IRB REFERENCE MANUAL
SECTION 03
CONTINUING IRB REVIEW OF RESEARCH PROTOCOLS

3.0 CONTINUING IRB REVIEW OF RESEARCH PROTOCOLS

3.1 Modifications to the Research Protocol and Informed Consent Document(s)

It is recognized that modifications of research protocols and informed consent documents may be required as the research study proceeds. *However, any proposed modification to an IRB-approved research protocol or informed consent document must be approved by the IRB prior to implementation.* The only exception to this requirement is a change in procedure that may be necessary to eliminate an apparent immediate hazard to a given research subject. It is not acceptable to modify extemporaneously (i.e., without prior IRB approval) an IRB-approved research protocol or consent form to permit the enrollment of a given individual who does not meet current eligibility criteria or to address any other specific issues related to the needs or desires of, a given individual or patient who may want to participate in the study. Requests for protocol exceptions should be made in writing to the IRB Chair at the same time the request for exception is submitted to the sponsor.

3.1.1 Categories of Modification Review – Submission Requirements

IRB approval of modifications to research protocols and informed consent documents can be requested at any time. The approval of a modification request by the IRB will not, in general, alter the original IRB-approval date and expiration of IRB-approval dates assigned to the protocol. However, if the requested modification alters substantially the risk-to-benefit ratio of study participation, the TCH IRB may alter the expiration date assigned to the research protocol. The category of review (i.e., expedited or full board) of proposed modifications to an IRB-approved research protocol or consent document is dependent upon whether the proposed changes are considered minor or major. The IRB Chair or his/her designee shall have final responsibility for this designation.

1) Minor modifications: The IRB Chair or his/her designee can expedite the review and approval of minor modifications to an IRB-approved research protocol or informed consent document. A minor modification is defined as a change that

would not materially affect an assessment of the risks and benefits of the study or does not substantially change the specific aims or design of the study. Examples of minor modifications may include:

- the addition of research activities listed under sections 2.2 Exempt Review or 2.3 Expedited Review.
- An increase or decrease in proposed human research subject enrollment supported by a statistical justification.
- Narrowing the range of inclusion criteria
- Broadening the range of exclusion criteria
- Alterations in the dosage form (e.g., tablet to capsule or oral liquid) of an administered drug, provided the dose and route of administration remain constant
- Decreasing the number or volume of biological sample collections, provided that such a change does not affect the collection of information related to safety evaluations
- An increase in the length of confinement or number of study visits for the purpose of increased safety monitoring
- A decrease in the length of confinement or number of study visits, provided that such a decrease does not affect the collection of information related to safety evaluations
- Alterations in human research subject payment or liberalization of the payment schedule with proper justification
- Changes to improve the clarity of statements or to correct typographical errors, provided that such a change does not alter the content or intent of the statement
- The addition or deletion of qualified investigators
- The addition or deletion of study sites
- Minor changes specifically requested by the IRB or Radiation Safety Committee

For minor modifications to a research protocol or informed consent document, submit the following:

- The current research protocol with any modifications highlighted
- The current informed consent document with any modifications highlighted
- If applicable, a copy of the sponsor's research protocol amendment addressing the respective modification(s)

NOTE: Modifications to the informed consent document must take into account both prospective research subjects and, if applicable, research subjects already enrolled in the study. The latter may be addressed using an addendum to the initial informed consent document, or less preferably, by re-consenting the subject using the modified informed consent document.

2) Major Modifications: Major modifications to an IRB-approved research protocol or informed consent document must undergo full board review and approval. A major modification is defined as any change which materially affects an assessment of the risks and benefits of the study or substantially changes the specific aims or design of the study. Examples of major modifications may include:

- Broadening the range of inclusion criteria
- Narrowing the range of exclusion criteria
- Alterations in the dosage or route of administration of an administered drug
- Extending substantially the duration of exposure to the test material or intervention
- The deletion of laboratory tests, monitoring procedures, or study visits directed at the collection of information for safety evaluations
- The addition of serious unexpected adverse events or other significant risks
- Changes which, in the opinion of the IRB Chair or his/her designee, do not meet the criteria or intent of a minor modification.

