The Christ Hospital IRB **Number:** 2.05
Submitted By: Erica Jones **Effective Date:** 03/27/09
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STANDARD OPERATING PROCEDURE

Reporting Unanticipated Problems Involving Risks to Subjects or Others

DESCRIPTION

It is the policy of The Christ Hospital (TCH) to comply with all applicable local, state, and federal regulations in the conduct of research studies. The Principal Investigator will promptly report Unanticipated Problems Involving Risks to Subjects or Others (UAPs) to the Institutional Review Board in order for the UAP(s) to be reviewed, investigated, and for any necessary action to be taken to protect subjects and others. Unanticipated Problems Involving Risks to Subjects or Others (UAPs) include adverse events (medical occurrences) which meet the definition of a UAP involving risk to subjects or others, protocol deviations, noncompliance, and other unanticipated problems that place subjects at risk of harm.

RESPONSIBILITIES

- **Principal Investigator**
  The Principal Investigator (PI) bears ultimate responsibility for the conduct of a research project. The PI must comply with the requirements of The Christ Hospital including TCH's Federalwide Assurance and the determinations of the IRB as outlined in policy, guidelines, meeting minutes and other correspondence.

- **Institutional Review Board**
  The review and evaluation of unanticipated problems are the responsibility of the IRB chairman and the IRB at a convened meeting. The UAP and its resolution may be reported to the institutional official and regulatory and funding agencies, as appropriate.

EXPANDED DESCRIPTION OF UAPS

Unanticipated Problems Involving Risk to Subjects or Others
Any problems which were not contemplated when the research was approved and which present risk of serious harm to subjects or to others including the research team, the hospital community, or the broader community. UAPs are always related to an approved study, either ongoing or closed.

An unanticipated problem is any incident, experience, or outcome that meets all the following three criteria:

1. The incident, experience, or outcome is related or possibly related to participation in the research (if, in the opinion of the PI, it was more likely related to the research than not related to the research), and

2. Unexpected in terms of nature, severity, or frequency given (a) the known foreseeable risks associated with the research procedures described in the approved protocol, consent form, or other study-related documents (e.g., Investigator Brochure, product labeling, package insert), and (b) the characteristics of the subject population being studies (e.g., expected natural progression of any underlying disease, disorder, or condition, of the subject(s) experiencing the adverse event; the subject(s) predisposing risks factor profile for the adverse event), and

3. Suggests that the research places the 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 Subjects or Others

- 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 initially expected
    - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected, and
    - A paper published from another study showing 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 Requiring 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, which 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.

The IRB 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.

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.

Unanticipated Problems That Occur External to TCH IRB Oversight

An Investigator participating in a multicenter study may rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor. In addition, if the investigator knows that the sponsor has reported the unanticipated problem directly to the IRB, because the investigator, sponsor, and IRB made an explicit agreement for the sponsor to report directly to the IRB, and because the investigator was copied on the report from the sponsor to the IRB, the FDA will not expect the investigator to provide the IRB with a duplicate copy of the report received from the sponsor. Ref. Guidance for Clinical Investigators, Sponsors and IRBs Adverse Event Reporting to IRBs-Improving Human Subject Protection, US, DHHS, FDA, January 2009

If the sponsor does not submit external adverse events that are determined to be unanticipated problems to the IRB on behalf of the investigative site, the investigator is required to submit the adverse events within 10 days of the date the investigator is notified of the event(s).

Other Subject Safety Reports Accepted by The Christ Hospital IRB

- **Non-Site-Specific Adverse Event Reports**
  Copies of non-site-specific adverse event reports (ie. IND safety reports and SUSAR reports), may be submitted by investigators and sponsors on behalf of the investigators if in accord with federal regulations, such as:
  - The event is both serious and unexpected
  - The report identifies all previous safety reports concerning similar adverse experiences
  - The report analyzes the significance of the current adverse experience in light of the previous reports, **and**
  - The report outlines a corrective action plan.

- **Sponsor Safety Reports**
  A copy of the sponsor's Safety Report (i.e., Safety Report and FDA MedWatch Report) is to be forwarded to the IRB within 30 days of receipt by the investigator

Note: Only sponsor-generated safety reports that meet the adverse event reporting of the IRB should be submitted to the IRB. Sponsors requesting different IRB reporting criteria should be referred to TCH IRB Office). Such reports are summarized for review by the full board at its next regularly scheduled meeting.

UAP DELEGATION OF RESPONSIBILITY

- **Principal Investigator**
  The PI is responsible and accountable for:
  - Assuring that the procedures for the clinical management of adverse events are carried out
  - Making the final decision regarding (a) attribution of the adverse event to study treatment and (b) clinical management of the participant
  - Assuring that the AE/SAE's are reported to the sponsor, the IRB, the Data Safety Monitoring Board (if applicable), and to the FDA if the study is investigator initiated
  - Assuring that the IND Safety Report information is reported to the sub-investigators on the trial

  The PI may delegate responsibilities to another qualified researcher involved in the study but may not delegate accountability.

- **Clinical Research Coordinator/Nurse**
  The clinical research coordinator/clinical research nurse is responsible for:
  - Screening for adverse events on an ongoing basis using patient-reported history, physical examination, laboratory data, chart review and other available data for each patient enrolled in a clinical trial.
  - Informing the PI about the procedures mandated in the protocol for the clinical management of adverse events. He/she should also attempt to judge the possible cause or relationship of the AE to the investigational product and document this relationship.

- **Research Personnel in Contact with Subjects**
  Research personnel in contact with subjects must be aware of their responsibility to note and report all adverse events directly observed or reported by the study subject to appropriate study personnel.

