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Boston Children's Hospital

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Owner Susan Kornetsky: Manager

Department Research

Applicability Boston Children's Hospital- Policies & Procedures

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

Internal Approval

SVP, Research Administration

EVP, Chief Scientific Officer

Scope

This policy applies to the Boston Children's Hospital (BCH) Research department and the respective staff.

Definitions

Unanticipated Problems Involving Risks to Subject or Others (UP): Any event, experience, or outcome that meets all of the following criteria:

1. **Unanticipated** (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;
    b. and the characteristics of the subject population being studied
2. **Related or possibly related to the research**; The event, situation, or issue arises from the conduct of the research and is determined to be related/possibly related to the research. Events may be related/possibly related to the research that arise from general system failures not simply events that arise from the investigator's conduct of the research according to the protocol.

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.

Unanticipated Adverse Device Effect: 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.

Adverse Event: Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Relying Institution: External institution that agrees to accept IRB review and oversight from a Reviewing IRB. For the purpose of this policy, Relying Institutions are those who rely on the BCH IRB for the review and oversight of the research.

Reviewing IRB: The selected IRB of record that conducts the ethical review of research for all participating sites of a multi-site study. Also referred to as the IRB of record, central IRB, or single IRB (sIRB).

Policy Statements

This policy is to assist Principal Investigators (PIs) in understanding their obligations to report events that pose unanticipated problems that may involve risks to subjects or others.

Federal regulations 45 CFR 46.108(a)4)(i) and 21 CFR 56.108(b)(1) require Institutional Review Boards (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 BCH IRB all UPs.

Procedures

The following events require reporting to the BCH 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 at BCH or a Relying Institution thought to be either related to research study or possibly related to research study.
2. **UNANTICIPATED ADVERSE DEVICE EFFECT** that result in the death of a research subject at BCH or a Relying Institution.
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 BCH 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 in a participant enrolled in the research at BCH or a Relying Institution:** Both must apply in order to be reportable:
    a. **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**
    b. **Related or possibly related** to a subject's participation in the research.
2. **UNANTICIPATED DEVICE EFFECT**
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 CONFIDENTIALITY/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:
    a. Impact subject rights, welfare or safety of present, past or future subject(s), or
    b. Increase the risks and/or decrease the benefit for research subjects(s), or
    c. Compromise the integrity of the study data, or
    d. Affect the subject's willingness to participate in the study.
6. **COMPLAINT**: A research related complaint by a research subject or any another person when the complaint cannot be resolved by the PI/research team.
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, new black box warning or another finding that indicates there are new or increased risks to participants or others or that participants are less likely to receive direct benefits from 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.

When the BCH IRB serves as the Reviewing IRB for a protocol, what events occurring at the Relying Institution must be reported to the BCH IRB?

This policy and the requirements for reporting events apply to all sites relying on the BCH IRB.

Which external safety reports need to be reported promptly to the IRB?

Adverse Events that occur in study participants who are not enrolled at BCH or a Relying Institution are under the oversight of another IRB. The PI typically receives notification of these External Safety Reports (e.g., SUSAR reports) from the study sponsor and these AEs are usually referred to as Sponsor Safety Reports or Safety Memos.

Only external safety reports determined by the sponsor and/or investigator to meet the definition of a UP should be reported to the BCH IRB. Such reports would likely warrant changes to the conduct of the research, consent process, or require notification to participants as outlined below. The timeframe for reporting these events is 10 business days of BCH PI awareness.

Investigator Reporting Procedures

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

1. 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.
2. Information such as a summary of the event, and/or reports from the coordinating center or drug company may be attached and submitted with the form.
3. The form will ask the investigator to independently determine whether the event was thought to be related or possibly related to the research study.
    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.
4. 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 UP that involves risk to subjects or others. They can report their concerns to the IRB Chair, the Senior Director of Clinical Research Compliance, or the Institutional Official.

Investigation and Evaluation of the Reports

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

1. The Senior Director of Clinical Research Compliance will screen the submission to determine whether it meets the criteria outlined in this policy.

