Guidance: Reporting New Information, Incidences or Adverse Events

Overview

During a research study, unintentional mistakes in following the IRB-approved protocol or unexpected issues may occur. The Principal Investigator (PI) is responsible for the accurate documentation, timely reporting, investigation, and follow-up of these events.
This guidance is intended to help the PI ensure that the reporting and review of these events occur in a timely, meaningful way so that research participants can be protected from avoidable harm. Below, find information on whether an event meets the IRB reporting criteria, reporting timelines, examples of what must be reported to the IRB, what to do when an event does not meet the reporting criteria, corrective and preventive action plans, and IRB Determinations and Definitions.

Definitions

Adverse Event (AE): any unfavorable or unintended event, including abnormal laboratory findings, a symptom of disease, or death, associated with the participant's participation in the research or the use of an investigational test article. An AE in research may occur even in the absence of any error or protocol deviation and is not necessarily caused by any identifiable aspect of the research.

Serious Adverse Events (SAE): those that result in death, life-threatening injury, hospitalization (or prolongation of existing hospitalization), results in a persistent or significant disability/incapacity, or a congenital anomaly or birth defect. An event that requires intervention to prevent one of these outcomes is considered a serious adverse event.

"Life-threatening" includes any adverse experience that places the participant, in the investigator's view, at immediate risk of death from the reaction as it occurred.

Internal adverse events: adverse events experienced by subjects at sites that are relying on the Northeastern for IRB review of the research

External adverse events: adverse events experienced by subjects enrolled at sites that are not relying on the Northeastern for IRB review of the research. In the case of an external adverse event, the principal investigator typically becomes aware of the adverse event upon receipt of a report from the sponsor, coordinating center or other monitoring group, such as a Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC), or collaborating investigator at another site.

Protocol Deviation/Violation

A protocol deviation is any alteration or deviation (whether accidental, unintentional, or intentional) from the IRB-approved research plan as defined in the IRB-approved protocol.

Unanticipated Problem: any information, including any incident, experience, or outcome that meets ALL of the following conditions:

1. Is unexpected (in terms of nature, severity, or frequency) given the procedures described in the research protocol documents (e.g., the IRB-approved research protocol and informed consent document) and the characteristics of the human subject population being studied;
2. Is 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 human subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized, even if no harm has occurred.

New information: any new information that does not involve a protocol deviation and/or risk to the participant. Examples may include data safety monitoring reports and incarceration of participants.

Other Unexpected Events: an event that exposes a research participant or others to an increased risk of harm (than was previously known or recognized) because of research activities. Also, any suspected serious, continuing non-compliance with the IRB-approved protocol or research-related injury, or any event that adversely affects the rights or welfare of participants or undermines the scientific integrity of the data.

IRB determinations

Incidences that meet the definition of serious non-compliance, continuing non-compliance, unanticipated problems involving risk or subjects or others (UPIRSO), or a combination of these are required to be reported to the IRB.

Non-compliance:
Failure to follow the federal regulations governing human research, requirements, and/or determinations of the IRB. Non-compliance may result from actions or omissions by study personnel and can range from relatively minor or technical deviations to serious deviations that threaten participants' rights or welfare.

- Examples of non-compliance which may not be reportable to the IRB may include, but are not limited to the following: Inadvertent use of an IRB approved but non-stamped informed consent form (ICF); an out of window study visit that did not cause any harm

or increase the risk of harm or adversely affect the participants' rights and welfare or negatively affect the integrity of the study data; or other administrative errors. Please note all occurrences of non-compliance should be documented within the study records, within the protocol deviation log or a note to file, or by using the Incident Assessment Tool, as applicable.

Serious Non-compliance

Non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB that cause harm, increases the risk of harm, adversely affects the rights or welfare of participants, and/or undermines the scientific integrity of the data.

Examples of serious non-compliance include but are not limited to the following:

- use of an incorrect version of an informed consent document that omitted a potential risk of participation;
- conducting study procedures before obtaining informed consent;
- numerous instances of not adhering to the protocol, such that the participant's data is no longer usable.

The IRB may consider mitigating factors, such as corrective action, that play a role in the determination of whether the event increased risk, decreased potential benefits, or negatively affected the integrity of the study data but if despite these factors, the panel may determine the event's occurrence meets the definition of serious noncompliance, and then the event will be categorized as such.

Continuing Non-compliance

A pattern of non-compliance through failure to adhere to the regulations or institutional requirements that protect the rights and welfare of participants and others and suggests a likelihood that non-compliance will continue without intervention or involves frequent instances of minor non-compliance. Continuing non-compliance may also include failure to respond to a request from the IRB to resolve an episode of non-compliance or a pattern of minor non-compliance.

