The Christ Hospital IRB
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IRB REFERENCE MANUAL
SECTION 08
REPORTING UNANTICIPATED PROBLEMS INVOLVING RISKS TO HUMAN SUBJECTS/ADVERSE EVENTS

8.0 REPORTING UNANTICIPATED PROBLEMS INVOLVING RISKS TO HUMAN SUBJECTS/ADVERSE EVENTS

Federal regulations at 45 CFR 46.103(b)(5) and 21 CFR 56.108(b) require IRBs to have written procedures for ensuring prompt reporting to the IRB of any unanticipated problems involving risks to subjects or others. Consistent with these regulations and IRB policies, investigators are required to report unanticipated problems involving risks to human subjects or others following the procedures outlined below. Reportable problems include, but are not limited to:

a. adverse events that are related to study participation and unanticipated;
b. any accidental or unintentional deviation from the IRB-approved protocol that involved risks or has the potential to recur;
c. any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a given research subject;
d. any publication in the literature, safety monitoring report, interim result or other finding that indicates an unexpected increase in the risk to benefit ratio of the research;
e. any complaint of a subject that indicates an unanticipated risk or which cannot be resolved by the research staff; or
f. any other untoward event that affects the welfare or the privacy, confidentiality or other rights of research subjects or members of their family; or that presents a risk to investigators and research staff involved in the conduct of the research;
g. any enrollment which is greater than what was approved by the IRB.
h. Information indicating a change in risks or benefits
i. Breach in confidentiality (laptop stolen)
j. Change in FDA labeling
k. Changes for an apparent immediate hazard
l. Incarceration
m. Event that requires prompt reporting to the sponsor
n. Unresolved complaint
o. Protocol violation

8.1 Definitions

Adverse Event: Any untoward medical occurrence that may present itself during administration or application of a research intervention and which may or may not have a causal relationship with the research intervention.

Continuing non-compliance: Repeated noncompliance of a quantity or type that suggests a failure to understand and consistently comply with federal regulations and TCH IRB policies governing human subject protections and that, in the judgment of TCH IRB, seriously compromises human research protection or the integrity of The Christ Hospital's human research protection program.

Internal adverse event: An adverse event that occurs at The Christ Hospital, or other site that falls directly under the authority of The Christ Hospital IRB.

Related to the research intervention: A reasonable possibility that the adverse event may have been caused by the research intervention (i.e., a causal relationship between the adverse event and research intervention cannot be ruled out by the investigator).

Research intervention: An experimental intervention or procedure performed specifically for the purpose of the research study.

Serious adverse event: An adverse event that is fatal or life-threatening, requires or prolongs hospitalization, produces a disability, or results in a congenital anomaly/birth defect, or jeopardized the subject and required medical attention.

Any other adverse event that, 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.

Unanticipated - problems involving risks to participants or others is defined as:

(1) The information is unexpected in terms of nature, severity, or frequency, given: a) the research procedures described in the protocol and informed consent document; and b) the characteristics of the subject population being studied; and

(2) The information indicates that participants or others are at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.2 Reporting of Other Unanticipated Problems Involving Risks to Human Subjects or Others to the IRB

Outlined below are the requirements for reporting unanticipated problems (UAPs) involving risks to human subjects or others to the IRB.

8.3.1 General Reporting Requirements

TCH IRB (based on OHRP definition) considers unanticipated problems, in general, to include any incident, experience or outcome that meets ALL of the following criteria:

(1) 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;

(2) related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been related to the procedures involved in the research); and

(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.

EXAMPLES OF UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECT OR OTHERS

The following problems/events represent examples of unanticipated problems involving risks to subjects or others. This list is not exhaustive.

- Information that indicates a change to the risks of potential benefits of the research, in terms of severity or frequency. For example:
    - An interim analysis indicates that participants have a lower rate of response to treatment than was initially expected
    - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected, and
    - A paper is published from another study that shows that an arm of the research study is of no therapeutic value.
- Any adverse event that represents a serious unexpected problem that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome)

- Adverse event that would cause the sponsor to modify the investigator's brochure, protocol, or informed consent to assure the protection of human subjects
- A change in FDA labeling or FDA withdrawal from marketing for safety concerns of a drug, device, or biologic used in a research protocol, and
- Change to the protocol taken without prior IRB approval.

Other Events that Require Prompt Reporting

- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team (Additional information in *SOP 3.08 Complaints and Inquiries for Research Participants, Investigators, Research Staff, and the Community*)
- Violation, meaning an accidental or unintentional change to the IRB approved protocol, that placed one or more participants at increased risk or has the potential to occur again (Additional information in *SOP 3.09 Protocol Violation, Deviation, and Non-Compliance Reporting*)
- Incarceration of a participant when the research was not previously approved under Subpart C, and the investigator believes it is in the best interest of the participant to remain in the study
- Internal adverse events that are serious, unexpected, and related
- Adverse device effects that are unanticipated
- Significant protocol deviations (or other accidental or unintentional changes to the protocol or procedures), involving safety or integrity risks or with the potential to reoccur (Additional information in *SOP 3.09 Protocol Violation, Deviation, and Non-Compliance Reporting*)
- Events requiring prompt reporting according to the protocol sponsor
- Unapproved changes made to the research to eliminate an apparent immediate hazard to a research participant
- Data and Safety Monitoring Board (DSMB) reports, interim analyses, or other oversight committee/monitoring reports/recommendations altering the risks/benefits
- New information indicating an unexpected change in risks or potential benefits (e.g., literature/scientific reports or other published findings)
- Investigator's Brochure (IB) updates or revisions to safety information, and
- Other problems or findings (e.g., breach of confidentiality, loss of study data or forms, etc.), that an Investigator or research staff member believes could influence the safe conduct of the research.

8.3.2 Submission Format for Reporting Other Unanticipated Problems Involving Risks to Human Subjects or Others

(Also see SOP 2.05 Reporting Unanticipated Problems)

Investigators shall submit all unanticipated problems involving risks to human subjects or others (other than adverse events) that occur during the conduct of a TCH IRB-approved research study utilizing the form entitled "Reportable Event Form". Reports that might represent an "unanticipated problem involving risks to human subjects or others" or might represent "serious noncompliance" or "continuing non-compliance" will be referred by the IRB Chair or designee to a convened IRB committee of inquiry.

8.3.3 Reporting (i.e., to the IRB) of Other Unanticipated Problems Involving Risks to Human Subjects or Others at the Time of Research Protocol Renewal

To fulfill the requirements for reporting unanticipated problems involving risks to human subjects or others, investigators may provide a detailed summary of the other unanticipated problems involving risks to subjects or others which includes information about the nature and severity of each event, the date of the event, the site at which the event occurred, and how the problem was resolved (if applicable).

8.3 Reporting of Adverse Events Occurring During the Conduct of an IRB-approved Research Study

Serious adverse events that are both unanticipated and related to study participation are considered a Reportable Event that requires prompt reporting to the IRB. It is the investigator's responsibility to report the event utilizing the IRB Reportable Event form within 10 business days with the exception of death of a human subject. In the case of a fatal Reportable Event of a TCH participant, the IRB must be notified within 24 hours of the research site's awareness of the event. If the Reportable Event poses an immediate threat to the subject or others, report to the IRB within (1) business day by telephone or email with a follow-up in writing. Serious adverse events that do not meet the criteria for an unanticipated problem involving risks to subjects or others do not require reporting to the IRB. However, The IRB Office will accept other reports when the investigator is unsure whether the event should be reported, and the IRB Chairman will review such reports to determine whether the event meets the threshold for an unanticipated event involving risks to subjects and others.