For major modifications to a research protocol or informed consent document submit the following:

- The current research protocol with any modifications tracked
- The current informed consent document with any modifications tracked
- If applicable, a copy of the sponsor's research protocol amendment addressing the respective modification(s)

Note: Modifications to the informed consent document must take into account both prospective research subjects and, if applicable, research subjects already enrolled in the study. The latter may be addressed using an addendum to the initial informed consent document, or less preferably by re-consenting the subject using the modified informed consent document.

3.1.2 Modification Turnaround Time

Minor modifications which qualify for expedited review will be reviewed by the IRB Chair or his/her designee in the order in which they were received in the IRB office. Turnaround time varies depending upon the number of submissions received. Major modifications require full board review and investigators will

receive correspondence from the IRB within approximately 5 working days of the scheduled meeting.

3.2 Research Protocol Renewals

The Christ Hospital IRB (TCH IRB) is responsible for continuing review on ongoing research to ensure that the rights, safety and wellbeing of human subjects are protected.

3.2.1. Review Period

At the time of initial review, The Christ Hospital IRB establishes a review period for each approved study that is appropriate to the degree of risk to subjects, but not less than once per year for applicable studies. [see SOP 1.01 Continuing Review]. The IRB maintains a fixed anniversary date for the expiration of annual IRB approvals in order to keep the IRB approval period constant from year to year throughout the life of a research project. The expiration date will be noted on the letter of approval and on subsequent continuing review reports. The expiration date is the first date that the protocol is no longer approved. TCH IRB also indicates in the letter of approval both initial and on continuing review approval which study requires review more often than annually and which study requires verification from sources other than the investigator that no material changes have occurred since the previous TCH IRB review [21 CFR 56.108(a)(2)].

The Christ Hospital IRB requires that changes in approved IRB research activities be promptly reported to the IRB and that any changes in approved research, during the designated period of IRB approval, must not be initiated without IRB review and approval, except when the PI believes it necessary to eliminate apparent immediate hazard to the subject [21 CFR 56.108(b)(2) and 56.113].

The Christ Hospital IRB is authorized to suspend or terminate approval of research that is not being conducted in accordance with the TCH IRB requirements [21CFR56.108(b)(2) and 56.113].

3.2.2 Criteria for Approved Research

Federal and FDA regulations establish the criteria for TCH IRB approved research [45 CFR 46.111 and 21 CFR 56.111], as applicable. The criteria are the same for approval of continuing review and include the determination by TCH IRB that:

- Risks to subjects are minimized.
- Risks to subjects are reasonable in relationship to anticipated benefits.

- Selection of subjects is equitable.
- Informed consent process is in place and appropriately documented.
- When appropriate, the research plan includes provision for monitoring of the data collected to ensure safety and privacy of subject and confidentiality of the data.
- When appropriate, additional safeguards have been included to protect vulnerable subjects.

3.2.3 Process for Continuing Review

A. PURPOSE: The purpose of continuing review is to review the progress of the entire study and not just the change. Continuing review may not be conducted through an expedited review process unless 1) the study was eligible and was initially reviewed by an expedited review procedure, or 2) where the research is closed to enrollment of new subjects, and all subjects have completed all research related interventions and collection and analysis of private identifiable information has been completed. See SOP 1.17- Expedited Review.

B. FREQUENCY/EXTENT: The Christ Hospital IRB determines that the frequency and extent of continuing review for each study is adequate to ensure the continued protection of rights, welfare and privacy of research subjects. Factors under such consideration may include the nature of the study, and the degree of risk involved and the vulnerability of the study population. The frequency and extent of continuing review are indicated in the approval letter and subsequent letters of approval of continuing reports.

C. DETERMINING CONTINUING REVIEW DATE: Federal regulations at 45 CFR 46.108(b) and 109(e) require respectively that (1) except when an expedited review procedure is used, each IRB must review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas; and (2) an IRB must conduct continuing review of research requiring review at intervals appropriate to the degree of risk, but not less frequently than once per year. The IRB should decide the frequency of continuing review for each study protocol necessary to ensure the continued protection of the rights and welfare of research subjects. For studies that are appropriate for a one year review cycle, the IRB will maintain a fixed anniversary date for expiration throughout the duration of the research protocol.

