



PROBLEMS OR EVENTS THAT REQUIRE PROMPT REPORTING TO THE IRB

Policy on Unanticipated Problems Involving Risks to Subjects or Others
11/20/2023

Federal regulations require prompt reporting to the Institutional Review Board, appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency head of unanticipated problems involving risks to subjects or others (UPIRTSO) that occur in the course of a subject's participation in a research study at DUHS. (45 CFR 46.108(a)(4)(i) and 21 CFR 56.108(b)(1)).

The purpose of this document is to define which problems or events, including protocol deviations, must be reported to the Duke University Health System Institutional Review Board (DUHS IRB), and the IRB's work flow and review process for handling protocol deviations and other events reported by DUHS investigators.

For **Definitions** of terminology, please see the **glossary** at the end of this policy.

A Protocol Deviation/Violation must be reported to the IRB if it:

- a) affects participant rights and welfare; or
- b) affects participant safety; or
- c) affects the integrity of study data; or
- d) affects the participant's willingness to continue in the study; or
- e) is specifically requested by a government agency, internal/external auditor, medical monitor, or the IRB.

Over-enrollment of study participants (i.e., exceeding the target enrollment) does not require the submission of a protocol deviation to the IRB but does require an amendment to increase enrollment.

Examples of Problems or Events that Require Prompt Reporting to the IRB:

- (a) Any unanticipated problem related to the research that involves risks to subjects or others.
- (b) Information that indicates an adverse change to the risks or potential benefits of the research. For example:
 - An interim analysis or safety monitoring report indicates that the frequency or magnitude of harms or benefits might be different from those initially presented to the IRB.
 - A paper is published from another study that shows that the risks or potential benefits of the research might be different from those initially presented to the IRB.
- (c) A Protocol Deviation/Violation if it meets one of the above criteria.
- (d) Change in FDA labeling associated with an increased risk; withdrawal from marketing of a drug, device, or biologic used in a research protocol; or withdrawal of FDA approval to conduct the study (including any clinical hold).
- (e) Incarceration of a subject in a protocol not approved to enroll imprisoned people.
- (f) Sponsor-imposed suspension of the study for participant safety.
- (g) Complaint of a participant when the complaint indicates unanticipated risks or cannot be resolved by the research team.
- (h) Any departure from the protocol that harmed participants or others; that indicates



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participants or others might be at increased risk of harm; or that compromises the integrity of the research data (including, but not limited to, process errors, deviations or violations, or medication errors).

- (i) Any 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 frequency 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 participants.)
- (j) An event that, as dictated by the protocol, requires urgent reporting to the sponsor, such as an unexpected pregnancy occurring in a study participant.
- (k) Any change made to the research without prior IRB approval in order to eliminate apparent immediate harm.
- (l) Any safety reporting requirements specified by the IRB as a condition of approval.
- (m) Any other problem that the investigator considers to be unanticipated and indicates that participants or others are at increased risk of harm or that may compromise the data integrity of the study.
- (n) Required prompt reporting to the IRB from any other component of the HRPP or regulatory authority overseeing the study.
- (o) Noncompliance with IRB or HRPP policies.
- (p) A PI loses a laptop that contains confidential information about participants in a research study.
- (q) A drug study requires close monitoring of drug levels. The lab calls the PI to report that the levels reported in the last week were in error.
- (r) A PI enrolls a participant who fails to meet inclusion criteria.
- (s) A study coordinator is injured while conducting research interviews in the community.
- (t) An adverse event occurs that is serious, unexpected and related to a drug administered as part of a clinical trial.
- (u) The participant receives an incorrect drug or dose as a result of a prescribing, dispensing or administration error, regardless of whether the participant experienced *detectable* harm.
- (v) A systems error occurring in the design, organization, training, or conduct of the study.

Reporting Timelines

Immediately (within 24 hours) upon learning of an unanticipated study-related death, study personnel will notify the IRB via phone or email by providing a brief summary of the event. Then within 1 week (five business days), study personnel will send to the IRB a Safety Event submission in iRIS.

