



Institutional Review Board

University of Missouri-Columbia

Standard Operating Procedure

Unanticipated Problems

Unanticipated Problems

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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 participants and other.

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

The monitoring and review of unanticipated problems involving risks to participants or others (unanticipated problem(s) hereinafter) 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.

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.

This policy also applies to investigators enrolling VA participants or using VA resources. For VA specific considerations please see the VA Hospital Research- Special Considerations SOP.

Federal regulations [45 CFR 45.103(b)(5)(i)] require prompt reporting to the IRB 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:

- **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 (*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

- 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:

- changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects;
- modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- implementation of additional procedures for monitoring subjects;
- suspension of enrollment of new subjects;
- suspension of research procedures in currently enrolled subjects;
- modification of informed consent documents to include a description of newly recognized risks; and
- 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 report the following items within 5 days of the investigator becoming aware of the unanticipated problem: *

- 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
- Any off site event or trends of events which in the opinion of the principal investigator is an unanticipated problem
- A protocol violation that put (or potentially put) the subject at a greater risk than previously known or recognized
- Information which indicates a change to the risks or potential benefits of the research, for example

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- An interim analysis indicates that participants have a lower rate of response to treatment than 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 your research study is of no therapeutic value
- Breach of confidentiality, privacy or data security
- Complaint of a participant when the complaint indicates unexpected risk(s) or can not be resolved by the research team
- Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol
- Unanticipated adverse device effect
- Any other problem which in the opinion of the investigators meets the definition of an unanticipated problem

*** On site death: the IRB must be notified within 24 hours of any on site death of a research participant.** This notification should be via the on-site death report. If the event meets the criteria for an unanticipated problem the Event Form must be completed as well.

Intervention studies--If the death is 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. **Report on the death report form within 5 days of awareness.**

Exceptions to on site death Reporting:

1. When an individual dies more than 30 days after she/he has stopped or completed all of the study procedures/interventions and required follow-up. **NO reporting required.**
2. PIs of protocols that do not include a research intervention and are only tracking outcomes in an observational study design. **These deaths may be reported to the IRB in the Continuing Review Application as part of the progress report.**

Note: * If the study is such that you have no way of knowing a death has occurred no reporting is expected.

*If you are studying dying populations you may address this as a comment on the CRR and not note individual deaths.

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

Investigators should report the above problems using the Event Report.

The investigator is responsible for reporting the event 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: Sponsor, FDA, and federally funded cooperative research groups.

Adverse Events

The key question regarding a particular adverse event is whether it meets the three criteria described below and therefore represents an unanticipated problem. To determine whether an adverse event is an unanticipated problem, the following questions should be asked:

- Is the adverse event unexpected?
- Is the adverse event related or possibly related to participation in the research?
- Does the adverse event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?

If the answer to **all three questions** is *yes*, then the adverse event is an unanticipated problem and must be reported.

A. Assessing whether an adverse event is *unexpected*

An *unexpected adverse event* is defined as follows:

Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which 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. *

* When assessing expectedness it is important to consider frequency and severity in relation to the natural progression of the subject's underlying disease or the subject's predisposing risk factor profile. An event normally expected within a subject population or expected due to predisposing risk factors may become unexpected due to the frequency or severity of the event.

Examples of *unexpected* adverse events under this definition include the following:

- liver failure due to diffuse hepatic necrosis occurring in a subject without any underlying liver disease would be an unexpected adverse event (by virtue of its unexpected nature) if the protocol-related documents and other relevant sources of information did not identify liver disease as a potential adverse event;
- Hodgkin's disease (HD) occurring in a subject without predisposing risk factors for HD would be an unexpected adverse event (by virtue of its unexpected nature) if the protocol-related documents and other relevant sources of information only referred to acute myelogenous leukemia as a potential adverse event; and
- liver failure due to diffuse hepatic necrosis occurring in a subject without any underlying liver disease would be an unexpected adverse event (by virtue of its unexpected greater severity) if the protocol-related documents and other relevant sources of information only referred to elevated hepatic enzymes or hepatitis as potential adverse events related to the procedures involved in the research.

In comparison, prolonged severe neutropenia and opportunistic infections occurring in subjects administered an experimental chemotherapy regimen as part of an oncology clinical trial would be examples of *expected* adverse events if the protocol-related documents described prolonged severe neutropenia and opportunistic infections as common risks for all subjects.

B. Assessing whether an adverse event is *related or possibly related to participation in research*

Adverse events may be caused by one or more of the following:

- 1) the procedures involved in the research;
- 2) an underlying disease, disorder, or condition of the subject*; or
- 3) other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

* When assessing relatedness it is important to consider frequency and severity in relation to the underlying disease, disorder, or condition of the subject. An event normally considered unrelated to the research procedures within a subject population may become related due to the frequency or severity of the event.

In general, adverse events that are determined to be **at least possibly caused by the procedures involved in the research** would be considered related to participation in the research. Adverse events determined **solely** caused by an underlying disease, disorder, or condition of the subject **or** other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject would be considered unrelated to participation in the research.

