Institutional Review Board

IRB REFERENCE MANUAL & INVESTIGATOR HANDBOOK

Version 2.0

Effective: 21 MAY 2026

Quick links:

IRB Submissions: The IRB utilizes a web-based IRB management system, Mentor IRB, for all submissions. Mentor IRB can be accessed through the following links:

TCH SSO Users: https://www.axiommentor.com/login/shibLogin.cfm?i=thechristhospital
External Users: https://www.axiommentor.com/login/axlogin.cfm

IRB Policies and Procedures: All TCH IRB policies and procedures can be found on The Christ Hospital Website at https://www.thechristhospital.com/services/research/irb/irb-forms-and-policies.

IRB Office Communications: The IRB Office can be reached for questions or consultation by any of the following:

Email:	IRB_Office@thechristhospital.com
Telephone:	(513) 585-2298
Fax:	(513) 585-2107
In Writing:	The Christ Hospital IRB Office 2139 Auburn Ave., Room 3140 (3 North) Cincinnati, OH 45219

What's new in this version:

- *Added cover page*
- *Added revisions page*
- *Added Statement of Compliance to Section 01*
- *Added IRB fees to Section 03*
- *Added requirement for study closure of exempted research to Section 03*
- *Added Appendix 1 IDE Decision Tree to Section 15*
- *Formatting changes throughout*
- *Minor administrative changes throughout*
- *Added references to corresponding TCH IRB policies*
- *Added links to regulation*
- *Added Appendix 1*

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SECTION 01 – JURISDICTION, STRUCTURE AND RESPONSIBILITIES OF THE CHRIST HOSPITAL INSTITUTIONAL REVIEW BOARD

Preface

Vision Statement: The Christ Hospital is to be a national leader in clinical excellence, patient experience, and affordable care.

Mission Statement: Improve the health of our community and create patient value by providing exceptional outcomes and the finest experiences, all in an affordable way.

The Institutional Review Board (IRB) of The Christ Hospital (TCH)

The Christ Hospital Institutional Review Board (TCH IRB) is charged with responsibility for protecting human research participants. The mission of TCH IRB is to facilitate research and ensure the protection of rights, privacy and welfare of all human participants who are the subjects of research.

To achieve this goal, the IRB has the authority to review, approve, modify or disapprove research protocols submitted to the IRB by investigators. The IRB will assist the investigators in designing their research projects in a manner which minimizes potential harm to human subjects, reviews all planned research involving human subjects prior to initiation of the research, approves research that meets established criteria for protection of human subjects, and monitors approved research to ensure that human subjects are indeed protected. The IRB review process is guided by ethical principles outlined in the Belmont Report (1979) and legal mandates outlined in the Code of Federal Regulations Title 45 Part 46 (2005).

The Christ Hospital IRB (TCH IRB) is designated to oversee research on human subjects conducted by the administration, nursing, medical and resident staff, or involving non-public information held by Christ Hospital. The purpose of the IRB is to protect the rights and welfare of human participants in research and to ensure that the human research conducted under this policy meets federal regulations, as applicable (HHS 45 CFR 46; FDA 21 CFR 50, 56, 812), conforms to federal and state laws and to The Christ Hospital institutional policies. The ethical principles are based on the Nuremburg Code, the Declaration of Helsinki, the Belmont Report, and the International Conference on Harmonization (Good Clinical Practices).

The president/CEO of The Christ Hospital is responsible for the appointment of members of the IRB and the oversight of the TCH IRB. The Christ Hospital may not approve research covered under this policy if it has not been approved by the IRB, however, the Institutional Official may decline to conduct research previously approved by the IRB. Investigators should not begin research involving human participants until the IRB has approved the study or has determined that the study is exempt.

Statement of Compliance

The Christ Hospital Institutional Review Board (TCH IRB) is duly constituted (fulfilling FDA requirements for diversity), has written procedures for initial and continuing review of clinical trials, prepares written minutes of convened meetings, and retains pertaining to the review and approval process; all in compliance with requirements of Health and Human Services (HHS) regulations Title 45 CFR (Code of Federal Regulations) Part 46, Protection of Human Subjects; Food and Drug Administration (FDA) Title 21 CFR Part 50, Protection of Human Subjects; FDA Title 21 CFR Part 56, Institutional Review Boards: FDA Title 21 CFR Part 312, International Conference on Harmonization (ICH), and Good Clinical Practice (GCP) guidelines as adopted by FDA/DHHS.

In addition, the TCH IRB operates in compliance with portions of the Health Insurance of Portability Act of 1996 (HIPAA Privacy Rule) that apply to research, as described in 45 CFR Parts 160 and 164, as applicable. TCH IRB is registered with OHRP/FDA; our Federal Wide Assurance (FWA) number is FWA00000702, and our IRB registration number is IRB00001448.

Relying on Other Institutions (Reliance Agreements)

Single IRB: The Christ Hospital permits the use of a single Institutional Review Board to be used in the ethical review of non-exempt human subjects' research protocols that are carried out at more than one site (multi-site research). The aim of single IRB review is to enhance and streamline the IRB review process in the context of multi-site research so that research can proceed as effectively and expeditiously as possible. Eliminating duplicative IRB review and reduces unnecessary administrative burdens and systemic inefficiencies without diminishing human participant protections. Eliminating redundancy in reviews also allows IRBs to concentrate more time and attention on the review of other, single site protocols, thereby enhancing research oversight. (Ref. NOT-OD-16-094: Final NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research). When relying on an external IRB for review of its human subjects research, a reliance agreement must be executed between TCH and the external institution/organization.

