The Christ Hospital IRB **Number:** 3.09
Submitted By: Erica Jones, CIP **Effective Date:** 03/27/09
Reviewed By: Michael Jennings, MD/Steve Roberts, MD
Revised/Reviewed Date: 03/17
Approved By: Steve Roberts, MD
(III.2.C, III.2.D)

STANDARD OPERATING PROCEDURE

Protocol Deviations/Violations

POLICY:

It is the policy of The Christ Hospital IRB to be notified of any major protocol deviation/violation and minor protocol deviations (as listed below, in Reporting Process). A protocol deviation occurs when there is an inconsistency in a research study between the protocol that has been reviewed and approved by the Institutional Review Board and the actual activities being done. Protocol deviations may be minor or major as defined below: (For more information, see Deviation/Violation Determination Chart at end of this document.)

I. Minor Protocol Deviation: Any difference or departure in the conduct of a study from the criteria and/or procedures prescribed in TCH IRB approved protocol which does not affect the participant's rights, safety, welfare, and/or the integrity of the study and resultant data. Deviations may results from action or inaction of the participant, investigator or staff.

- Deviation has no substantive effect on the risks to research participants;
- Deviation has no substantive effect on the value of the data collected (i.e., the deviation does not confound the scientific analysis of the results);
- Deviation did not result from willful or knowing misconduct on the part of the investigator(s) and;
- The deviation did not result in or require any substantive action to be taken or result in any change to the subject's condition or status (i.e., did not affect the subject's participation in any way, did not result in a change to the subject's emotional or clinical condition, did not cause an adverse experience or require a change to the clinical care of the subject, etc.)

II. Major Protocol Deviation (Violation): Any difference or departure from the criteria and/or procedures prescribed in TCH IRB approved protocol that affects the participant's rights, safety, welfare, increases the risk/benefit ratio, or compromises the integrity of the study's data.

- Deviation resulted in or required a substantive action to be taken or resulted in a change to the subject's condition or status;
- Deviation has harmed or posed a significant risk of substantive harm to research participants;
- Deviation has damaged the scientific integrity of the data collected for the study;
- Deviation is evidence of willful or knowing misconduct on the part of the investigator(s);
- Deviation involves serious or continuing noncompliance with federal, state or local research regulations;

- There have been repeated minor protocol deviations from the same investigator/research staff;
- There has been a failure to follow action ordered to correct minor protocol deviations.

REFERENCE:
21 CFR 56.108(b)
45 CFR 46.103(b)(5)
38 CFR 16.103(b)(5)(1)(i)
21 CFR 312.32
21 CFR 812.60-66: 812.150
Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs Improving Human Subject Protection, DHHS, FDA, January 2009

PROCEDURE:

I. Reporting Process

Investigators are required to obtain prior approval from the sponsor/clinical study manager before initiating major deviations from the investigational plan, except in emergency situations when it is necessary to protect life and/or well being of a subject. Any such approval must be documented in writing and be maintained in the clinical study management and investigator files. Prior approval is not expected in situations where unforeseen events are beyond the investigator's control (i.e. subjects not available for a follow up visit, specimen loss by laboratory, etc.); however, such events are still deviations and must be reported to the TCH IRB in the form of a memo or letter.

Deviations must be reported to clinical study management and the IRB in all circumstances, whether medically justifiable, previously approved or carried out to protect the subject in an emergency, in compliance with provisions in the protocol/investigator's brochure. For guidance on determining a minor deviation vs. a major deviation/violation, a Determination Chart is attached for reference.

1. Minor Deviations: Minor protocol deviations that do not alter the risk/benefit analysis do not require IRB reporting unless they represent a trend that may affect project safety or integrity, or if specifically required by the sponsor's protocol/investigator's brochure. However, the IRB Chair or designee will review any minor protocol deviation that comes to the attention of TCH IRB and may require that corrective action be taken. Minor deviations may be reported in the form of a memo or letter to the IRB Chair, or may be reported at the time of continuing review.

2. Major Deviations (Violations): All major protocol deviations are to be reported as violations to The Christ Hospital IRB. A major protocol deviation is interpreted by The Christ Hospital IRB as any deviation from the research study plan that increases the risk or decreases the benefit, affects the integrity of the resultant data or affects the rights, safety or welfare of the study subjects. All major deviations/violations are to be reported to The Christ Hospital IRB within

10 working days of recognition or identification and must be reported on the Major Protocol Deviation/Violation Report Form.

II. Review Process

All minor and major deviations are reviewed by the IRB staff and the IRB Chair. Minor deviations are noted by the Chair and filed in the study folder. The IRB file maybe opened for review by the PI or any approved outside agency for auditing purposes. If there is a trend in minor deviations, the Chair will report this to the Board. In the case of a major deviation/violation, the following will occur:

1. Enrollment for the study in question is put on hold.

2. The IRB Chair may call a Board of Inquiry to discuss the violation. This Board of Inquiry should include: IRB Chair, IRB Associate Chair, Hospital Institutional Official, 1 additional scientific IRB board member.

3. The Board of Inquiry meets with the investigator and brings all documentation and discusses facts of the case being evaluated. The Board of Inquiry reports findings to the full IRB at the next convened meeting.