Examples of continuing non-compliance may include but are not limited to the following:

- non-safety related laboratory assessments were not completed on day 15 for cycles 1-12;
- the quality-of-life assessments were not administered for participants #6-15;
- despite a corrective action plan the study team continues not to distribute the drug diary.

Note: multiple instances of non-compliance that are deemed not serious individually may constitute serious and/or continuing non-compliance when considered collectively.

Unanticipated Problem Involving Risks to Subjects or Others (UPIRSO)

Any information, including any incident, experience, or outcome that meets ALL of the following conditions:

- is unexpected (in terms of nature, severity, or frequency) given the procedures described in the research protocol documents (e.g., the IRB-approved research protocol and informed consent document) and the characteristics of the human participant population being studied;
- is 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 human participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized, even if no harm has actually occurred.

Suspension of IRB Approval

An action of the IRB, IRB Executive Director, Institutional Official/Organizational Official, or designee of the Institutional Official/Organizational Official to temporarily or permanently withdraw IRB approval of some or all research procedures short of a Termination of IRB Approval. Suspended studies remain open and are subject to continuing review.

Termination of IRB Approval

An action of the IRB, IRB Executive Director, Institutional Official/Organizational Official, or designee of the Institutional Official/Organizational Official to permanently withdraw IRB approval of all research procedures. Terminated studies are permanently closed and no longer require continuing review.

Additional information needed before the determination

When additional information is needed before the board can make a determination. The PI should consult the RNI letter and/or eIRB+ and follow the directives of the IRB to complete any required action/provide the requested information and submit the RNI back to the IRB for a final determination.

None of the above

When an event does not fit the criteria for UPIRSO, Non-compliance (including Serious or Continuing), suspension/termination of IRB approval, or Allegation of non-compliance with no basis in fact, the IRB acknowledges the event as none of the above.

Does the event meet the IRB reporting criteria?

The Principal Investigator must determine whether or not a problem is caused by or related to the study. The regulations at 45 CFR 46.108 (a)(4)(i) and 21 CFR 56.108 (b)(1) allow the PI to make the initial reporting determination.

The PI is also responsible for meeting all reporting obligations (i.e., notifying the study sponsor, lead site, etc.).

The DHR has developed an Incidence Assessment Checklist that may be used to determine when new information should be reported to the IRB. Note: This may be used as a resource and it is not required to be submitted.

What if the event does not meet the reporting criteria?

1. Document in the research record how the deviation does not meet the reporting criteria. The completed Incident Assessment checklist can be used for documentation.
2. Log the deviation such that it can be evaluated in the future if other deviations occur.

What if the event does meet the meeting criteria?

- Complete the IRB incident report form and submit it to IRBReview@northeastern.edu.
- Refrain from including participant identifiers (name, date of birth, etc.) within the New Information & Incidence Form.
- Provide any supporting documents with the application to explain the event.
- If changes are being made based on the reported information, complete and submit a Modification form. Indicate the modification is based on an incident and changes are being proposed as part of the corrective and preventive action plan.

Are there reporting timelines?

Internal Adverse Events which are fatal or life-threatening, and related or possibly Related to the research intervention must be reported to the IRB within 24 hours of learning of the event. (Note: It is recognized that the information available during these 24 hours may not be sufficient to permit accurate completion of the required adverse event reporting forms. However, the IRB should, at a minimum, be notified of the fatal or life-threatening internal

adverse event during this time frame, with subsequent follow-up submission of a more detailed written report.) All other internal Adverse Events will be reported to the IRB within 10 working days of the investigator learning of the event.

Unanticipated Problems Involving Risks to Human Subjects or Others and incidents of reportable non-compliance (see below) must be submitted within 10 working days of the investigator becoming aware of the event.

External Adverse Events should be reported if they affect local participants, require a change in protocol or revision of the consent document, and completed within an appropriate time frame after the IRB of record has made a determination.

Institutional reporting obligations

Northeastern University is obligated to report to institutional officials and all applicable federal oversight agencies information that represents Serious Non-Compliance, Continuing Non-Compliance, Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO), Suspension of IRB Approval, Termination of IRB Approval, or any combination of the above.

If any of these are reported to the IRB, the PI should confirm the current funding source(s) is/are identified in the IRB protocol. The DHR uses the protocol's funding sources to help determine the parties to whom to report. Outdated or inaccurate funding information may cause unnecessary reporting, which poses an institutional risk. Adding or removing funding sources from a protocol may be completed via the modification process.