SMART IRB: TCH utilizes and maintains an agreement with SMART IRB, an integrated, comprehensive platform for multi-site studies. SMART IRB is TCHs preferred method of documenting reliance. The "SMART IRB Reliance Agreement" supports IRB reliance in facilitating multi-site human subjects research and allows participating institutions to cede IRB review to the IRB of another participating institution. TCH strongly encourages the use of the SMART IRB SOPs with the agreements. However, Participating Institutions may opt to use their own policies and procedures for the reliance relationship if doing so would not render the Participating Institutions in violation of any term of the SMART IRB Reliance Agreement. In such cases, Participating Institutions agree that if a provision of their own policies or procedures conflicts with a term of the SMART IRB Agreement, then the SMART IRB Agreement will govern as to that term.

Dual Review: In the absence of a reliance agreement, human subject research conducted by TCH personnel as indicated at another institution will require review and approval by

both TCH IRB and the IRB of the other institution. If the other institution does not have an Institutional Review Board, approval of TCH IRB may be the only IRB approval requirement, depending upon the nature of the activities to be conducted at the other institution and specifying that all institutional commitments and regulations, applicable laws, and standards for professional conduct in practice have been appropriately addressed by the investigators. Note: If human subject research will be conducted in or involving the staff, patients, students, etc., of an institution which has not executed a reliance agreement with The Christ Hospital IRB, and which does not have its own Institutional Review Board, the respective TCH submission must include a letter from a responsible administrator of the institution indicating his/her permission for the research to be conducted at that institution.

Assurance: Conduct of federally supported human subject research at another institution is subject to the requirement that the other institution have in place a Federal Wide Assurance (FWA) agreement with The U.S. Department of Health & Human Services (HHS) Office for Human Research Protection (OHRP). If the other institution does not have an FWA in place, it may be required, depending upon the research activities to be conducted at that institution, to execute an FWA agreement with OHRP prior to conducting the research at that site. Contact the TCH IRB office for clarification of this requirement as it pertains to the specific research activities to be performed at the other institution.

Composition of the IRB

The Christ Hospital IRB is directed by a chairperson and is comprised of at least five board members with multidisciplinary expertise and backgrounds as required by federal policy and FDA regulations:

Core Membership

Chairperson: Presides over IRB meetings, manages discussions, provides supervision, acts as the primary link between the board and the institution's senior management, and ensures the overall effectiveness of the board.
Scientist Member: At least one member whose primary training and background are in a scientific discipline, such as a physician, Ph.D. researcher, or biomedical health professional.
Non-Scientist Member: At least one member whose primary concerns are in nonscientific areas, such as a lawyer, ethicist, or member of the clergy.
Unaffiliated Member: At least one member who has no professional or personal affiliation with the institution (and no immediate family member affiliated). This person often serves as a "community member" representing the perspective of research participants.
Alternate Members: Appointed to substitute for regular members in their absence. They must have comparable expertise to the member they are replacing (e.g., a scientist for a scientist).

IRB members are covered for liability under one of the following:

- TCH employee members are covered by the self-insured trust fund

- Volunteer members are covered under The Christ Hospital National Union Policy, located in the Risk Management office, which covers past, present and future members

Specialized and Support Roles

Consultants (ad hoc): Non-voting experts invited to assist in reviews that require specialized knowledge beyond the current board's expertise.
Ex Officio: Serves in the capacity of an IRB member without voting, such as the Institutional Official.

IRB Office Staff

IRB Administrator: Manages the daily operations, systems, and compliance of the Institutional Review Board, ensuring human research protections adhere to federal regulations, policies, and ethical standards.
IRB Regulatory Coordinator: Assures that the IRB meets federal regulations, as well as institutional policies and procedures.

Appointment of the IRB

The president/CEO of The Christ Hospital will appoint IRB members and IRB chairperson in accordance with federal regulations for a non-specific term. Members will serve without compensation, although the chair may receive compensation due to the extended duties and time requirements. The board will be multi-disciplined and comprised of at least five voting members, including the chair. Voting members will be representative of the active medical staff, a pharmacist, at least one member of scientific and one member of non-scientific discipline, and at least one community member. There will be ethnic and gender diversity. In addition, individuals may be appointed to serve in ex officio capacity without vote, such as the institutional official. Consultants may be asked to serve without vote where their expertise and competence would assist the consideration of the board (e.g., an attorney, clergy, social worker, medical specialist). Attendance is recorded and if a member misses a majority of convened IRB meetings without substantive cause or explanation, the IRB chair will discuss the advisability of resignation with the board member and report to the institutional official.

When appointing members to the IRB, the following qualities should be considered:

- Commitment to institutional goals for human research protections
- Commitment to the time commitment and the workload including the ability to regularly attend IRB meetings, arrive on time, and be prepared for discussion
- Good communication skills including the ability to present issues and concerns clearly and succinctly, and provide other members with clearly articulated required changes to the research, if any
- Willingness to contact investigators and the IRB chair and/or administrator prior to the meeting to discuss issues and initiate solutions, thus using the IRB meeting to make decisions, not gather information

- Ability to communicate with the IRB office in a timely manner if unable to attend a meeting, or if conflicts of interest require recusal from the voting process for a particular protocol

Additional qualifications of an IRB chair include, but are not limited to:

- Demonstrable knowledge and the ability to consistently apply the regulations governing research and the IRB review process
- Demonstrable knowledge of The Christ Hospital's human research protection program (HRPP) and the ability to consistently apply IRB policies and procedures
- Demonstrable knowledge and the ability to apply the ethical principles of human research protections
- The ability to appropriately apply the relevant knowledge to the individual protocols under review
- Ability to lead IRB members in a thorough review while abiding by all policies, procedures and applicable federal, state and local laws, rules and regulations
- Demonstrable meeting and time management skills including the ability to act as a facilitator, timekeeper, summarizer and consensus taker

Duties of IRB Members

The IRB is appointed as a TCH committee. As such, the IRB members serve The Christ Hospital as a whole, rather than a particular school or department. Therefore, members must not allow their own interests or those of their departments to supersede their duty and primary responsibility to protect the rights and welfare of the individuals serving as research participants. To fulfill his or her duties, each IRB member is expected to be knowledgeable of the regulations governing human subject protection, biomedical and behavioral research ethics, and The Christ Hospital policies relevant to human subject protection. The IRB must be fair and impartial, and immune to pressure by the institution's administration, investigators bringing protocols before the board, or other professional and nonprofessional sources.