For example, for subjects with cancer participating in oncology clinical trials testing chemotherapy drugs, neutropenia and anemia are common adverse events related to participation in the research. Likewise, if a subject with cancer and diabetes mellitus participates in an oncology clinical trial testing an investigational chemotherapy agent

and experiences a severe hypoglycemia reaction that is determined to be caused by an interaction between the subject's diabetes medication and the investigational chemotherapy agent, such a hypoglycemic reaction would be another example of an adverse event related to participation in the research.

In contrast, for subjects with cancer enrolled in a non-interventional, observational research registry study designed to collect longitudinal morbidity and mortality outcome data on the subjects, the death of a subject from progression of the cancer would be an adverse event that is related to the subject's underlying disease and is unrelated to participation in the research. Finally, the death of a subject participating in the same cancer research registry study from being struck by a car while crossing the street would be an adverse event that is unrelated to both participation in the research and the subject's underlying disease.

Determinations about the relatedness of adverse events to participation in research commonly result in probability statements that fall along a continuum between definitely *related* to the research and definitely *unrelated* to participation in the research. This policy considers *possibly related* to participation in the research to be an important threshold for determining whether a particular adverse event represents an unanticipated problem. *Possibly related* is defined as follows:

There is a reasonable possibility that the adverse event may have been caused by the procedures involved in the research.

C. Assessing whether an adverse event suggests that *the research places subjects or others at a greater risk of harm than was previously known or recognized*

An important step in assessing whether an adverse event meets the third criterion for an unanticipated problem is to determine whether the adverse event is *serious*.

Serious adverse events include any adverse event that:

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

Adverse events that are unexpected, related or possibly related to participation in research, and *serious* are the most important subset of adverse events representing

unanticipated problems because such events always suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized and routinely 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.

Non serious adverse events:

Adverse events that are unexpected and related or possibly related to participation in the research, but *not* serious, would also be unanticipated problems if they suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. Again, such events routinely 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.

For example, a subject enrolled in an investigational drug study complains of occasional mild nausea. The investigator determines that the nausea is not due to disease progression or the subject's predisposing risk factors nor is it discussed in any of the protocol related documents. Given the timing of when the mild nausea occurs the investigator suspects it may be related to the investigational drug. Within a month's time multiple other subjects complain of mild nausea that is not expected and given the circumstances of the adverse event could be related to the drug. At this time the investigator should report this trend of adverse events as an unanticipated problem and revises the consent document to inform the subjects that nausea may be a side effect of the drug.

Other Important Considerations for Adverse Events

A. Reporting of internal adverse events by investigators to IRBs

Any on site adverse event which in the opinion of the principal investigator was an unanticipated problem should promptly be reported to the IRB.

If the investigator determines that an adverse event is not an unanticipated problem, but the monitoring entity i.e. sponsor, FDA or other monitoring agency subsequently determines that the adverse event does in fact represent an unanticipated problem (for example, due to an unexpectedly higher frequency of the event), the monitoring entity should report this determination to the investigator, and such reports must be promptly submitted by the investigator to the IRB.

B. Reporting of external (off-site) adverse events by investigators to IRBs

The Office of Human Research Protections (OHRP) and the Food and Drug Administration (as related to investigational drugs) have recognized that IRBs and investigators engaged in a multicenter clinical trial are generally not appropriately suited to assess the significance of individual adverse events. OHRP and the FDA note that

reports of individual external adverse events often lack sufficient information to allow investigators or IRBs to make meaningful judgments about whether the adverse events represents an unanticipated problem.

Taking into account the guidance recommendations from OHRP and the FDA this policy requires the following reporting with respect to off-site adverse events:

- 1) The investigator is responsible for monitoring off-site reports for events or trends of events which meet the definition of an unanticipated problem.
- 2) The investigator may rely on the sponsor's assessment of the off-site event and provide to the IRB a report prepared by the sponsor.
- 3) If the sponsor indicates further information is needed to fully evaluate the adverse event reporting is not necessary unless, in the opinion of the investigator, the adverse event represents an unanticipated problem.
- 4) The criteria is the same to determine if an off-site adverse event or series of events represents an unanticipated problem:
 - (i.) unexpected;
 - (ii.) related or possibly related to participation in the research; and
 - (iii.) serious or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.
- 5) Only when a particular adverse event or series of adverse events is determined to meet the criteria for an unanticipated problem should the adverse event form be submitted and should include: (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.

C. Clinical Investigations of Devices under Investigational Device Exemption (IDE) Regulations

In addition to the reporting requirements of this policy the sponsor must immediately conduct an evaluation of an unanticipated adverse device effect (UADE), and must report the results of the evaluation to the FDA, all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect (21 CFR 812.46(b) and 812.150(b)(1)).

D. Clinical Investigations of Drugs, Including Biological Drugs

Under FDA guidance for reporting adverse drug experiences it is important to note that many times an individual adverse event report cannot be readily concluded to represent an unanticipated problem, even if the event is not addressed in the investigator's brochure, protocol or informed consent documents. 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.

However, there are occasions when an adverse experience, even without a detailed analysis, can represent a serious, unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis and Stevens-Johnson syndrome). These adverse events should be reported as unanticipated problems.

