University of Missouri-Columbia
Human Research Protection Program/Institutional Review Board
Unanticipated Problems Policy

1.0 Purpose

To outline the procedure to ensure prompt reporting to the IRB, appropriate institutional officials, sponsor, coordinating center, and the appropriate regulatory agency heads of unanticipated problems involving risks to subjects or others.

2.0 Scope

The SOP applies to all human participant research falling under the purview of the University of Missouri Institutional Review Board.

3.0 Policy/Procedure

Federal regulations [45 CFR 45.108(a)(4)(i)] require prompt reporting to the IRB, appropriate institutional officials, and the department or agency head, of any unanticipated problems involving risks to participants or others.

What are Unanticipated Problems?

The phrase "unanticipated problems involving risks to subjects or others" includes any incident, experience, or outcome that meets **all** of the following criteria:

1. **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. **related or possibly related** to participation in the research (*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

3. 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.**

Note: An incident, experience, or outcome that meets the three criteria above generally will warrant consideration of changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

Examples of corrective actions or changes that might need to be considered in response to an unanticipated problem include:

1. changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects;
2. modification of inclusion or exclusion criteria to mitigate the newly identified risks;
3. implementation of additional procedures for monitoring subjects;
4. suspension of enrollment of new subjects;
5. suspension of research procedures in currently enrolled subjects;
6. modification of informed consent documents to include a description of newly recognized risks; and/or
7. provision of additional information about newly recognized risks to previously enrolled subjects.

Unanticipated problems can include adverse events and other types of incidents, experiences, or outcomes that occur during the conduct of human subjects research. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

Unanticipated Problem Reporting

The IRB requires investigators to promptly report the following items within 5 business days of the investigator becoming aware of the unanticipated problem (note: onsite deaths have different reporting timeframes):

1. Any on site event (including adverse events, injuries, side effects, deaths, or other problems), which in the opinion of the principal investigator was an unanticipated problem;
2. Any off-site event or trends of events which in the opinion of the principal investigator is an unanticipated problem;
3. A protocol violation that put (or potentially put) the subject at a greater risk then previously known or recognized;
4. Information which indicates a change to the risks or potential benefits of the research, for example:
    a. An interim analysis indicates that participants have a lower rate of response to treatment than initially expected;
    b. Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected; and
    c. A paper is published from another study that shows that an arm of your research study is of no therapeutic value
5. Breach of confidentiality, privacy, or data security;
6. Complaint of a participant when the complaint indicates unexpected risk(s) or can not be resolved by the research team;

7. Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol;
8. Unanticipated adverse device effect; and
9. Any other problem which in the opinion of the investigators meets the definition of an unanticipated problem.

   *Investigators should contact the IRB administrative office if they are unsure whether the problem should be reported.

Investigators must report the above unanticipated problems using the Event Report. It is the responsibility of the investigator and study staff to track all events occurring in relation to a particular study to ensure accurate reporting.

The investigator is responsible for reporting the unanticipated problem to the applicable regulatory or sponsor division in accordance with their requirements. Examples of possible entities to which reporting are required include, but are not limited to, the sponsor, FDA, and federally funded cooperative research groups.

On-Site Deaths

The IRB must be notified within 24 hours of any on-site death of a research participant that meets the criteria of an unanticipated problem. Investigators must submit the Death Report and Event Report in eCompliance.

Exceptions:

1. Intervention Studies: If the death is not an unanticipated problem, report on the Death Report within 5 business days of awareness. For example, not related to the study procedures and/or anticipated due to the nature of the participant's underlying disease or condition, or identified as caused by a possible risk of the study procedure/intervention as described in the protocol and consent form.
2. When an individual dies more than 30 days after s/he has stopped or completed all of the study procedures/interventions and required follow-up, the death will be reported in the Annual Update Form.
3. Protocols that do not include a research intervention and are only tracking outcomes in an observational study design, the deaths will be reported in the Annual Update Form.
4. If you are studying dying populations, you may address this as a comment on the Annual Update Form and not note individual deaths.
5. If the study is such that you have no way of knowing a death has occurred, no reporting is required.

Adverse Events

Refer to the DHHS guidance on "Unanticipated Problems Involving Risks & Adverse Events Guidance" to determine whether an adverse event requires reporting:

https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html

Refer to the FDA guidance on "Adverse Event Reporting to IRBs" to determine whether FDA regulated studies with adverse events require reporting:

https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126572.pdf

IND Safety Reports

The MU PI must submit all IND safety reports to the MU IRB according to FDA guidance regarding safety reporting on an Event Report.

IND safety reports and reports of SAEs from IND-exempt BA/BE studies received from the sponsor describe important safety information representing unanticipated problems involving risk to human participants or others.

The investigator must submit IND safety reports18 to the IRB (§ 312.66) because FDA considers safety information that meets the IND safety reporting criteria under § 312.32(c) to be an unanticipated problem involving risk to human participants or others.

FDA considers the occurrence of any SAE in an IND-exempt BA/BE study to be an unanticipated problem involving risk to human participants or others that must be reported to the IRB (§ 56.108(b)(1)).

https://www.fda.gov/media/152530/download

Protocol Deviations/Non-Compliance that Result in Unanticipated Problems

A protocol deviation is any deviation from the protocol or process that is not approved by the IRB prior to its initiation or implementation. Sometimes these deviations result in unanticipated problems. See Non-Compliance SOP for more information about non-compliance.