All members are expected to review and be familiar with all material prior to each convened IRB meeting and come prepared to discuss the material at the meeting.

Nonaffiliated members: Nonaffiliated members are expected to provide input regarding their knowledge about the local community and be willing to discuss issues and research from that perspective.

Non-scientific members: Non-scientific members are expected to provide input on areas germane to their knowledge, expertise and experience, professional and otherwise. For example, members who are lawyers should present the legal views of specific areas that may be discussed such as exculpatory language or state requirements regarding consent. Non-scientific members should advise the board as to whether additional expertise in a non-scientific area is required to assess whether the protocol adequately protects the rights and welfare of research participants, and to comment on the readability of the consent document.

Scientific members: Scientific members are expected to contribute to the evaluation of studies based on scientific and statistical merits and standards of practice. These members should also be able to advise the board if additional expertise in a scientific or non-scientific area is required to assess whether the protocol adequately protects the rights and welfare of subjects.

Chairperson: In addition to responsibilities relevant to the IRB member's capacity, the IRB chairperson:

- Presides over IRB meetings, provides supervision, manages discussions
- Evaluates each protocol
- Assigns a primary reviewer with appropriate scientific expertise to conduct an in-depth review of greater than minimal risk protocols
- Performs, or delegates authority to an appropriate voting board member to perform, review of no greater than minimal risk research studies
- Oversees the administrative (i.e., IRB office) review and approval of research studies qualifying for exempt or expedited review status
- May, pending IRB review, suspend the conduct of a research project or clinical trial
- Deemed to place research participants at unacceptable risk, or
- If he/she determines that an investigator is not following the IRB's policies or procedures (i.e., continuing noncompliance)
- Acknowledges submissions of Emergency Use of a test article
- May delegate any of his/her responsibilities, as appropriate, to other qualified individual(s); such delegation must be in writing or documented in the record of the IRB
- May appoint a co-chair or associate chair to assist or act on behalf of the chair in particular IRB matters and at IRB meetings, either as a general procedure or on a case-by-case basis; the co-chair or associate chair is required to hold the same qualifications as the chair

Co-chair/Associate chair: Performs the responsibilities of the chairperson noted above in the absence of the chair and/or as delegated by the chair.

Primary Reviewers: The chairperson or his/her designee will act as primary reviewer of research studies at convened meetings. The primary reviewer presents his or her findings regarding application materials and an assessment of the soundness and safety of the protocol and recommends specific actions to the board. The primary reviewer is required to read and be familiar with the entire submission and be prepared to conduct an in-depth review of all materials at the IRB meeting. He or she leads the board's discussion The primary reviewer is expected to contact the investigator, IRB chair or IRB administrator in advance of the convened meeting for clarification of unresolved issues related to the submission.

Reporting Undue Influence: Any IRB members or TCH staff who becomes aware of an allegation of undue influence or coercion regarding IRB policies and/or procedures must

report the incident(s) immediately to the IRB chairman. The chairman, along with a selected community member of the IRB, will initiate an inquiry into the allegation and initiate a report to the president/CEO of The Christ Hospital. The president/CEO will resolve the issue and notify the IRB of the outcome.

IRB Membership Roster

A roster of IRB members and alternate members is created and maintained by the IRB Coordinator. The roster identifies members by:

- Name
- Earned degrees
- Experience, qualifications, specialty (e.g., board certification, licenses, IRB certification)
- Designation as Principal, Ad Hoc or Ex Officio Member
- Scientific/non-scientific designation
- Employment by or relationship to the IRB or other member
- Hospital or institutional affiliation

The membership roster is reviewed at least annually by the IRB office staff and the IRB chair to assure appropriate membership and diversity as outlined in 45 CFR 46 and 21 CFR 50.

Meeting Attendance

Members are requested to attend the scheduled meetings in order to maintain their appointments to the Board. The IRB office staff will maintain an attendance log with cumulative attendance recorded on a calendar-year basis for review with the IRB chair at each meeting. The chair will contact members who miss 6 consecutive meetings and determine the action to be taken. The chair may ask for the resignation of the member if deemed necessary. Unaffiliated members are expected to attend 80% of their convened IRB meetings a year. Unless there is a last-minute emergency or illness and a substitute cannot be found, there will be an unaffiliated member at every IRB meeting. The attendance of the unaffiliated members will be documented in the meeting minutes. Unaffiliated members are non-scientific members and represent the general perspective of research participants. At a meeting in which the IRB reviews research that involves subjects vulnerable to coercion or undue influence, one or more individuals who are knowledgeable about or experienced in working with such individuals must be present.

Member Removals, Resignations, Vacancies

Removals**:** A member, alternate, ad hoc, or ex officio member (including the IRB chair) may be removed, with or without cause, from the IRB:

- By the action of the President/CEO or Institutional Official of The Christ Hospital, at the recommendation of the IRB chair;
- If the member misses 6 consecutive meetings or has a pattern of non-attendance.

Resignations: The IRB chair may resign with a one-month notice. An IRB member may resign from the IRB by submitting a letter of resignation to the chair.