4. To make the determination of serious or continuing noncompliance, an audit of study records may be needed. The PI will be required to produce, at a minimum, (1) all signed consent forms and (2) all data related to the study project. The results of the review of study records and discussions with the PI will determine whether the situation is of a non-serious and non-continuing nature.

    a. *Non-serious and non-continuing problem:* If the problem appears to be isolated or is a misunderstanding of a non-serious and non-continuing nature, the incident will remain internal. A letter from the IRB office to the PI describing a summary of the audit will be written. A response from the PI describing corrective actions is also required. This will be considered the final step if the incident is considered non-serious and continuing noncompliance was not found. The hold on patient enrollment will be lifted.

    b. *Serious or continuing:* If the audit indicates noncompliance that is serious or continuing, the Office for Human Research Protections (OHRP) will be notified within 48 hours regardless of the funding source. If applicable, the FDA will be notified. This will be via a phone call to HRP (or FDA) to inform the office of the incident of serious, continuing noncompliance. A letter will follow the phone call within 48 hours. The letter should: a) briefly describe the incident; b) outline the preliminary steps taken, and c) indicate the time frame for full audit and full report to follow, including corrective actions for this specific incident as well as for the research program in general at The Christ Hospital to ensure that similar incidents will not occur again.

- An audit (See "III. Audit Process" below) will be performed of all research conducted by the PI.
- Communication with PI, OHRP, and FDA will occur.
- Holding of patient enrollment will be lifted once the audit process and communication process are completed to the satisfaction of the IRB.

When Suspension Is Not Necessary

If the situation does not merit suspension of the research study, the report is reviewed and signed by the IRB chair and filed in the study folder.

When Suspension Is Necessary

If the report does merit suspension of the research study, further steps are required:

- Notice of suspension effective immediately will be sent to the PI, department chair and IRB Institutional Official. The notification includes the requirement to halt further participant enrollment.

- Within 2 days, a meeting should be called and attended by any combination of the following individuals: IRB chair, PI, PI's department chair. The attendees should discuss the nature of the situation and determine whether a designation of serious or continuing noncompliance is warranted. At this meeting, it should also be determined whether any other studies being conducted by the PI should be suspended.

III. Audit Process

The IRB Chair will audit the researcher and the study, and will report findings to the IRB. An audit report shall include:

- Review protocols in question.
- Review FDA audit report of the investigator/study, if appropriate.
- Review any relevant documentation, including consent documents, case report forms, subjects' investigational and/or medical files, as they relate to the investigator's execution of his or her study involving human subjects.
- Interview subject(s) involved in the study, if appropriate.
- Interview appropriate study or hospital personnel, if necessary.
- Prepare either a written or oral report of the subcommittee's findings that is presented to the full IRB at its next convened meeting.
- Recommend actions to the full IRB, if appropriate, based on its findings.

The IRB then makes the final determination of the appropriate action(s) to be taken in the case based on its own knowledge of the facts and the additional facts gathered by the subcommittee during the course of its audit and investigation.

IV. Reporting Audit Results

After the final determination is made by the IRB, the investigator is informed in writing. If the determination includes suspension of an investigator because the research was not conducted in accordance with the IRBs requirements or has been associated with unexpected serious harm to subjects, the IRB, under federal regulations[1(Sec.113)] has the responsibility to report that suspension promptly to the OHRP. If the study in question involves an investigational drug, biologic, or device, regulations[2(Sec.113)] also require a report to the FDA. This report must include reasons for the IRBs action, and this action by the IRB must also to be reported to the appropriate institutional officials (The Christ Hospital Institutional Official for Research).

V. Eligibility Exceptions

The IRB requires pre-approval of subjects who do not meet the eligibility criteria. If a researcher wishes to enroll an individual who does not meet the eligibility criteria, an eligibility exception request is submitted to the IRB Chair. This request must include protocol title, investigator's name, reason for eligibility deviation request, and if applicable, whether the eligibility exception has been approved by the sponsor. The only exception to this is when the eligibility exception is necessary to eliminate apparent immediate hazards to the subject.

If an eligibility deviation has occurred without prior IRB approval, the deviation must be reported to the IRB as noncompliance. The IRB cannot retrospectively approve the eligibility exception request and, therefore, must review the exception as a protocol deviation, following the same steps outlined above.

