Reportable Events: Unanticipated Problems and Adverse Events Involving Risks to Research Subjects and Others

Purpose

This policy is to assist investigators in understanding their obligations to report events that pose unanticipated problems that involve risks to subjects or others.

Serious and unexpected events that are related or possibly related are one category of unanticipated problems involving risks to subjects or others and other forms of unanticipated problems that may cause risk to the subject or others are listed below.

This policy provides:

1. Criteria for Reporting
2. How to Report
3. Investigation and Evaluation of the Report
4. Determinations Concerning Appropriate Remedies
5. Additional Reporting Requirements

Policy

Federal regulations 45 CFR 46.108(a)(4)(i) and 21 CFR 56.108(b)(1) require IRBs to have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the federal department or agency head of any unanticipated problems involving risks to subjects or others. In keeping with this regulatory requirement, investigators are required to promptly report to the IRB unanticipated problems involving risks to subjects or others.

Unanticipated Problem Involving Risks to Participants or Others (UP): Any event that:

1. Is unanticipated, not expected given the nature of the research procedures and the population being studied and
2. Suggests that the research places subjects or others at a greater risk of harm related to the research than was previously known or recognized.

To be defined as an **Unanticipated Problem that Involves Risks to Subjects or Others** the event must meet all the following criteria:

1. **Unanticipated:** The event is unexpected or unforeseen in type, frequency, scope, consequences, or severity; or, if anticipated or referred to in part, is not fully addressed or specified within the initial protocol application, any amendments, consent forms, investigator brochures, minutes, and any existing documentation regarding the research conducted to date under the protocol.

2. **Potential for Risk: Caused Harm or Placed a Person at Increased Risk of Harm**. As a result of the event, participants or other individuals are either placed or are likely to be

placed at physical, psychological, social, or emotional harm that has increased since the time the research was approved by the IRB.

3. **Problem Related to the Research:** The event, situation, or issue arises from the conduct of the research and is determined to be related or probably related to the research and is of concern for the research participants or others directly affected by the research. Problems may:
   a. Be attributable to the conduct of the research or
   b. May result from failures or errors in general systems outside of the research, or factors that are not controlled by the researcher under the protocol, but on which ethical conduct of the research depends, according to the protocol.

***Possibly Related*:** An event is possibly related to the drug, device, or intervention if there is a reasonable possibility that the event may have been caused by the research protocol, even if there is insufficient information to determine the likelihood of this possibility.

Related/Probably Related: An event is determined to be definitively related to the use of the drug, device, or intervention, or there is a reasonable probability that the event may have been caused by the drug, device, or intervention. A related or probably related event has a strong temporal relationship to the study protocol and an alternative etiology is unlikely or significantly less likely.

Unanticipated problems that involve risks to subjects or others include not only materialized adverse events and risks to persons who are not research subjects. Investigators should note that this definition also includes problems that arise from general system failures that contribute to such risks, not simply events that arise from the investigator's conduct of the research according to the protocol.

Procedure

The following information is provided to assist investigators in their obligations to report unanticipated problems that involve risks to subjects or others:

Criteria and Timeline for Reporting

The following events require reporting to the IRB within 72 hours of the occurrence of the event or notification to the PI or research team of the event;

1. **DEATH** of research subject thought to be either related to research study or possibly related to research study.

2. **UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)** that result in the death of a research subject.

3. **TERMINATION OR SUSPENSION** of the study by the sponsor, DSMB or federal agency overseeing the research due to a safety issue.

The following events require reporting to the IRB within 5 business days of the occurrence of the event or notification to the PI or research team of the event;

1. **ADVERSE EVENT:** Both must apply in order to be reportable:
   - **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 protocol and informed consent document; and the characteristics of the subject population being studied, and
   - **Related or possibly related** to a subject's participation in the research.

2. **UNANTICIPATED ADVERSE DEVICE EFFECT (UADE):** Any serious adverse effect on health or safety, 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 of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

3. **MEDICATION OR LABORATORY ERRORS** that have or could have caused risk to subjects or others. This includes if there is an error or an overdose of a drug or biologic administered as part of a research protocol or a miscalculation of a drug dose; a mix-up that results in a wrong drug being administered (e.g., placebo instead of intervention drug).