Vacancies: Vacancies in the membership shall be filled by the appointment process following the guidelines described above in "Appointment of the IRB".

Quorum

Quorum shall be established with a majority of the members present, including at least one member whose primary interest is in a non-scientific area. All members of the IRB have full voting rights, and a project is deemed approved with a positive vote of simple majority of those present at the meeting where quorum has been established. If quorum is lost during a meeting (e.g., if required members such as non-scientific members, leave the room) the IRB cannot take votes until the quorum is restored, even if half of the total members are still present. Voting by proxy is prohibited. An investigator may not cast a vote on the consideration of his/her own project and is required to leave the meeting room during the discussion and when the vote is cast on a project in which he/she has a conflict of interest.

No Quorum Present

In the event quorum is not present, the IRB chair will cancel the meeting and schedule a make-up meeting before the beginning of the following month. The make-up meeting will ensure that all IRB protocols scheduled for continuing review can be reviewed by the expiration dates.

Purpose of IRB Review

The IRB review is to assure, both in advance and by periodic monitoring, that appropriate steps are taken to protect the rights and welfare of human research subjects, and to ensure the confidentiality of the subject's protected information. The focus of the IRB review process is outlined in Section 11.

IRB Office Staff and Responsibilities

Administrator: Responsible for oversight of administration and operation of the IRB office; responsible for ensuring IRB and IRB office compliance with federal and state regulations and institutional policies governing human subject research and human subject research protections; assists in the provision and educational support to the research community.
Regulatory Coordinator: Responsible for ensuring compliance with federal regulations, and internal policies and procedures; oversees communication respective to federal-wide assurance agreements, inter-institutional amendments and cooperative agreements, and is responsible for maintaining and updating IRB policies and procedures and IRB reference manual; provides education and support to research community, as well as to the IRB staff. Maintains up-to-date information regarding federal regulations and IRB policies related to the use of human subjects in research.

Definitions of Research and Human Subjects

TCH IRB is required to review and approve all research activity involving human subjects prior to implementation of research activity. A question may sometimes arise as to whether a planned activity is "research involving human subjects" and therefore requires IRB review and approval.

TCH IRB Definition of Human Subjects Research: Under the institution's policies and procedures, an activity is human subjects research if it is either (1) human subject research subject to DHHS regulations, or (2) human subject research subject to FDA regulations.

Refer to Section 02 for more information on Designation of Research.

Definitions for DHHS Regulated Research

- *Research* means a systematic investigation including research development, testing and evaluation designed to develop or to contribute to *generalizable knowledge*.

- *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. (Ref. 45 CFR 46.102(e))

- *Intervention* includes both the physical procedures by which data are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. (Ref. 45 CFR 46.102(e)(2))

- *Interaction* includes communication or interpersonal contact (e.g., questionnaires, interviews) between the investigator and the subject. (Ref. 45 CFR 46.102(e)(3))

- *Private information* includes information about behaviors that occur in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by the individual and which that individual can reasonably expect will not be made public (i.e., a medical record). Private information must be individually identifiable (i.e., the identity of the subject is (or may be readily ascertained) by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. (Ref. 45 CFR 46.102(e)(4))

Definitions for FDA Regulated Research

- *Clinical investigation* means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the Federal Food, Drug and Cosmetic Act ("the Act") or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the Act, but the results of which are intended to be later submitted to, or held for inspection by, FDA as part of an application for a research or marketing permit. Clinical investigations regulated by the FDA under sections 505(i) and 520(g) of the Act includes investigations of food, dietary supplements that bear a nutrient content claim or health claim, infant formulas, food and color additives,

drugs for human use, medical devices for human use, biological products for human use, and electronic products. The term "clinical investigation" does not include experiments that must meet the provisions of Part 58 regarding non-clinical laboratory studies. The terms *research, clinical research, clinical study, study,* and *clinical investigation* are deemed to be synonymous for purposes of this part. Research is subject to 21 CFR parts 50 and 56 when it involves the use of any drug/device other than the use of an approved drug/device in the course of medical practice. (Ref. 21 CFR 56.102(c))

- *Test article* means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act. (Ref. 21 CFR 56.102(l))

- *Subject* means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or have a medical condition or disease (Ref. 21 CFR 812.3(p)).

- *Human subject* means an individual who is or becomes a participant in research either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient (Ref. 21 CFR 56.102(g)). If the research involves a medical device, human subjects are individuals when they participate in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control (Ref. 21 CFR 812.3(p))

Definition of "Research" in the Belmont Report

Research designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby develop or contribute to generalizable knowledge (i.e., in theories, principles, and statements of relationships).

Innovative Practices vs. Research

Innovative or newly introduced procedures or therapies do not require IRB review and approval except when they include "research" as defined by the above criteria. An innovative clinical practice is an intervention designed solely to enhance the well-being of the individual, patient or client. The purpose of the innovative clinical practice is to provide diagnosis, preventative treatment, or therapy to particular individuals. The introduction of innovative procedures or therapies into clinical practice (i.e., independent of a research activity approved by the IRB) should be reviewed with the applicable department chair and section chief, if applicable.

Quality Assurance vs. Research

Quality assurance projects do not require IRB review and approval except when the project involved includes "research" as defined by the above criteria. Precise definitions to permit the distinction between research studies and quality assurance projects are difficult and have not been established. In general, a quality assurance project is a project

that is focused primarily on improving patient care within a given patient care environment (i.e., hospital or healthcare organization) and as such, the outcome of the project may not be generalizable to other patient care environments. Publication of a quality assurance project is not, per say, under the project "research"; however, if the outcome of a quality assurance project is published, attention should be given to avoiding the terminology "research" in the publication.