Several scenarios for determining the date of continuing review apply for protocols reviewed by the IRB at a convened meeting. To determine the date by which continuing review must occur, focus on the date of the convened meeting at which IRB approval occurs. (These examples presume the IRB has determined that it will conduct continuing review no sooner than within 1 year).

Scenario 1: The IRB reviews and approves a protocol without any conditions at a convened meeting on June 8, 2021. Continuing review must occur within 1 year of the date of the meeting, that is, by June 1, 2022.

Scenario 2: The IRB reviews a protocol at a convened meeting on June 18, 20121 and approves the protocol contingent on specific minor conditions the IRB chair or his/her designee can verify. On June 15, 2021, the IRB chair or designee confirms that the required minor changes were made. Continuing review must occur within 1 year of the date of the convened IRB meeting at which the IRB reviewed and approved the protocol, that is, by June 1, 2022.

Scenario 3: The IRB reviews a study at a convened meeting on June 8, 2021, and has serious concerns or lacks significant information that required IRB review of the study at subsequent convened meeting on July 13, 2021. At their July 13, 2021 meeting, the IRB completes its review and approves the study. Continuing review must occur within 1 year of the date of the convened meeting at which the IRB reviewed and approved the protocol, that is, by July 1, 2022.

D. PI RESPONSIBILITY: The PI is responsible for the prompt reporting to the IRB. This includes continuing review reports by the stated date in the approval letter. TCH IRB will send a Continuing Review form and reminder letter to the PI approximately 4 weeks before the approval expiration date. The completed form must be returned to TCH IRB by the due date indicated (at least 21 days prior to the approval expiration date) to allow adequate IRB review at the next regularly scheduled meeting. This form must be submitted unless a Closure/Final Report has been submitted (see SOP 2.07 Study Closure). TCH IRB will follow up with the PI who has not submitted the Continuing Review Report by the due date with a phone call, FAX and/or an Email.

Scenario: A study has an expiration date of 10/01/2021. This study must be reviewed by the full board at the September 14 Convened IRB meeting. The deadline for submission of the report to the IRB is 21 days prior to the meeting date, August 24, 2022.

E. STUDY EXPIRATION: The continuation of research after expiration of IRB approval is a violation of federal and FDA regulations If TCH IRB has not received, reviewed and approved a research study by the study's current expiration date, i.e. TCH IRB approval has expired, research activities must cease. A Notice of Study Closure memo will be sent to the PI. No new subjects may be enrolled. If the PI is actively pursuing renewal with the TCH IRB and the IRB determines that an overriding safety concern or other ethical issue is involved, the IRB may permit the study to continue for the brief time required to complete the review process when study approval is terminated by TCH IRB. All currently participating subjects should be notified that the study has been terminated. Procedures for withdrawal of enrolled subjects should consider the rights and welfare of the subjects. If follow up of subjects for safety/welfare reasons is permitted/required by the IRB, the subjects should be notified and adverse events and outcomes should be reported to the IRB and sponsor.

F. EXPEDITED REVIEW: TCH IRB uses the expedited review procedure to review (1) some or all of the research appearing on the list and found by the reviewer to involve no more than minimal risk; (2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized, done by the Chair or Co-Chair or by an experienced person delegated by the Chair to review from TCH IRB. In this process the reviewer may exercise all the authorities of the IRB except to disapprove the research. A research activity may be disapproved and only after review in accordance with non-expedited review set forth in [21 CFR 56.108(c)]. The reviewer will present the expedited review report at the next full board meeting for consideration, discussion and acknowledgment.

G. FULL BOARD REVIEW: Each continuing review report (non-expedited) will be presented to full board for consideration, discussion and vote for approval, modification for approval or disapproval. Appropriate correspondence will be forwarded to the PI in a timely fashion with a letter for a) approval with date for next review; b) approval pending modification with date for next

review; or c) disapproval and notice of termination of the study.

