The Christ Hospital IRB **Number:** 2.05
Submitted By: Erica Jones **Effective Date:** 03/27/09
Reviewed By: S. Roberts, MD & M. Jennings, MD **Revised/Reviewed Date:** 10/19
Approved By: Steve Roberts, MD
(II.2.F, II.2.H. III.2.D)

STANDARD OPERATING PROCEDURE

Reporting Unanticipated Problems (UAPs) Involving Risks to Subjects or Others

Description

It is the policy of The Christ Hospital 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 to the Institutional Review Board, in order to be investigated and action taken to protect subjects and others. Events involving risk to subjects or others must be reported as "Unanticipated Problems Involving Risks to Subjects or Others". This category includes adverse events (medical occurences) which meet the definition of an unanticipated problem (UAP) involving risk to subjects or others and can also include protocol deviations, noncompliance, and other unanticipated problems that place subjects at risk of harm. The IRB will review and investigate the UAP to determine whether the event involves risks to subjects or others and, if so, what further action the situation neccesitates.

Responsibility

The review and evaluation of unanticipated problems are the responsibility of the IRB Chair and the IRB at a convened meeting. In appropriate cases, the problem and its resolution may be reported to regulatory and funding agencies by the IRB Chairman and/or the Institutional Official (IO), if appropriate.

Expanded Description of UAPs:

Unanticipated problems (UAP) 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 defined as any incident, experience, or outcome that meets all of the following three criteria:

1. Related or possibly related to the research if, in the opinion of the PI, it was more likely related to the research than not related to the research.

2. Unexpected because the nature, severity, or frequency of the event is not consistent with either the known foreseeable risks associated with the research that are described in the

approved protocol, consent form, or other study-related documents (e.g., Investigator Brochure, product labeling, package insert), Or

Unexpected because the adverse event is not consistent with the expected natural progression of any underlying disease, disorder, or condition, of the subject(s) experiencing the adverse event and the subject(s) predisposing risks factor profile for the adverse event.

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.

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.

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.

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.

For 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 would not expect the investigator to provide the IRB with a duplicate copy of the report received from the sponsor (*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 them, along with the required explanantion outlined above, within 10 days of the date the investigator receives them.

Other Subject Safety Reports Accepted by TCH IRB

1. **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.

2. **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 their 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). These reports are summarized for review by the full board at its next regularly scheduled meeting.

UAP Delegation of Responsibility

1. The **Principal Investigator** (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 (and to the FDA if the study is investigator initiated), to the IRB, and to the Data Safety Monitoring Board, if applicable
   - 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.

2. **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.

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

UAP IRB Submission Process

1. **Principal Investigators** (PIs) will promptly submit 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 submit the UAP utilizing the IRB Reportable Event form. 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.

2. **IRB Office Staff**

- Stamps the Reportable Event form with a date stamp, initials it and places the report in the IRB Chair's in-box for review
- Copies reports signed by the IRB Chair and returns to the investigator as acknowledgement of receipt
- Files original report in the IRB study folder
- Documents outcome of IRB discussion from the convened meeting in the meeting minutes, and
- Sends correspondence to PI outlining IRBs recommended action.

3. **IRB Chair**
   - Reviews, signs, and dates the Reportable Event form
   - Assesses whether or not the UAP reported on the Reportable Event form represents an true unanticipated problem involving risk to subjects or others, and if so, it is referred to the next convened IRB full board meeting for review
   - Investigates and summarizes the UAP, and
   - Presents findings to the full board and gives a recommendation.

IRB Review Procedure:

All members of the convened committee will have access to the following:
- The Reportable Event form reporting the unanticipated problem involving risks to subjects or others
- The protocol, if applicable
- The consent, if applicable

Each UAP will be summarized by the IRB Chair give 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.

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

1. Investigating the Event by:
   - 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.

2. Implementing Administrative Actions, such as:
   - 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.

3. Requiring Modifications of the Protocol, such as:
   - 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.

4. Terminating or Suspending IRB Approval of the Research Study:
   When terminating or suspending some or all research activities, the IRB will consider what additional actions the principal investigator or institution should take in order 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.

5. Requiring other action as determined to be appropriate by the IRB committee.

6. Requiring no further action.

IRB Vote and Documentation in the Meeting Minutes
The IRB will determine the recommended actions, call for a vote and document the outcome in the meeting minutes. The IRB votes as to whether the event represents an unanticipated problem involving risks to human subjects or others, serious non-compliance and/or continuing non-compliance. This vote will 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.

REFERENCES:
45 CFR 46 Protection of Human Subjects
21 CFR 56 Institutional Review Boards
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

REVISION HISTORY:

Date Revised	Reason For Change	Revised By
05/15/09	Addition of Sponsor Safety Report Reporting Requirements	Erica Jones
10/13/09	Addition of time frame for IRB Chairman to report events to appropriate officials.	Becky
11/06/14	Removal on IND before safety report	Becky
12/10/14	Addition of Persons Responsible	Becky
08/11/16	Broadened definition list	Becky
03/23/17	Corrected spelling error of "description"	Emily
03/19/18	Updated the reporting procedure	Emily
12/02/19	Updated reporting criteria and procedure	Erica