4. **BREACH OF COFIDENTIALITY/HIPAA VIOLATION** resulting from disclosure of confidential information or identifiable private information or loss/stolen confidential information (i.e. lost laptop, inadvertent email distribution).

5. **NONCOMPLIANCE/PROTOCOL DEVIATION**: Any violation of human subject research regulation, institutional policy, or any conditions imposed by the IRB, **or** a deviation/departure from an IRB-approved protocol that has or had the potential to:
   - Impact subject rights, welfare or safety of present, past or future subject(s), or
   - Increase the risks and/or decrease the benefit for research subjects(s), or
   - Compromise the integrity of the study data, or
   - Affect the subject's willingness to participate in the study.

6. **COMPLAINT**: A research related complaint by a research subject or any another person.

7. **INTENTIONAL CHANGE TO PROTOCOL WITHOUT IRB APPROVAL** to eliminate apparent immediate hazard to research subject(s).

8. **INTERIM FINDINGS, PUBLICATION OR SAFETY REPORT** – An interim safety report (including a Data and Safety Monitoring report), publication in the literature, report of interim results, or another finding that indicates an unexpected adverse change to the risks or potential benefits of the research.

9. **ENFORCEMENT ACTION** – An unfavorable audit report; suspension or disqualification of an investigator; FDA Form 483, or Warning Letter.

10. **INCARCERATION OF A RESEARCH SUBJECT** during study participation (Note: Required for regulatory purposes, so additional mandated IRB review can be accomplished for the participant to remain in the trial).

11. **REQUIRED PROMPT REPORTING**: An event that required prompt reporting to the sponsor or IRB in accordance with the protocol.

12. **OTHER**: Any other event that the PI thinks (or is unsure if it) may represent an unanticipated problem involving risk to subjects or others.

Please note for reporting allegations of research misconduct, contact the Research Integrity Officer for Boston Children's: rio@childrens.harvard.edu or call the anonymous Compliance Department Hotline: 888-801-2805.

Events That Do Not Meet Reporting Criteria

Events that do not meet the criteria as defined in this policy do not require submission to the IRB. Events from protocols that are not conducted at Boston Children's Hospital but involve same drugs/devices do not need to be reported. An unanticipated drug/device event only needs to be submitted for the protocol under which the event occurred unless the investigator determines that:

1. The event impacts the risk/benefit assessment of other approved protocols and
2. A change to the protocol and or consent are required.

It is important for investigators to remember that even if an event does not meet criteria for reporting to the IRB they must continue to meet their obligations to report events to the sponsor, the Food and Drug Administration (FDA), and the data safety monitor.

How to Report

In accordance with the criteria listed above, investigators are required to complete and submit to the IRB a ***Reportable Event*** form.

The form must be completed regardless of whether other forms (e.g. sponsor IND safety reports or CRO/monitoring reports, MedWatch reports, etc.) have already been completed.

Information such as a summary of the event, and/ reports from the coordinating center or drug company may be attached and submitted with the form. The form will ask:

1. The investigator to independently determine whether the event was thought to be related or possibly related to the research study.

2. The investigator to independently determine whether the event was thought to be anticipated or unexpected.
    a. In some cases, the Principal Investigator may not agree with a sponsor's assessment of the relationship between the study drug and the UP.
    b. If either the PI or the sponsor considers the event to be a UP, then a report should be filed. The contrary opinions can be elaborated in the report.
3. Any other individual (e.g. research staff, subject, IRB member, or the general public) may report an event, issue, or situation for a research protocol if they are concerned that it

    represents a potential unanticipated problem that involves risk to subjects or others. They can report their concerns to the IRB Chair, the Director of Clinical Research Compliance, or the Institutional Official.
4. Incidents that may potentially be considered unanticipated problems that involve risk to subjects or others may also become apparent during continuing renewals, incidents of noncompliance, quality improvement initiatives and report, review of data and safety monitoring reports, protocol violations, deviations, complaints, concerns from subjects or family members, concerns raised by research staff or investigators, participant injuries, deaths, and hospitalizations.