3.2.4 Continuing Review Report

A Continuing Review Report must be completed in its entirety and submitted for consideration along with a copy of the most recently approved consent form.

3.3 Reporting Unanticipated Problems Involving Risks to Human Subjects

Federal and FDA 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 in Section 8.0 "Reporting Unanticipated Problems Involving Risks to Human Subjects/Adverse Events". See SOP 2.05- Reporting Unanticipated Problems (UAPs) Involving Risks to Subjects or Others for reporting requirements.

3.4 Reporting Protocol Deviations/Violations

A protocol deviation occurs when there is a change, divergence, or departure from the approved study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB, and does not affect the participant's safety, rights, or welfare and/or the completeness, accuracy and integrity of the study data. . A protocol violation is any deviation that does affect the subject's rights, safety, or welfare, and/or the completeness, accuracy and integrity of the study data. This term though sometimes used interchangeably with "deviation" is often considered a major, more serious, variance from an approved protocol than a deviation. Protocol deviations do not require IRB reporting and should be documented in the study file to be reviewed at specific intervals by the PI to determine if continuing non-compliance and becomes reportable. Protocol violations must be reported to the IRB on the Reportable Event Form. See SOP 3.09- Protocol Violation, Deviation, and Non-Compliance Reporting for more details.

3.5 Revised Sponsor Protocols or Investigational Drug Brochures

Revised sponsor protocols or investigator brochures must be submitted to the IRB in a timely manner. The submission of a revised sponsored protocol or investigator brochure should include a memo from the principal investigator indicating his/her review of the document as well as an assessment of whether changes are required to the approved IRB protocol and/or consent document.

3.6 Research Protocol Termination or Suspension

3.6.1 Definitions

IRB-Initiated suspension of approval: IRB-initiated suspension of approval refers to a determination made by TCH IRB to temporarily withdraw IRB approval for some or all activities of a currently approved research study.

IRB-Initiated termination of approval: IRB-initiated termination of approval refers to a determination made by TCH IRB to permanently withdraw IRB approval for some or all activities of currently approved research study.

Investigator-initiated suspension of approval: Investigator-initiated suspension of approval refers to a determination made by the principal investigator or sponsor of the research study to temporarily suspend some or all activities of a currently approved research study.

Investigator-initiated termination of approval: Investigator-initiated termination of approval refers to a determination made by the principal investigator or sponsor of the research study to permanently terminate some or all activities of a currently approved research study.

Serious non-compliance: Failure to comply with any of the federal or state regulations or institutional policies governing human subject research that, in the judgment of TCH IRB, seriously compromises human research subject protection or the integrity of TCH IRB's human research protection program. Examples of serious non-compliance include, but are not limited to:

1. performing non-exempt human subject research without obtaining TCH IRB approval;
2. failing to obtain TCH IRB approval of substantial modifications implemented in a TCH IRB-approved research study;
3. failing to systematically obtain the required written or, when prior approved by TCH IRB, verbal informed consent of research subjects;
4. material failure of TCH IRB (including TCH IRB office staff) to comply with federal regulations governing human subject protections.

3.6.2 IRB-Initiated Termination or Suspension of a Research Protocol

The IRB has the authority to terminate or suspend its approval of a research protocol that is not being conducted in accordance with regulatory or IRB requirements or that is associated with serious harm to human research subjects. Such suspension or termination of approval shall be reported promptly to the investigator and shall include a written statement of the reasons for the IRB's action. Termination or suspension of IRB approval initiated by the IRB shall be reported to the Authorized Institutional Office and, if applicable, to the Office of Human Research Protections (for federally funded research), the FDA (for research subject to FDA oversight), the sponsor (e.g., industry sponsor or federal granting agency), and/or other relevant regulatory agencies.