Questions directed at providing guidance and distinguishing quality assurance projects from research:

- Is there a commitment in advance of data collection to a corrective plan given any one of several study outcomes? Does the principal investigator of the study have both clinical supervisory responsibility and the authority to impose change? If the answer to either question is no, then the study requires prior review and approval by the TCH IRB.
- Is the research being sponsored/funded by an external agency? If yes, the study *may* require prior review and approval by TCH IRB.
- Does the proposed study involve prospective assignment of patients to different procedures or therapies based on a predetermined plan such as randomization? If yes, the study requires prior review and approval by TCH IRB.
- Does the proposed study involve a control group from which the therapeutic or study intervention is intentionally withheld to allow an assessment of its efficacy? If yes, the study requires prior review and approval by TCH IRB.
- Will the study intervention be delivered in blinded fashion, wherein neither the physician nor the patient knows to whom the study intervention or comparative intervention (i.e., placebo, standard care) was given? If yes, the study requires prior review and approval by TCH IRB.
- Is the assessment of outcome blinded to the study intervention for the purpose of establishing efficacy of the intervention? If yes, the study requires prior review and approval by TCH IRB.
- Does the proposed study involve the prospective evaluation of a drug, biologic, or device that is not currently approved for general use by the FDA, including evaluations of off-label indications? If yes, the study requires prior review and approval by TCH IRB.
- Will patients involved in a proposed study be exposed to additional risks or burdens (i.e., other than the completion of patient satisfaction surveys) beyond standard clinical practice in order to make the results of the study generalizable? If yes, the study requires prior review and approval by TCH IRB.

Refer to IRB SOP 2.19 "*Quality Improvement Projects"* for more details.

Research on or Involving Deceased Individuals

Research performed on individuals who have been declared legally dead and/or research involving the tissues of deceased individuals is not subject to review and approval of TCH IRB. (Note: Federal policy regulations governing human research subject protections

define “human subjects” as living [emphasis added] individuals about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.) There are, however, ethical issues associated with research conducted on or involving deceased individuals. To address these issues, all personnel who desire to perform such research involving deceased individuals must submit a project application through their department chair. Research involving the medical records of the deceased individuals is subject to obtaining written consent of the descendant’s next of kin or the executor of the descendant’s estate. Please check with the HIPAA Privacy Officer in the Compliance department. For studies that include both living and deceased subjects, TCH IRB is the institutional community with jurisdiction for oversight and approval.

Section 1 Regulatory History
Effective Date: 01/07
Revised/Reviewed Date: 04/26
AAHRPP Element(s): II.1.A, II.1.B, II.1.D, II.1.E, II.2.D

SECTION 02 – IRB REVIEW OF PROPOSED RESEARCH STUDIES

The Christ Hospital Institutional Review Board (TCH IRB) must review and approve all research activities involving human subjects that fall under the Institution's Human Research Protection Program prior to the implementation of such research activities. Notification to the IRB chair, or in his absence, designee, is required for emergency use of a non-approved investigational drug or a non-approved investigational device (refer to Section 13).

There are four categories of IRB review of proposed research study:

1. Not Human Subjects Research (NHSR)
2. Exempt
3. Expedited (No greater than minimal risk research)
4. Full Board (Greater than minimal risk research)

At The Christ Hospital, the IRB, not the researcher, determines the review level. Studies determined by the IRB to qualify for exempt or expedited review are reviewed by the IRB upon receipt. Studies determined by the IRB to qualify for full board review and which are received by the meeting deadline are placed on the agenda for review at the next scheduled IRB meeting. Studies received after the meeting deadline may be placed on the agenda for review at the next scheduled IRB meeting if it is determined there is adequate time for review.

Refer to SOP 2.01 "*Guidelines for New Protocol Submission"* for more information on protocol submission.

Researcher Training Requirements: All investigators and key research personnel listed on the study application for a research project involving human research are required to complete Human Subject Research (HSR) and Good Clinical Practice (GCP), as training, as applicable, through the Collaborative Institutional Training Initiative (CITI) web-based education and certification program This course must be completed every 3 years.

Refer to SOP 3.12 "*Education of IRB Staff/Board Members/Investigators/Research Staff*" for more details.

Not Human Subjects Research (NHSR) Determination

Certain studies submitted for exempt review may not meet The Christ Hospital's definition of human subject research because the activity meets neither the DHHS definition of human subjects research [i.e., does not meet the DHHS definition of "research" as specified under 45 CFR 46.102(l) involving "human subjects" as specified under 45 CFR 46.102(e) or the FDA definition of "research" as specified under 21 CFR 56.102(c) involving "human subjects" as specified under 21 CFR 56.102(e).] For example, Quality

Assurance projects may not meet the DHHS definition of "research" if they are not designed to develop or contribute to generalizable knowledge (45 CFR 46.102(l)) and do not meet the FDA definition of research if they do not involve the administration of drugs or devices (21 CFR 56.102(c)). Studies that are research, but do not involve human subjects (according to the regulations) might include those in which (a) the investigator conducting research neither interacts nor intervenes with an individual to obtain data (including specimens) about that person, or (b) does not obtain identifiable private information. This determination is made by TCH IRB Chair or his/her designee.

Refer to SOP 1.06 "*Not Human Subjects Research Determinations"* for more details.

Exempt Review

Research activities in which the only involvement of human subjects will be in one or more of the categories listed below are exempt from the HHS Federal Policy regulations (45 CFR 46.104(d)(1-8) including the requirement to obtain informed consent. However, the exemption criteria at 45 CFR 46.104(d) do not apply to research that is subject to FDA oversight except for research activities involving taste and food quality evaluation as provided for in 45 CFR 46.104(d)(6). (See RM Section 1.13). The Christ Hospital requires IRB review of human research activities appearing to meet these exempt criteria to ensure regulatory compliance. Research protocols qualifying for exempt review are reviewed administratively by the IRB Chair or his/her designee. Following an initial IRB determination of exempt status, exempt research activities are not subject to annual renewal requirements; however, the IRB requires a formal notification of study closure once all research activities—including data analysis and destruction of identifiers—are complete.