REVISION HISTORY:

Date Revised	Reason For Change	Revised By
4/01/11	Update study file	Becky
06/11/15	Revised Reference list	Becky
03/16/17	Removed "Informed Consent not signed by physician"	Emily
03/16/17	Removed "Informed Consent not initialed by physician"	Emily

PROBLEM	Major/ Violation	Minor Deviation	Prog. Note	Comments
INFORMED CONSENT:				
Executable informed consent form mailed to potential subject			X	
Executable informed consent form taken by potential subject			X	
Incorrect informed consent, unapproved version	X			
Incorrect informed consent, incorrect version	X			
Incorrect informed consent, incorrect study	X			
Consent not obtained for amendment	X			
Informed consent not obtained	X			
Informed consent not signed by subject	X			
Informed consent not initialed by subject		X		If required by IRB
Informed consent not dated by subject	X			
Informed consent signed, but not properly dated by subject	X			
Informed consent not properly signed or dated by consenter	X			
Informed consent without required witness	X			
Informed consent without required authorized representative	X			
Informed consent improperly obtained	X			
Informed consent obtained late	X			
Informed consent modified by subject	X			
ENROLLMENT:				
Underage subject improperly enrolled	X			
Vulnerable subject improperly enrolled	X			
Subject enrolled without meeting medication condition eligibility criteria	X			
Subject enrolled without meeting test condition eligibility	X			
Subject enrolled without meeting conflicting study eligibility criteria	X			Not enough elapsed time between studies
Subject enrolled without meeting eligibility criteria, other	X			
Subject enrolled with approved			X	

PROBLEM	Major/ Violation	Minor Deviation	Prog. Note	Comments
exception				
TESTS:				
Test incorrect	X			
Test not attempted	X	X		Violation if safety issue
Test unsuccessful		X		
Extra tests performed	X			
Test prior to window		X		Violation if safety issue
Test after window		X		Violation if safety issue
Test data lost		X		
Test performed by someone not on 1572 (if required)	X			
ASSESSMENTS:				
Assessment incorrect	X			
Assessment not attempted	X	X		Violation if safety issue
Assessment unsuccessful		X		
Extra assessment performed	X			
Assessment prior to window		X		Violation if safety issue
Assessment after window		X		Violation if safety issue
Assessment data lost		X		
Assessment performed by someone not on 1572 (if required)	X			
EXAMS:				
Exam incorrect	X			
Exam not attempted	X	X		Violation if safety issue
Exam unsuccessful		X		
Extra exam performed	X			
Exam prior to window		X		Violation if safety issue
Exam after window		X		Violation if safety issue
Exam data lost		X		
Exam performed by someone not on 1572 (if required)	X			
PROCEDURES:				
Procedure incorrect	X			
Procedure not attempted	X			
Procedure unsuccessful		X	X	Not a deviation if safety issue or subject objected
Procedure prior to window		X		
Procedure after window		X		
Procedure data lost	X			Same as not attempted
Procedure performed by someone not on 1572 (if required)	X			

PROBLEM	Major/ Violation	Minor Deviation	Prog. Note	Comments
SPECIMENS:				
Specimen collection unsuccessful		X		
Specimen collected with wrong type of collection kit			X	
Specimen collected with expired lab kit			X	
Specimen mishandled			X	
Specimen lost			X	
Specimen damaged in shipment			X	
DATA COLLECTION:				
Data collection incorrect	X			e.g., chart review
Data collection not attempted			X	
Data collection unsuccessful			X	
Data collection prior to window		X		
Data collection after window		X		
Data collection data lost			X	
Data incorrectly transcribed from source document to CRF			X	
VISITS & TELEPHONE CALLS:				
Study visit before window		X		
Study visit after window		X		
Study visit missed		X		
Telephone follow-up before window		X		
Telephone follow-up after window		X		
Telephone follow-up missed		X		
DOCUMENTATION:				
Documentation missing			X	Same as lost data
Documentation incomplete			X	
Documentation incorrect			X	
Documentation signed by incorrect person			X	
Documentation not signed correctly, other			X	
Documentation back-dated			X	
Documentation not dated correctly			X	
STUDY DRUG:				
Study drug administered before window		X		
Study drug administered after window		X		
Study drug not administered	X			
Study drug dosage incorrect	X			

PROBLEM	Major/ Violation	Minor Deviation	Prog. Note	Comments
Study drug administered incorrectly (other)	X			
Study drug administered based on incorrect randomized	X			
Incorrect rescue medication administered	X			
Prohibited concomitant medication taken			X	Contact sponsor
Study drug unblended improperly by study personnel	X			
Subject took dose before window			X	
Subject took dose after window			X	
Subject missed dose			X	
Subject took wrong study dose			X	
Subject took dose incorrectly (other)			X	
Study medication lost			X	
Study medication damaged			X	
Non-subject took study medication			X	
Subject unblended study medication			X	Contact sponsor
DIARIES:				
Subject made diary entry before window			X	
Subject made diary entry after window			X	
Subject did not make diary entry			X	
Subject made diary entry incorrectly			X	
IVRS:				
Subject made IVRS entry before window			X	
Subject made IVRS entry after window			X	
Subject did not IVRS diary entry			X	
Subject made IVRS entry incorrectly			X	
SUBJECT NON-COMPLIANCE:				
Subject diet incorrect			X	
Subject not fasting before test or procedure		X		
Subject using improper contraception	X			
Subject not using contraception	X			
Subject non-compliance, other	X	X	X	Need scenarios
ADVERSE EVENTS:				
SAE reported late	X			

PROBLEM	Major/ Violation	Minor Deviation	Prog. Note	Comments
SAE reported with incorrect data			X	
SAE reported with missing data			X	
SAE reported incorrectly, other			X	
SAE not corrected	X			
SAE not reported	X			
AE recorded late			X	
AE recorded incorrectly			X	
AE not recorded			X	