present risk of serious harm to participants or to others, including the research team, the university community, or the broader community. Unanticipated problems (UPs) are always related to an approved study, either ongoing or closed.

An unanticipated problem is defined as any incident, experience, or outcome that meets all of the following criteria:

a. Unexpected (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
b. Suggests that the research places the subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

The following problems/events represent unanticipated problems involving risks to participants or others. This list is not exhaustive.

- Information that indicates a change to the risks of potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than was initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of the research study is of no therapeutic value.
- Any adverse event that represents a serious unexpected problem that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
- Adverse event that would cause the Sponsor to modify the Investigator’s brochure, protocol, or informed consent to assure the protection of human subjects.
- A change in FDA labeling or FDA withdrawal from marketing for safety concerns of a drug, device, or biologic used in a research protocol.
- Change to the protocol taken without prior IRB review to eliminate the apparent immediate hazard to a research participant.

2. **Unanticipated Adverse Device Effect:** Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree or incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

3. **Adverse Events (AE):** Any untoward occurrence (physical, psychological, social, or economic) in a human subject participating in research that is undesirable and has an unintended outcome, but is not necessarily unexpected. The event may have been described in the informed consent as a risk of the study. Adverse events include abnormal laboratory findings, a symptom, or disease temporally associated with the use of an investigational agent, or the progression of
disease, whether or not related to the medicinal (investigational) product.

**Serious Adverse Event (SAE):** The events listed are examples and are not limited to the following:

- The death of a study subject, whether related to an investigational agent or not related
- A reaction which, in the opinion of the Investigator, threatens the study subject with risk of death
- A disability or incapacity which, in the opinion of the Investigator, causes substantial disruption of a study subject's ability to conduct normal life functions
- Hospitalization or extension of an existing hospitalization (excluding elective hospitalization for conditions unrelated to the study)
- A birth defect in an offspring of a study participant, regardless of the time after the study the congenital defect is diagnosed
- Any intervention required to prevent one of the above outcomes

Note: drug overdose and cancer are not characterized as serious adverse events unless the overdose or cancer meets the above criteria.

**Related Adverse Event:** - The adverse event could have been caused by any drug given to a subject as part of the study, a device used in the study, or a procedure that is carried out as part of the study. The term “adverse drug reaction” (ADR) is also used if the AE or SAE is related to the investigational product.

**Unexpected Adverse Event:** -the adverse event is not an anticipated event for the study drug, device, or procedure and is not explained in the Informed Consent Statement that the study subject signed.

**Imminent Threat of an AE in Research** – Any situation in which an AE in research has not yet occurred but is very likely to occur without preventative measures (used for research associated with Veterans Administration Medical Center, VAMC)

**Unexpected Death**- The death of a research participant in which a high risk of death is not projected, as indicated by the written protocol, informed consent form, or Sponsor brochure. This definition does not include deaths associated with a terminal condition unless the research intervention definitely, probably or possibly hastened the participant’s death. A participant’s death that is determined to be clearly not associated with the research is also not an “unexpected death” for purposes of the reporting requirements of these procedures.
4. Protocol Deviations –

**Significant Deviations** – Accidental or unintentional change to the IRB approved protocol may be considered a failure to protect the rights, safety and welfare of participants because the non-compliance exposes participants to unreasonable risks. The following listed deviations are examples:

- Failure to adhere to the inclusion/exclusion criteria that are specifically intended to exclude participants for whom the study drug or device poses unreasonable risks (e.g., enrolling a participant with decreased renal function in a research study in which decreased function is exclusionary because the drug may be nephrotoxic)
- Failure to perform safety assessments intended to detect drug toxicity within protocol-specified time frames (e.g., blood work for an oncology therapy that causes neutropenia)

**Subject Non-Compliance** – Subject non-compliance occurs when, despite the best efforts of the research staff, the subject fails to follow the protocol. Note that failure of the research staff should not be classified as Subject Non-Compliance (e.g. the subject did not complete a six-month telephone follow-up because a staff member forgot to call). Subject Non-Compliance may become a substantial deviation if it occurs in a number of subjects. Subject Non-Compliance may also be considered a Safety Violation (e.g. the subject takes medication that is contraindicated by the study drug).

5. **Complaints** - an expression of dissatisfaction or concern about safety, privacy or protection of a subject regarding human subjects research.

- **Minor complaint** – a complaint that alleges an inconvenience to human participants but does not result in an unanticipated problem or serious adverse event or increase in risk. Examples are questions about the amount of participant payment; no close parking available; study personnel were rude; incorrect form was used.