Considerations for Protocol Violations/Deviations

A protocol violation/deviation is any deviation from the protocol or process that is not approved by the IRB prior to its initiation or implementation. Please note: 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 HS IRB on the inclusion/exclusion exception form.

Emergency deviations: When a deviation occurs in an *emergency situation*, such as when a departure from the protocol is required to protect the life or physical well-being of a participant, the sponsor and the reviewing IRB must be notified as soon as possible, but in no event later than 5 days after the *emergency* occurs. [[21 CFR 812.150\(a\)\(4\)](#) .] Please notify the IRB as soon as possible and submit the report using the Event Report.

Many times protocol violations occur in a study and when the violation as an individual event does not place the subject or others at a greater risk of harm than was previously known or recognized. Some example could include: follow up visits that occurred outside the protocol required time frame because of the participant's schedule, or blood samples obtained at times close to but not precisely at the time points specified in the protocol but should be submitted to the IRB using the Event Report regardless.

Please note: Sometimes an overall trend of events occurring in the study may rise to the level of placing the subject or others at a greater risk of harm than was previously known or recognized.

For example, a blood sample drawn for a biomarker sub-study in an investigational drug study is not shipped to the sponsor in the specified time frame. The cause of the delay in shipment is an inadequate supply of dry ice. As an individual event it is considered unexpected and related to the research procedures. However, there is no harm to the subject because the biomarker sub-study is an optional portion of the study and does not affect the subject's treatment. The investigator then discovers a trend of protocol violations due to untimely blood sample submissions for the biomarker study caused by an inadequate supply of dry ice. In the same study blood samples are also shipped for toxicology analysis. This trend of events is an unanticipated problem because of the potential for harm if a blood sample shipped for toxicology analysis is delayed. The investigator should report this as an unanticipated problem and include a plan to resolve the issue of an inadequate supply of dry ice.

Other times the violation/deviation alone actually places a subject at greater risk such as completing study procedures prior to obtaining consent or the violation/deviation is considered non-compliance. All violations/deviations should be reported on the Event Report for review.

Protocols that involve an Investigational Device Exemption (IDE)

FDA device regulations at [21 CFR 812.150\(a\)\(4\)](#) require prior approval from the sponsor of all planned deviations, including administrative and minor deviations. Planned deviations requested of a sponsor must be submitted for IRB review as a “change in research” approved by the HS IRB prior to instituting any IDE research planned deviations. For device research, the PI must keep on file a copy of the written approval document from the sponsor when a deviation is granted.

Does the FDA Good Clinical Practice (GCP) Guidance affect reporting of deviations?

Many sponsors require investigators to follow [Good Clinical Practice \(GCP\)](#) guidelines. The GCP Guidance for Industry states that an investigator: should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazard to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)). [GCP 4.5.2. at <http://www.fda.gov/cder/guidance/959fnl.pdf>, p. 15.]

Monitoring

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

- changes in frequency and severity of all events for shifts in expectedness
- shifts in the relatedness analysis represented by an increase of events due to disease progression or the subject’s predisposing risk factors
- 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 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

Initial Review - The IRB Administrative Staff in conjunction (with consultation of the IRB Chair or Vice-Chairs) 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
- c) other relevant documents pertaining to the event or problem

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 the electronic IRB file.

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 will not be reviewed by the board.

All other submitted unanticipated problems are placed on the agenda of the next available IRB meeting for review.

Full Board review - each board member will receive a copy of the complete packet of materials pertaining to the review of this event, including

- The IRB Event Report
- Documents submitted in support of the form
- Original application and protocol
- Current approved consent form
- Investigator's brochure, if applicable to the event
- Project history log outlining all action items for this project including amendments and previously reported unanticipated problems

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.

The IRB reviews and votes whether the event represents an unanticipated problem by considering:

- 1) unexpected;
- 2) related or possibly related to participation in the research; and
- 3) serious or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

The IRB considers the following actions:

- Request for more information pending final decision
- Modification of the research protocol
- Modification of information disclosed during the consent process
- Notification of current participants (required when such information may relate to participants' willingness to continue to take part in the research)
- Requirement that current participants re-consent to participation
- Additional information provided to past participants
- Alteration of the frequency of continuing review
- Observation of the research or the consent process
- Requiring additional training of the investigator
- Notification of investigators at other sites
- Suspension or termination of the research according to the Suspension and Termination of IRB Approval SOP
- Refer to other organizational entities (e.g. legal counsel, institutional official)
- Other actions appropriate for the local context

If the IRB considers the event to not represent an unanticipated problem involving risks to participants or others no further action is taken.

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.

If the board requires re-consent of the subjects, this must be accomplished within 60 days of notification. If not, 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.

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 the electronic records of the IRB.

If the event does not meet the criteria of an unanticipated problem, the form will be returned to the investigator as acknowledged.

4.0 Regulatory Guidance

[OHRP Guidance on Reviewing and Reporting Unanticipated Problems](#)
[FDA Guidance on Adverse Event Reporting](#)

5.0 Related SOP

Reporting

Suspension and Termination

VA Hospital Research – Special Considerations

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