For a reportable serious adverse event, study personnel will notify the IRB within five business days of the investigator becoming aware of the event. Study personnel will send a Safety Event submission in iRIS.

For any other problem or event requiring prompt reporting to the IRB, within ten business days of the investigator becoming aware of the event, study personnel will send to the IRB a Safety Event submission in iRIS.

Note: Whether an event is internal or external does not affect the requirement for prompt reporting to the IRB, but may impact actions taken by the IRB upon reporting.



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IRB Procedure for Review

The Protocol Deviation/Violation/Safety Event Report is received via iRIS. IRB staff perform an initial review of the report using the following criteria:

If the reported deviation/violation/event involves a drug, device or biologic or other interventional activity, the IRB Staff assigns it to a Chair/Vice Chair. For the purposes of this document, “interventional activity” shall mean any activity described in the protocol that directly involves the administration of a drug/device/biologic or that comprises a clinical or research procedure administered to the research participant.

If the reported deviation/violation/event involves the consent process or other non-interventional activity, the IRB Staff can either complete the review and define the corrective actions or assign it to the Executive Director or Chair/Vice Chair. Deviations/violations/events that meet the qualifications for expedited review as defined by 45 CFR 46.110(b)(2) can be reviewed and finalized by the IRB Staff, Executive Director, Chairs or Vice Chairs. All other deviations/violations/events will be assigned for review and presentation at a convened IRB meeting.

If the reported deviation/violation/event involves a failure to follow federal regulations, institutional policies governing human subject research, or requirements or determinations of the IRB, then the policy titled “Non-Compliance with the Requirements of the Human Research Protection Program” will be followed.

The assigned reviewer will complete the expedited reviewer checklist in iRIS and define corrective actions, if any. If no further reply is required from the Principal Investigator, the assigned reviewer will complete the review process. If a reply is required, the assigned reviewer will send comments (using the modifications requested function) for the Principal Investigator.

If a reply is required from the Principal Investigator, the Principal Investigator will be instructed to provide any requested information or documents via iRIS. When a reply from the Principal Investigator has been submitted via iRIS, the assigned reviewer will review the proposed corrective actions and complete the reviewer process.

If the Principal Investigator fails to agree to any part of the corrective action plan, the assigned reviewer will consider the failure to agree using the policy titled “Non-Compliance with the Requirements of the Human Research Protection Program”.

If the reviewer concludes that the deviation/violation/event does not need to be reviewed for further consideration of UPIRTSO or Non-Compliance, and no further action is required, then the reviewer completes the review process.

Review for UPIRTSO

The Executive Director/IRB Chair/Vice Chair (by way of expedited review) or the convened IRB (by way of convened board review) will determine if the problem or event meets the definition of an unanticipated problem involving risks to subjects or others (UPIRTSO), defined as:

Any incident, experience, or outcome that meets both of the following criteria:

- (a) unanticipated
- (b) indicates 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.



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Any such incident, experience or outcome generally will warrant consideration of a quality improvement (corrective) action, such as a change in the research protocol and/or consent document, in order to protect the safety, rights and welfare of research subjects.

If the Executive Director/IRB Chair/Vice Chair determines that the problem is an unanticipated problem involving minimal risk to subjects or others

The Executive Director/Chair/Vice Chair can require minor modifications to the research (as defined in procedures for review using the expedited procedure) or follow the procedure for unanticipated problems involving more than minimal risk to subjects or others.

If the Executive Director/IRB Chair/Vice Chair determines that the problem is an unanticipated problem involving more than minimal risk to subjects or others

The IRB specialist places the matter on the agenda at the next available IRB meeting. The IRB specialist provides all members with a copy of the report, the IRB application, the currently approved IRB protocol summary, and the currently approved consent documents. All IRB members are expected to review these materials. The primary reviewer is additionally provided a copy of the investigator brochure and any previous reports of unanticipated problems involving risks to subjects or others related to the protocol.