- **Major complaint** – a complaint that alleges that human participants are being put at risk or increased risk compared with what is described in the consent form. Examples include the Principle Investigator (PI) not allowing enough time for the consent process; PI not following inclusion/exclusion criteria; failure to follow protocol; failure to report unanticipated problems or SAEs; participant feels like their rights have been violated; PI not complying with policies or regulations; and/or a series of minor complaints.
Human Research Protection Program Policy

6. Other Reportable Events

- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Violation, meaning 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.
- Breach of confidentiality
- Incarceration of a participant when the research was not previously approved under Subpart C and the Investigator believes it is in the best interest of the participant to remain in the study.

The IRB will accept other reports when the Investigator is unsure whether the event should be reported, and the IRB will review such reports to determine whether the event meets the threshold for an unanticipated event presenting risk to the participant.

Additional terms relevant to this policy

Relatedness

- **Related**: Associated or having a timely relationship with the study agent or procedures; a reasonable possibility exists that an outcome may have been caused or influenced by the study in question (e.g., administration of a study drug, devices or procedures), although an alternative cause/influence may also be present. Related events may be definitely, probably, or possibly related.

- **Unrelated**: Unassociated or without a timely relationship to the study agent or procedures; evidence exists that an outcome is definitely related to a cause other than the event in question (e.g., underlying disease, environment).

Location

- **Internal**: An event occurring in research at University of Cincinnati (UC), sites affiliated with UC or at a site(s) under an UC IRB’s jurisdiction.

- **External**: An event occurring in research at a site(s) other than UC, over which another (non-UC) IRB has jurisdiction.
Reporting Events to the IRB

The IRB will accept reports when the Investigator is unsure whether the event should be reported, and the IRB will review such reports to determine whether the event meets the threshold requiring reporting.

All reports to the IRB of unanticipated problems should explain clearly why the event is “unanticipated” and clearly explain why the event represents a “problem involving risks to human subjects or others.”

The UC IRB expects reports of unanticipated problems to include a corrective action plan to address the issue, or written justification for why none was provided.

FDA guidance documents state:

1. “individual adverse event reports generally require an evaluation of their relevance and significance to the study, including an evaluation of other adverse events, before they can be considered to be an unanticipated problem,” and
2. “all reports to the IRB of unanticipated problems should explain clearly why the event described represents a ‘problem’ for the study and why it is ‘unanticipated’.”

Timeframe for reporting

The events described as requiring prompt reporting above should be reported to the IRB within 10 days of the research staff member’s learning of the event.

VAMC researchers are required to report the event in writing to the IRB within 5 business days.

Events resulting in temporary or permanent interruption of the study activities by the PI or Sponsor to avoid potential harm to participants must be reported immediately (within 48 hours).

All internal and external events that may represent unanticipated problems involving risks to participants or others shall be promptly reported (as above), regardless of whether they occur during or after the study, or to a participant who has withdrawn from or completed study participation. If changes to the research or consent process are proposed as a result of the event, or if additional information will be provided to current and/or past participants, a modification request must be submitted for IRB review.
Events Requiring Prompt Reporting

The following events may represent unanticipated problems involving risks to participants and others and shall be promptly reported:

- Internal adverse events that are unexpected, related to the research, and involve new or increased risks to participants or others;
- Unanticipated adverse device effects;
- Significant protocol deviations (or other accidental or unintentional changes to the protocol or procedures) involving safety or integrity risks or with the potential to reoccur;
- Events requiring prompt reporting according to the protocol Sponsor;
- Complaints made by research participants indicating an unanticipated event, or complaints that cannot be resolved by the research staff;
- Unapproved changes made to the research to eliminate an apparent immediate hazard to a research participant;
- Data and Safety Monitoring Board (DSMB) reports, interim analyses, or other oversight committee/monitoring reports/recommendations altering the risks/benefit profile;
- New information indicating an unexpected change in risks or potential benefits (e.g., literature/scientific reports or other published findings);
- Investigator’s Brochure (IB or IDB) updates or revisions to safety information; and
- Other problems or findings (e.g., breach of confidentiality, loss of study data or forms, etc.) that could influence the safe conduct of the research.

Events Not Requiring Prompt Reporting

Potential risks and adverse events that may be reasonably anticipated (i.e., “expected”) must be described in the informed consent process/form and do not require prompt reporting to the IRB. The following are examples of events that do not require prompt reporting:

- Adverse events or injuries that are BOTH non-serious and unrelated;
- Adverse device effects that are non-serious, anticipated, or unrelated;
- Deaths not attributed to the research, e.g., from “natural causes,” accidents, or underlying disease and the Investigator has ruled out any connection between the study procedures and the participant’s death;
- Protocol deviations or violations not involving risks to participants or unlikely to recur;
- DSMB reports, interim analyses, or other reports, findings, or new information not altering the risk/benefit profile;
- IB updates not involving safety information; and
- Problems or findings not involving risk (unless the information could affect participants’ willingness to continue in the research).
Events not serious and unrelated do not require prompt or routine reporting.

For a flowchart of event reporting requirements, see Figure 1.