Investigation and Evaluation of the Reports

Once a ***Reportable Event*** form is received by the IRB, the following actions will occur:

1. The Director of Clinical Research Compliance will screen the submission to determine whether it meets the Criteria of Reporting. The Director will obtain initial feedback from the investigator when there are questions or additional information is required
2. Based on the information received, if there is any immediate concern that subjects already enrolled or subjects to be enrolled in the trial may be subject to immediate increased harm to their health, safety, or welfare, the IRB Chair will be immediately contacted.
    a. If necessary, the IRB Chair will require that the protocol be suspended or terminated in accordance with the ***Suspensions and Terminations*** policy.
    b. In most situations this will not be necessary.
3. IRB Chair Review: All submitted reportable events will be reviewed by the IRB Chair or Vice Chair who will determine if the event should be placed before the convened IRB.
    c. The Chair will review the event and ask for any associated documentation and/or information they feel necessary to understand and review the event.
    d. The investigator will receive written notification as to whether the report was accepted, whether additional information or action is required or placed before the convened IRB for consideration
4. Full IRB review:
    a. Each event will be assigned a primary reviewer.
    b. All IRB members will receive a copy of the event form and have access to the entire protocol, approved consent and history through the electronic system.
    c. At the IRB meeting the reviewer will report on the event to the full committee and determine whether any further action as listed below required.

d. The IRB will make a final determination as to whether the event needs to be reported as an unanticipated problem involving risks to participants or others. If the IRB determines that the event is an unanticipated problem involving risks to participants or others, the event will be reported according to the IRB ***Reportable Event*** policy.

e. The investigator will receive written notification as to whether the report was accepted, if additional information or action is required, and/or reporting is required.

Determinations Concerning Appropriate Remedies

In reviewing and addressing any unanticipated problem the IRB Chair or IRB may impose any remedy or take any action authorized by law or regulation, including:

- Initiate immediate corrective action, if necessary.
- Delegate a subcommittee or individual to perform further investigation.
- Require that individuals who have already consented to participation be notified.
- Require modification of any other aspect of the conduct of the research including recruitment, informed consent, research and clinical procedures, monitoring and safety assurance, and continuing review.
- Alter the frequency of continuing review.
- Require that enrolled subjects be provided with an amended informed consent form and that the process of providing for informed consent be repeated with revised information. This will be required whenever the information may relate to the participants willingness to continue participating.
- Determine the protocol should be terminated or suspended. See IRB policy: ***Termination and Suspension***.
- Require the investigator to inform other research participants or individuals who may be affected by the event or problem.
- Notification of investigators at other sites.
- Observation of the consent process.
- Refer concerns or findings to other parts of the organization that administer other policies, laws, and regulations.
- Any other action necessary to resolve the incident and address the safety and welfare of current and future research subjects.

Additional Reporting Requirements

This policy concerns only what needs to be submitted to the IRB and does not impact what investigators need to record or document as part of their research records. There may be additional reporting requirements.

Depending upon the protocol, the investigator may be required to report other events that are not required by the IRB such as: the sponsor (e.g. NIH) or coordinating center, DSMB charter, and/or regulatory authorities (HHS or FDA).

In addition, the annual IRB application for continuing review reports will ask if the risk profile has changed for the protocol and to summarize these events as part of the continuing review.

Related Content

IRB Policies

Noncompliance: Investigations and Determinations
Reportable Events
Suspensions and Terminations

IRB Form

Reportable Event

Federal Guidance

OHRP: Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events U.S. Department of Health and Human Services: Office for Human Research Protections, (January 15, 2007).
https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html

FDA : Adverse Even Reporting to IRBs – Improving Human Subject Protections – Guidance for Clinical Investigators, Sponsors, and IRBs
U.S. Department of Health and Human Services: Food and

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adverse-event-reporting-irbs-improving-human-subject-protection

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