The convened IRB may consider the following actions:

- Suspension of the study
- Termination of the study
- Modification of the protocol
- Coordination of care planning with clinical staff
- Revised plan for research staff competencies, roles and/or responsibilities
- Referral to institutional safety officer for root cause analysis and quality improvement plan
- Other appropriate quality improvement action plan
- Modification of the information disclosed during the consent process
- Providing additional information for current or past participants
- Re-consent of current participants taking part in the study.

The Institutional Official is notified.

Actions of the Institutional Official

The Institutional Official or designee, with assistance from the IRB Executive Director, the IRB Chair, or designee, will report the institution's determination and findings to all appropriate entities within DUHS and to relevant regulatory agencies, as described in the policy titled "Reporting of IRB Findings to Institutional Officials and Federal Regulatory Agencies."

Non-Compliance with This Policy

In the case of possible non-compliance with this or other institutional/IRB policies, the IRB will request that the investigator file a Safety Event in iRIS to describe the occurrence, and present a plan for preventing future occurrences.



Glossary

Protocol Deviation

An inadvertent act (from the perspective of the PI and study staff) in which the protocol is not followed. Examples of protocol deviations include the accidental destruction of a bone marrow sample intended for phenotyping to characterize the participant's type of leukemia in order to determine study eligibility, or an accidental misread of a laboratory value as being within the reference range when it actually is sufficiently abnormal to preclude study participation by the individual.

Protocol Violation

An intentional act (from the perspective of the PI and study staff) in which the protocol is not followed. Examples of protocol violations include the PI prescribing or administering the wrong drug on the study, or the study subject being scheduled to return for follow-up intervention outside the protocol-dictated window as a convenience to the PI or the study staff.

Unanticipated

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 participant population being studied.

Possibly Related

There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research. The IRB interprets "reasonable possibility" to mean "more likely than not". Therefore "possibly related" means "more likely related than unrelated".

Serious Adverse Experiences or Events that Require Prompt Reporting

A serious adverse experience or event requires prompt reporting when it meets both of the following criteria:

- unanticipated (defined above)
- indicates that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Non-serious Adverse Experiences or Events that Require Prompt Reporting

A non-serious adverse experience or event requires prompt reporting when it meets both of the following criteria:

- unanticipated (defined above)
- indicates that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

External event

From the perspective of one particular institution engaged in a multicenter clinical trial (e.g., Duke), external events are those events experienced by participants enrolled by investigators at other institutions engaged in the clinical trial.

Internal event

From the perspective of one particular institution (e.g., Duke) engaged in a multicenter clinical trial, internal events are those events experienced by participants enrolled by the investigator(s) at that institution (i.e., Duke). In the context of a single-center clinical trial, all events would be considered internal events.



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Medication Error

Any error occurring in the medication use process, e.g. prescribing, dispensing, administering, or monitoring. All medication errors should be reported promptly to the hospital safety reporting system, whether requirements for prompt reporting to the IRB are met or not.

Systems Error

Errors in the design, organization, training, or maintenance that lead to operator errors and errors whose effects typically lie dormant in the system for lengthy periods of time. Examples include poor design, incorrect installation, faulty maintenance, bad management decisions, and poorly structured organizations. Systems errors pose the greatest threat to safety in a complex system because they are often unrecognized and have the capacity to result in multiple types of active (i.e., operator) errors.

Corrective Action

An action, usually required of the Principal Investigator, which is necessary to reduce the risk to the participants and/or prevent a recurrence of the reported protocol deviation/violation/event. Examples of corrective actions include revision of the protocol and/or consent form, re-consent of participants, further training of study staff, or formal notification to the appropriate government oversight agencies.

IRB Management Team

The Executive Director, Director of Research Review, Director of IRB Compliance, Chairs and Vice Chairs.

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