2. The Senior Director will obtain initial feedback from the investigator when there are questions or additional information is required.
    a. 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.
        i. If necessary, the IRB Chair may suspend the protocol in accordance with IRB policy: Suspensions, Terminations, Administrative Closures, and Investigator-Initiated Voluntary Suspension or Termination Policy/ Procedure.
3. IRB Chair Review: All submitted reportable events will be reviewed by the IRB Chair or Vice Chair who will determine if the event can be accepted or referred for review by the Convened Committee:
    a. The IRB Chair will review the event and ask for any associated documentation and/ or information they feel necessary to understand and review the event.
    b. If the event suggests noncompliance, the procedures in Noncompliance: Investigations and Determinations policy are followed.
4. UPs Reviewed by the Convened IRB:
    a. Each event will be assigned a primary reviewer.
    b. At the IRB meeting the reviewer will report on the event to the full committee and determine whether any further action as listed below is required.
    c. All IRB members will receive a copy of the event form and have access to the entire protocol, approved consent and history through the CHeRP system.
    d. The IRB will make a final determination as to whether the event meets the definition of Unanticipated Problem that Involves Risks to Subjects or Others.
    e. If the IRB determines that the event is an unanticipated problem involving risks to participants or others, the event will be reported in accordance with BCH IRB policy: Internal and External Reporting.
    f. If the event occurred at sites that are not under the oversight of the BCH IRB, the BCH IRB will not make an Unanticipated Problem determination for the event. The IRB may still take other actions, as noted below.
    g. The investigator will receive written notification of the IRB's determination and action.

Corrective or Preventative Action

In reviewing and addressing reportable event, the IRB Chair or the Convened IRB may take the following action:

1. Accept the report and approve the proposed corrective action, if any, with no further action required.
2. Require additional information from the investigators and/or others (e.g., pharmacy, legal,

privacy, or departmental chairpersons).

3. Require modifications in the proposed corrective action plan, protocol and/or consent form and any other aspect of the conduct of the research including recruitment, monitoring and safety assurance, and frequency of continuing review.
4. Require that participants currently on protocol be notified of the event.
5. Require that participants whose participation has ended be notified of the event.
6. Require that participants currently on protocol be re-consented.
7. Request a For Cause Audit or further investigation by subcommittee or individual.
8. Determine the protcol should be terminated (Convened Committee only) or suspended (Convened Committee or IRB Chair).
9. Require notification of investigators at other sites.
10. Require third party observation of the consent process.
11. Refer concerns or findings to other parts of the organization that administer other policies, laws, and regulations.
12. Any other action necessary to resolve the incident and address the safety and welfare of past, 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), Coordinating Center, Data Safety Monitoring Board (DSMB) charter, and/or regulatory authorities (Department of Health & Human Services (HHS) or U.S. Food & Drug Administration (FDA).

References/Citations

Department of Health and Human Services, Office of Human Research Protections (OHRP): ***Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 15, 2007.***

U.S. Food & Drug Administration (FDA): ***Adverse Even Reporting to IRBs – Improving Human Subject Protections – Guidance for Clinical Investigators, Sponsors, and IRBs, January 2009.***

Related Content

- Department of Health and Human Services Regulations - 45 CFR 46.108(a)4)(i)
- U.S. Food & Drug Administration CFR – Code of Federal Regulations Title 21 CFR 56.108(b)(1)
- IRB Policies
    - Internal and External Reporting

    - Noncompliance: Investigations and Determinations
    - Suspensions and Terminations
- IRB Form: Reportable Event

Approval Signatures

Step Description	Approver	Date
Co-chair Approval	David Davis	3/1/2025
Site Administrator: Education/ Training Requirement	Dwight Mayfield	2/25/2025
Steering Committee	Dwight Mayfield	2/25/2025
Required Departmental Review/Approval	August Cervini	2/2/2025
Committee Chair(s)	Susan Kornetsky: Manager	2/1/2025
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Applicability

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