**External Unanticipated Events**

For unanticipated problems that occur external to UC:

The UC IRB will accept non-site adverse event reports (safety reports submitted to FDA, etc.) submitted by Investigators and Sponsors on behalf of the Investigators, if in accord with federal regulations the event is:
- both serious and unexpected,
- the report identifies all previous safety reports concerning similar adverse experiences
- the report analyzes the significance of the current adverse experience in light of the previous reports, and
- the report outlines a corrective action plan.

An Investigator participating in a multicenter study may rely on the Sponsor’s assessment and provide to the IRB a report of the unanticipated problem prepared by the Sponsor. In addition, if the Investigator knows that the Sponsor has reported the unanticipated problem directly to the IRB, because the Investigator, Sponsor and IRB made an explicit agreement for the Sponsor to report directly to the IRB, and because the Investigator was copied on the report from the Sponsor to the IRB, the FDA would not expect the Investigator to provide the IRB with a duplicate copy of the report received from the Sponsor.

If the Sponsor does not submit external adverse events that are determined to be unanticipated problems to the IRB on behalf of the investigative site, the Investigator is required to submit them, along with the required explanation outlined above, within 10 days of the date the Investigator receives them.

**VAMC Research**

For VAMC research, the terms “unanticipated” and “unexpected” refer to an event or problem that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol-related documents and the characteristics of the study population. The term "Unanticipated Problem Involving Risks to Subjects or Others" includes any event or problem that is serious, unexpected, and related to the research, where “related” means the event or problem might reasonably be regarded as caused by, or probably caused by, the research. Serious unanticipated problems involving risks to participants or others may include:
• Interruptions of participant enrollments or other research activities due to concerns about the safety, rights, or welfare of human research participants, research staff, or others.
• Any work-related injury to personnel involved in human research, or any research-related injury to any other person, that requires more than minor medical intervention (i.e., basic first aid), requires extended surveillance of the affected individuals, or leads to serious complications or death;
• Any VAMC National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to one or more of the VA facility’s research projects;
• Any Sponsor analysis describing a safety problem for which action at the VAMC facility might be warranted;
• Any unanticipated problem involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research participants, research staff, or others;
• Any problem reflecting a deficiency that substantively compromises the effectiveness of the VAMC facility’s HRPP.

For VAMC research the unfounded classification of a serious adverse event as “anticipated” constitutes Serious Non-Compliance. For IRB review of serious unanticipated problems and unanticipated serious adverse events, all determinations of the IRB reviewer (regardless of outcome) must be reported to the IRB at its next convened meeting. If it was determined that the problem or event is serious, unanticipated, and related to the research, the convened IRB must determine and document whether a protocol or consent document modification is warranted. If the convened IRB determines that a protocol or consent document modification is warranted, the IRB must also determine and document 1) Whether previously enrolled participants must be notified of the modification and 2) When such notification must take place and how such notification must be documented.
REPORTING EVENTS TO THE IRB

Did the Event involve risks to Participants or others or a complaint?
- Includes adverse events, participant complaints, protocol deviations, other untoward events

YES

Was the event related to the research?
- Reasonable possibility that the event was caused or affected by the research procedures
- Includes events that are definitely, probably or possibly related

YES

Was the event unanticipated?
- Unforeseen given the nature of the research and the subject population
- Not described in the protocol, consent form, or other information given to participants

YES

Report event using UC Event Reporting Form. For more information see Event Reporting Form. Submit a modification for proposed changes

NO

Do not report the event unless it could affect participant(s) willingness to continue in the study

NO

Report event in summary form at continuing review or DSMB report for external events

Policy Number: IL02
Reporting To the IRB: Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems
Page: 10 of 11
Reporting To the IRB: Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems


Other Applicable AAHRPP Domains:

Domain III

<table>
<thead>
<tr>
<th>Adoption Date</th>
<th>Created by</th>
<th>Date of Revision</th>
<th>Revised By</th>
<th>Summary of Revision</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-2009</td>
<td>J. Gerlach</td>
<td>10-2009</td>
<td>J. Gerlach per AAHRPP</td>
<td>Revise description of internal adverse events; Delete definition “Related or possibly related…”</td>
</tr>
<tr>
<td>10-2010</td>
<td>J. Gerlach</td>
<td>10-2010</td>
<td>J. Gerlach</td>
<td>Add text regarding reporting time of unanticipated events for VA researchers; revise examples of UE, add reference to 21 CFR 812 and 21 CFR 312</td>
</tr>
<tr>
<td>9/2014</td>
<td>A. Braggs-Brown</td>
<td>9/2014</td>
<td>A. Braggs-Brown</td>
<td>Revised to include AAHRPP recommendations</td>
</tr>
<tr>
<td>3/2015</td>
<td></td>
<td>3/2015</td>
<td>J. Strasser</td>
<td>Revisions for clarification</td>
</tr>
</tbody>
</table>

Date Adopted: March 2015 Signature: signed copy on file