UAP IRB SUBMISSION PROCESS

- **Principal Investigators** (PIs) will promptly report all unanticipated problems involving risks to subjects or others, occurring to human subjects in studies conducted at the institution's facilities or under TCH IRB oversight, within 10 business days with the exception of death of a human subject. In the case of a fatal UAP event of a TCH participant, the IRB must be notified within 24 hours of the research site's awareness of the event. If the UAP 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. The investigator will report the UAP in Mentor IRB utilizing the Reportable Event tab. The PI must also inform, in writing, the appropriate research team members, pharmacist, support staff, administrative officials, DSMB/DSM/Medical Monitor, funding or sponsoring agencies, if applicable, of the unanticipated problem.

- **IRB Office Staff**
    - Reviews the Reportable Event submission in Mentor IRB and assigns it to the IRB Chair or designee for review
    - Assigns to the Full Board Panel for review and discussion as directed by the IRB Chair
    - Documents the outcome of IRB discussion from the convened meeting in the meeting minutes
    - Sends correspondence to PI and research coordinator outlining IRBs recommended action

- **IRB Chair**
    - Reviews the Reportable Event submission utilizing the Reportable Event questionnaire
    - Assesses whether the UAP reported represents a true unanticipated problem involving risk to subjects or others; if so, the UAP is referred to the next convened IRB full board meeting for review
    - Investigates and summarizes the UAP
    - Presents findings to the full board and gives a recommendation

IRB REVIEW PROCEDURE

All members of the convened committee will have access to the electronic protocol files including the:

- Reportable Event submission reporting the unanticipated problem involving the UAP(s)
- Protocol, if applicable
- Informed Consent, if applicable

Each UAP will be summarized by the IRB chair, giving his/her their recommendation. After the presentation from the IRB chair, all members of the convened committee will be given the opportunity to comment on the recommendation.

IRB Actions

The convened IRB takes whatever actions deemed necessary to address the unanticipated problem(s). Examples of actions that might be taken include, but are not limited to:

- Investigating the Event
    - Requesting additional records or information about the event and its outcome
    - Interviewing the involved investigators, research staff, and/or research subjects
    - Interviewing other individuals who may have knowledge of the event, and/or
    - Requesting an independent audit of the event/protocol or of other related protocols

- Implementing Administrative Actions
    - Requesting the IRB Chair (designee) to meet with the involved investigator and/or research staff, and the appropriate department chair to discuss the event/problem
    - Requesting a corrective plan of action and/or written standard operating procedures from the involved investigator and/or his/her department chair

- Requiring members of the research team to participate in pertinent training and education programs
- Notifying other organizational entities (e.g., legal counsel, institutional risk management, the Institutional Official) as warranted, and/or
- Suspending the PI's privilege to serve as a PI or requiring a replacement of the PI for the protocol(s) in question.

- Requiring Protocol Modification(s)
  - Instructing the investigator to develop an addendum consent form to provide information concerning the event to subjects currently enrolled in the study
  - Requiring the investigator to perform additional follow-up or monitoring of the enrolled subjects, and/or
    Revising the timeframe for continuing IRB review

- Terminating or Suspending IRB Approval
  In instances where the study some or all research study activities are terminated or suspended, the IRB will consider what additional actions the principal investigator or institution should take to protect the rights and welfare of current human subjects. These additional actions may include but are not limited to:
  - Transferring the human subjects to another research study; i.e., based on equivalent inclusion/exclusion criteria
  - Making arrangements for clinical care outside the research
  - Allowing continuation of some research activities under the supervision of an independent monitor
  - Requiring or permitting follow-up of the human subjects for safety reasons
  - Requiring adverse events or outcomes to be reported to the IRB and the sponsor
  - Notifying current human subjects of the IRB's decision to terminate or suspend the research study, and/or
  - Notifying former human subjects of the IRB's decision to terminate or suspend the research study.

- Requiring Other Action(s) as Determined Appropriate by the IRB Committee

- Requiring No Further Action

IRB Vote and Documentation in IRB Meeting Minutes
The IRB shall determine the recommended actions, call for a vote, and document the outcome in the meeting minutes. The IRB vote determines whether the event represents a UAP, a serious non-compliance, and/or continuing non-compliance. The vote shall be recorded in the meeting minutes. If the IRB votes to suspend or terminate the research study, the reasons for the suspension or termination will be documented.

REPORTING REQUIREMENTS

Within 30 days of the initial IRB determination, the IRB chairman shall direct the IRB office to report Unanticipated Problems Involving Risks to Subjects or Others and any subsequent follow-up reports to:

- Institutional Official and Appropriate Hospital Department Head
- Principal Investigator

- OHRP, when the research is covered by DHHS regulations
- Other federal agencies when the research is overseen by those agencies and the agencies require reporting separate from that to OHRP
- FDA, when the research is FDA-regulated
    - Drug Products: CDER-OSI-GCPReferrals@fda.hhs.gov
    - Biologic Products: CBERBIMONotification@fda.hhs.gov
    - Medical Devices: Email: bimo@cdrh.fda.gov

REFERENCES:

- 45 CFR 46 Protection of Human Subjects
- 45 CFR 46.108(a)(4)(i)
- 21 CFR 56 Institutional Review Boards
- 21 CFR 56.108(b)(1)
- TCH IRB Reference Manual, Section 8.0 Reporting Unanticipated Problems Involving Risks to Subjects
- TCH IRB Reference Manual, Section 12.0 Allegations of Noncompliance
- TCH IRB SOP 3.08 Complaints and Inquiries for Research Participants, Investigators, Research Staff, and the Community
- TCH IRB SOP 3.09 Protocol Violation, Deviation, and Non-Compliance Reporting
- U.S. Department of Health and Human Services Office for Human Research Protections Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events: OHRP Guidance (2007)