Category 1

Research conducted in established or commonly accepted educational settings that specifically involves normal educational practices that are not likely to adversely impact (1) students' opportunity to learn required educational content or (2) the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of, or the comparison among, instructional techniques, curricula, or classroom management methods.

Category 2

Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

- The information obtained is recorded by the investigator in such a manner that the identity of the human participants cannot be readily ascertained, either directly or through identifiers linked to the participants;
- Any disclosure of the human participants' responses outside the research would not reasonably place the participants at risk of criminal or civil liability or be

damaging to the participants' financial standing, employability, educational advancement, or reputation; or
- The information obtained is recorded by the investigator in such a
- manner that the identity of the human subjects can readily be
- ascertained, directly or through identifiers linked to the subjects, and
- an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

Category 3
Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

- The information obtained is recorded by the investigator in such a manner that the identity of the human participants cannot readily be ascertained, directly or through identifiers linked to the subjects;
- Any disclosure of the human participants' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the participants' financial standing, employability, educational advancement, or reputation;
- The information obtained is recorded by the investigator in such a manner that the identity of the human participants can readily be ascertained, directly or through identifiers linked to the participants, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

For the purposes of this provision, benign behavioral interventions are brief, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

If the research involves deceiving the subjects regarding the nature or purpose of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

Category 4
Secondary research for which consent is not required; secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria are met:

- The identifiable private information or identifiable biospecimens are publicly available;
- Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human participants cannot readily be ascertained directly or through identifiers linked to the participants, the investigator does not contact the participants, and the investigator will not re-identify participants;
- The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care options" or "research" as those terms are defined at 45 CFR 164.501 or for "Uses and disclosures for public health activities" as described under 45 CFR 164.512(b);
- The research is conducted by, or on behalf of, a federal department or agency using government-generated or government-collected information obtained for non-research activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501; NOTE: If all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.

Category 5
Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs.

Category 6
Taste and food quality evaluation and consumer acceptance studies (45 CFR 46.104(d)(6)).

Category 7
Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by §46.111(a)(8).

Category 8

Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if criteria in 45 CFR 46.104(d)(8) are met.

Note on Categories 7 and 8: The Christ Hospital has made an Institutional decision that broad consent will not be permitted at this time. As a result, the TCH IRB will not consider applications under exempt category 7 or 8 which requires broad consent.

Submission Requirements for Exempt Review

If an investigator is uncertain if his/her research meets the requirements for exempt research, he/she may contact the IRB Office at IRB_Office@thechristhospital.com to determine if the study is eligible for exempt status. If an investigator believes that his/her research study meets the federal regulations, as well as institutional and ethical criteria for an exemption from IRB review, they must submit the IRB Exempt Application along with any applicable questionnaires and screening or recruitment instruments, etc. to the IRB for review and approval.

Refer to SOP 1.16 "*Exempt Research"* for more details.

Expedited Review

Research activities involving no more than minimal risk and in which the only involvement of human subjects will be in one or more categories listed below (carried out through standard methods) may be reviewed by the IRB through an expedited (i.e., administrative review) procedure. This means that these types of reviews are not conducted by the convened TCH IRB, but rather administratively. As defined by federal regulations, minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. Under the expedited review procedure, the initial review of the research is carried out by TCH IRB chair or his/her designee. In conducting the review, these individuals may exercise all the authorities of the IRB except that they may not disapprove the research. A research activity may be disapproved only after the full board review. The Christ Hospital IRB will report each protocol approved by expedited review at its next regularly scheduled meeting.

*Noted Exceptions***:**

- The expedited review procedure may not be used where identification of the subjects or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation or may be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- The expedited review procedure may not be used for classified research involving human subjects.

Standard requirements for informed consent or its waiver, alteration or exception apply to the research protocol qualifying for expedited review.

Research activities eligible for expedited review are limited by federal policy and FDA regulations to the following: 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included in this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

Categories in this list apply regardless of age of subjects except as noted. The IRB recognizes that the standard requirements for informed consent or its waiver, alteration or exception apply regardless of the type of review, expedited or convened, utilized by the IRB. Categories 1 through 7 below pertain to both initial and continuing review. NOTE: Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted."

Category 1: Clinical studies of drugs and medical devices only when either condition below is met:

- Research on drugs for which an investigational new drug application (21 CFR 312) is not required. NOTE: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.
- Research on medical devices for which (1) an investigational device exemption application (21 CFR 812) is not required; or (2) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

Category 2: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week; or
From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week.

Category 3: Prospective collection of biological specimens for research purposes by noninvasive means. Examples include:

- Hair and nail clippings in a non-disfiguring manner
- Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction
- Permanent teeth if routine patient care indicates a need for extraction

- Excreta and external secretions (including sweat)
- Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue
- Placenta removed at delivery
- Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor
- Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques
- Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings
- Sputum collected after saline mist nebulization

Category 4: Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications). *Examples include:*

- Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy
- Weighing or testing sensory acuity
- Magnetic resonance imaging
- Electrocardiography, electroencephalography, thermography detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography
- Moderate exercise, muscular strength testing, body composition assessment and flexibility testing where appropriate given the age, weight, and health of the individual

Category 5: Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for non-research purposes (such as medical treatment or diagnosis). NOTE: Some research in this category may be exempt from the federal regulations or TCH Policy and procedure. This listing refers only to research that is not exempt.