3.6.3 Investigator/Sponsor-initiated Termination or Suspension of a Research Protocol – IRB Notification

1. Termination or suspension of an IRB-approved research protocol by the principal investigator and/or sponsor of the research study shall be reported promptly (i.e., within 1 day of the receipt of the sponsor termination/suspension notice) to the IRB office if the termination/suspension is based on a change in the risk-to-benefit ratio of study participation (e.g., serious adverse events, non-effectiveness of the research intervention). Termination/suspension of a research study for other (e.g., administrative) reasons shall be reported to the IRB office within 10 working days of receipt of the termination/suspension notice. IRB notification shall include reference to the current IRB approval number and a letter that addresses:

    a. The reason for study termination or suspension (e.g., subject accrual complete and data analyzed; demonstrated absence of benefit based on interim data analysis; serious adverse event).

    b. The number of subjects currently enrolled in the study at The Christ Hospital and the status (e.g., currently undergoing research intervention and monitoring; completed intervention follow-up monitoring only; completed study) of each of these enrolled subjects.

    c. A description of the procedures that will be used to notify subjects currently participating in the study of the study termination/suspension; and the procedures that will be undertaken to ensure their orderly and safe withdrawal

from the study and their follow-up care, if applicable.

d. A description of the procedures that will be used to notify subjects who previously participated in the study of the study termination/suspension, if felt to be important to their rights or welfare.

2. For terminated research protocols, a Study Closure Report/Final Report or a Closure Letter shall be submitted to the IRB office within 10 working days of notification of closure by the sponsor. This report will be reviewed by TCH IRB staff and IRB Chair or Designee and will be presented at the next TCH IRB meeting for their review, consideration, discussion and acknowledgment. The IRB does not routinely send confirmation of receipt of study closure to the research site.

   Study closure is defined by TCH IRB when *all* of the following have been accomplished: 1) all subjects have completed final visits and follow up, 2) the sponsor or its representative has indicated closure at the research site, 3) if the study was conducted under a Federal Wide Assurance, all data analysis at the site is completed.

   This Final Report shall address, at a minimum:

   a. The final number of subjects enrolled in the study at The Christ Hospital.

   b. A summary of outcomes and conclusions to include:

      -- statement of the extent to which the specific aims of the protocol were addressed
      -- impact of the study on the relevant scientific/medical issues under investigation (e.g., a description of new knowledge, findings, or information bearing on the risks or benefits to human research subjects).

3. For research protocols suspended due to serious adverse events, IRB approval is required to reinitiate the research study. The written request for study re-initiation shall address:

   a. The outcome of investigations on the causality of the serious adverse event(s).

   b. The frequency of occurrence of the serious adverse event at TCH IRB or external sites, if applicable.

c. Modifications of the protocol and consent form to address the serious adverse event.

3.6.4 Research Protocol Termination of Suspension – Human Research Subject Notification and Withdrawal

Human subjects currently participating in a research study must be notified of its termination or suspension due to safety issues and/or other problems (e.g., unanticipated problems, failure to obtain continuing IRB approval, investigator non-compliance) and the reasons therefore. It is strongly recommended that such notification be in the form of a consent form addendum to document subject receipt and understanding of this information. Procedures for withdrawal of enrolled human research subjects should consider their rights and welfare. If follow-up of the subjects for safety or effectiveness reasons is permitted or required by the IRB (e.g., under a research protocol that is suspended or closed to enrollment), the subjects should be so informed (i.e., through the use of a consent form addendum) and any adverse events or other outcomes identified during follow-up should be reported to the IRB, the research study sponsor, authorized institutional official, OHRP and the FDA if applicable.

3.6.5 IRB Record Retention After Study Termination

Research files will be retained in the IRB Office for three years after completion of the research [45 CFR 46.115(b) and/or 21 CFR 56.115(b)].

3.7 Study Audits

The IRB conducts audits of research studies annually.
Selection of Studies to Review – Research studies will be chosen for QA/QI review primarily from among studies meeting one or all of the following characteristics:

- Not receiving study monitoring by the study sponsor or another organization
- Present greater than minimal risk to participants
- Involve investigator-initiated research
- Enroll vulnerable populations, including TCH employees and students, cognitively-impaired participants, pregnant women/fetuses/neonates and children.
- Have potential for conflict of interest
- Are requested by the IRB or Institutional Official

A minimum of two audits will be performed yearly. See SOP 1.09-Quality Improvement Activities in Human Research Protection/Audits.