Eligibility exceptions (or eligibility waivers granted by a sponsor) for enrollment of a specific individual who does not meet the inclusion/exclusion criteria in the IRB approved protocol are not deviations. Eligibility exceptions are considered changes in research that require IRB review and approval before a subject who does not meet the approved protocol inclusion/exclusion criteria may be enrolled. These may be submitted

to the IRB on the Inclusion/Exclusion Exception Form. See the Amendment SOP regarding changes to the research.

Investigator Monitoring Unanticipated Problems

It is the investigator's responsibility to monitor all adverse events, protocol deviations, or other incidents, experiences, or outcomes that occur during the conduct of human subjects' research. A system should be developed by the investigators to record and track all events. The system should enable the investigator to routinely monitor:

1. changes in frequency and severity of all events for shifts in expectedness;
2. shifts in the relatedness analysis represented by an increase of events due to disease progression or the subject's predisposing risk factors; and
3. events that alone do not represent an unanticipated problem but may represent a trend of a reoccurring problem which considered as a whole is an unanticipated problem

The monitoring and review of unanticipated problems and the impact they may have on the risk/benefit ratio within a study is an important component in the ethical, safe conduct of a study. The investigator, as the point of responsibility for the conduct of the study must review all documentation of problems to make an informed conclusion as to the impact of the problem and take appropriate steps to alleviate the identified risks.

The IRB reviews all submitted problems to also come to a conclusion of the impact of the problem(s) on the risk/benefit ratio of the study. The IRB will concur with the investigator's recommendations or recommend actions needed to alleviate identified risks.

The Cumulative AE Log is available in the eCompliance system as a tool for investigators to track non-reportable events. The IRB does not review the log.

IRB Review of Potential Unanticipated Problems

Initial Review

1. The IRB Staff (with consultation of the IRB Chair or Vice-Chairs as needed) will initially review all reported unanticipated problems. If appropriate to the problem, other project materials will be reviewed, such as
    a. the application or protocol;
    b. current informed consent; and
    c. other relevant documents pertaining to the event or problem
2. The IRB staff reviews the submitted information for verification. If any applicable sections of the Event Report are incomplete or have been answered unsatisfactorily,

the IRB staff contacts the investigator or the designated contact person to obtain additional information. Corrections are documented in eCompliance.

3. If the IRB staff (with consultation of the IRB Chair or designee as needed) considers the submitted information to be inconsistent with the investigator's assessment and the event is not considered to be an unanticipated problem, the IRB staff indicates this on the form and documents in the eCompliance system that the event is not reportable.
4. All other submitted unanticipated problems are placed on the agenda of the next available IRB meeting for review.

Full Board review

1. Each board member will receive a copy of the complete packet of materials pertaining to the review of this event, including
   a. The Event Report;
   b. Documents submitted in support of the form;
   c. Original application and protocol;
   d. Current approved consent form;
   e. Investigator's brochure, if applicable to the event; and
   f. Project history log outlining all action items for this project including amendments and previously reported unanticipated problems
2. A primary reviewer system is used for the review of unanticipated problems. A reviewer will be assigned with the responsibility of presenting a summary of the research and unanticipated problem to the Board.
3. The IRB reviews and votes whether the event represents an unanticipated problem.
4. The IRB considers the following actions:
   a. Request for more information pending final decision;
   b. Modification of the research protocol;
   c. Modification of information disclosed during the consent process;
   d. Notification of current participants (required when such information may relate to participants' willingness to continue to take part in the research);
   e. Requirement that current participants re-consent to participation;
   f. Additional information provided to past participants;
   g. Alteration of the frequency of continuing review;
   h. Observation of the research or the consent process;
   i. Requiring additional training of the investigator;
   j. Notification of investigators at other sites;
   k. Suspension or termination of the research according to the Suspension and Termination of IRB Approval SOP;
   l. Refer to other organizational entities (e.g. legal counsel, institutional official); and
   m. Other actions appropriate for the local context.
5. If the IRB considers the event to not represent an unanticipated problem involving risks to participants or others, no further action is taken and the investigator will be notified.

6. If an action is requested, the board will make a determination if the action should be reviewed by expedited procedure or must return to the full board for review of the action taken.
7. If the board requires re-consent of the subjects, this must be accomplished by the next study visit or within 60 days of notification. If this did not occur as required, the investigator must contact the IRB office to provide a justification as to why this has not occurred. This information will be reviewed by the board at the next available agenda as non-compliance. See Non-Compliance SOP.
8. The determinations and vote will be reported in the Minutes and the investigator will be notified of the action.

Notification of Action

The investigator will be notified of actions taken on each unanticipated problem in a timely manner. Documentation of the action will be provided to the investigator for placement in the study file. The action will also be appropriately noted in eCompliance.

If the event does not meet the criteria of an unanticipated problem, the investigator will be notified.

VA Research

This policy also applies to studies falling under VA purview. For review of VA unanticipated problems, please see the Truman VA Hospital Human Subject Research- Special Considerations SOP regarding VA requirements.

Effective and Revision Dates:
January 21, 2019; January 21, 2020; March 1, 2020; June 15, 2021; November 18, 2022, September 1, 2026

Approved By: Michele Kennett, JD, MSN, LLM, PhD, Associate Vice Chancellor for Research and Institutional Official

References:

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December 5, 2006; April 23, 2007; December 24, 2009; July 1, 2011; March 1, 2015; July 1, 2015; June 8, 2017, May 3, 2018