Category 6: Collection of data from voice, video, digital, or image recordings made for research purposes.

Category 7: Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Submission Requirements for Expedited Review

For expedited research in which TCH IRB will provide oversight, the following documents must be completed and/or uploaded in Mentor IRB, as applicable to the research:

- Application (Mentor Smart form), which may include the following (as applicable):
- Request for Full or Partial Waiver of HIPAA Authorization
- Waiver of Informed Consent Request
- Waiver of Documentation of Informed Consent Request
- Informed Consent Documents, such as:
  - Informed Consent using the TCH template
  - The HHS-approved sample consent document (when available)
- Protocol/Clinical Investigation Plan (CIP), such as:
  - Sponsor-approved protocol
  - Complete HHS-approved protocol (when available)
- Annual Financial Conflict of Interest (FCOI) Disclosure form for all investigators and other key research personnel on sponsored/funded research, if applicable.
- Recruitment/Advertising Materials
- Any relevant grant applications
- Data Collection Materials
- Documentation of Qualifications for all investigators and other key research personnel:
  - Certificates of completion for the required CITI courses including training in Human Subjects Research (HSR) and Good Clinical Practice (GCP), or approved alternative. Transcripts of required CITI training must reflect completion within the most recent three years.
  - Most recent CV
  - Medical or Nursing License, as applicable
  - Agreement to Comply with Human Research Regulations

Expedited Review Turnaround Time

Research protocols qualifying for expedited review will be reviewed by the IRB chair or designee for exempt/expedited review in order of date received by the IRB Office. Depending upon the volume of submissions received, expedited review turnaround time varies.

Refer to SOP 1.16 "*Expedited Review Procedures"* for more details.

Full Board Review

Research activities which do not qualify for exempt review or expedited review under the stated categories must be reviewed and approved by the full board at a regularly scheduled convened meeting. For complete requirements refer to Section 07.

IRB Meeting Dates

All meetings of TCH IRB are held on the second Tuesday of each month at 7:30 a.m. The deadline for IRB submission is 21 days prior to the meeting date.

Submission Requirements for Full Board Review

For greater than minimal risk research in which TCH IRB will provide oversight, the following documents must be completed and/or uploaded in Mentor IRB, as applicable to the research:

- Application (Mentor Smart form), which may include the following (as applicable):
- Request for Full or Partial Waiver of HIPAA Authorization
- Waiver of Informed Consent Request
- Waiver of Documentation of Informed Consent Request
- Investigational Drug Information
- Investigational Device Information
- Informed Consent Documents, such as:
  - Informed Consent using the TCH template
  - The HHS-approved sample consent document (when available)
- Protocol/Clinical Investigation Plan (CIP), such as:
  - Sponsor-approved protocol
  - Complete HHS-approved protocol (when available)
- Annual Financial Conflict of Interest (FCOI) Disclosure Form for all investigators and other key research personnel on sponsored/funded research, if applicable.
- FDA documentation for investigational products
- Recruitment/Advertising Materials
- Investigator's Brochure
- Instructions for Use
- Any relevant grant applications
- Data Collection Materials
- Documentation of Qualifications for all investigators and other key research personnel:
  - Certificates of completion for the required CITI courses including training in Human Subjects Research (HSR) and Good Clinical Practice (GCP), or approved alternative. Transcripts of required CITI training must reflect completion within the most recent three years.
  - Most recent CV
  - Medical or Nursing License, as applicable
  - Agreement to Comply with Human Research Regulations

Refer to SOP 1.07 "*Full Board Review Submission Guidelines"* for more details.

Pre-Review of Research

All research protocols shall undergo departmental review (and section review, if applicable). This includes a) industry initiated and sponsored clinical trials of drugs or devices that are subject to prior FDA acceptance of an IND or IDE application, b) research reviewed by an external scientific committee as a condition of research funding (e.g., NIH sponsored research) or for inclusion in cooperative group trials, and c) studies which meet one of the exempt criterion defined by the federal regulations (see RM Section 2.0). The purpose for this review is to assure that the department head is aware of the research being conducted in his/her department so that the department head can disseminate this information throughout the department and aid in recruitment. The department head should be aware of all scholarly research conducted by department members so that the department head can communicate this to any resident training program director for

incorporation in their reports to their respective accrediting bodies. In addition, all research projects other than those indicated above will be reviewed by the department head and, if applicable, section chiefs or their designees or designated committee for approval and indication that the principal investigator has a) the appropriate training and experience, b) adequate resources, c) sufficient time allocation to conduct the research, d) determined that the research is pertinent to the needs and goals of the institution, department and community, and e) confirmed that the research has been found to be acceptable for IRB submission.

Substantial modification to the aims and/or design of a research protocol (with the exception of the categories of research defined above) may also need departmental review prior to submission of the modifications for IRB approval.

Contract Review

The Christ Hospital General Counsel reviews clinical trial agreements (CTA), if applicable, for consistency between AAHRPP Elements I.8.A – I.8.E, as applicable, and the research. Legal Counsel also ensures that the language regarding research-related injury is consistent with the local consent form.

The Christ Hospital Cancer Center Protocol Review Process

The Cancer Research Administrative Team performs a timely and thorough review, and a respondent commentary (written or verbal when applicable) on potential projects and relevant research. The Christ Hospital Cancer Collaborative Committee (CCC) members are also generally consulted regarding potential research projects. The review and commentary may be requested by the entire committee or select members as determined by the research director and may occur in a group setting or on an individual basis depending on the timing and specific situation.

The Christ Hospital Cancer Center Research Department also utilizes varying Christ Hospital support individuals in the study selection process, depending on the nature and depth of the project. These individuals include, but are not limited to, the research nursing staff (regarding clinical and regulatory implications), Cancer Center Director (regarding facility, financial and staffing feasibility), IRB Chairman (regarding complicated drugs, devices, and or techniques with regards to safety and accountability), The Christ Hospital Administration officers (regarding complicated fiscal, assurance and/or public relation concerns), Departmental Managers (regarding the feasibility of complicated medical or radiation oncology devices and or techniques), and Tumor Registry (for patient population feasibility).

Research Protocols Involving Human Subject or Patient Exposure to Ionizing Radiation

All new and investigational procedures involving potential radiation exposure will be reviewed by the Radiation Safety Officer and another Senior Physicist. The Radiation Safety Committee votes to approve the protocol given the recommendation of the RSO before initiation. (Ref. Radiation Safety Committee ATT 10.1a, 10.1b)

Investigational Drug Service and Pharmacy Utilization

Before IRB consideration of potential drug studies, protocols are reviewed for design and safety. Medication is reviewed for safety, side effects, and preparation/storage issues. Questions regarding any issues are addressed with the investigator at the IRB meeting. The pharmacy's role in the study is determined during Site Initiation Visit Meetings and procedures are worked out for pharmacy/nursing handoffs. Questions may also be addressed with the sponsor at these meetings. The staff is educated on procedures and accountability prior to study initiation. (Ref. The Christ Hospital Pharmacy Services Investigational Drug Study & Research Service)

Fiscal (Contract) Review

The Chief Clinical Officer reviews contracts after IRB approval. This review includes an evaluation of the costs associated with the study and resources needed. The IRB fee typically covers the cost of initiating a research study.

Community-Based Participatory Research Considerations

Community-based participatory research (CBPR) is a collaborative approach to research involving stakeholders outside of academic research organizations, equitably involving all partners in the research process and recognizing the unique strengths that each may bring. The process typically (but not always) starts with a topic of importance to the community and has the aim of combining knowledge with action with the intention of instituting change to improve community well-being. Community residents may participate in the full spectrum of the research from concept, design, conduct, data analysis, interpretation, conclusions, and communication of results. Academic research and community partners join to develop models and approaches to building communication, trust and capacity, with the ultimate goal of increasing community participation in the research process. CBPR is an alternative research model integrating education and social action to improve communities and enhance the scientific knowledge base and is most often associated with improving community health outcomes through transfer of evidence-based research from clinical settings to communities that can benefit most.

Community-based participatory research can present distinct challenges not addressed in traditional research paradigms including ethical and practical considerations particular to the design, review, and conduct of community-engaged research. CBPR requires that the researcher follow the best practices for respectful and productive relationships. The following principles are in addition to those required for all human research:

- Certainty that the research topic addresses a community-defined need, question or problem
- Recognizing the research as a partnership, i.e., engagement of research projects is to be led by a team of academic and community Co-Investigators collaborating as partners
- Respect for the community partner's interest in the research
- Openness to the guidance of community insights and experiences
- Maintaining a balance in decision making between the researchers and community participants
- Provision of continuous feedback to enhance the partnership and its outcomes

- Dissemination of research findings to community stakeholders and participants.
- Recognition that partnerships can dissolve and development of a plan for closure, as applicable

Submission Requirements for Community-Based Participatory Research

In addition to the submission requirements for exempt, expedited or full board review as outlined above, principal investigators of CBPR studies shall submit enough information to assess whether the study adequately meets the criteria for approval of a CBPR research study, including:

- Evidence that an equitable partnership between the investigator and the community partner exists
- That investigators have defined the relevant community or communities
- That investigators have identified the appropriate community or communities for the project
- That the investigator has identified the appropriate research partner for the project
- That community engagement is an integral part of the research
- That letters of support (from the community) are clear and well-defined
- That an appropriate division of funding (if applicable) exists
- Adequate training opportunities for investigators and community members
- That the research environment is adequate including (1) the community benefits from the presence and implementation of the research, and (2) the research is conducted in an environment that enhances the likelihood of success
- That the research strives for positive change in community outcomes
- That the research fosters long-term relationships between the Institution and the Community for the benefit of both

- Plan for Modifications: It is often necessary to make changes to the procedures or survey/data collection instruments as the research progresses or is implemented in the field. Researchers must anticipate and plan for this by including in the IRB application information that is sufficient to allow for a thorough review but general enough to allow flexibility.
- Plan for Disclosure of Research Findings**:** To minimize the risk of group harms resulting from inappropriate disclosure of research findings, researchers should work with the community to inform its members about the research findings and plans to disclose the results, as well as possible implications of disclosure. Thus, the possibility of harm resulting to the community as the research is published or presented may be reduced.
- Benefits Are Available to Groups: Productive partnerships between researchers and community members should be encouraged to last beyond the life of the project with the research designed to provide benefits to the communities involved. Efforts should be made to increase the likelihood that research findings will be incorporated into ongoing community programs, therefore providing the greatest possible benefit to the community.
- Community Involvement: A description of the aspects of the research in which community members will be involved, and how they will be involved. In community-based research, investigators often involve the community members

in the research design or conceptualization, conduct or implementation of the study, and dissemination or distribution of study results. With some topics or research areas, it may also be necessary to involve the community members in the analysis and interpretation of data, and to seek their input into how the findings will be distributed to others, thus providing the community members the opportunity to include their views about the interpretation prior to final publication.

Informed Consent in CBPR

In all research, informed consent forms should meet federal regulatory requirements of the U.S. Department of Health and Human Services (HHS) 45 CFR 46.116 and the US Food and Drug Administration (FDA) 21 CFR 50.20 to ensure that:

- Participants understand the research study and voluntarily agree to participate
- Consent explanations are in language understandable to the potential study participant or the individual's legally authorized representative
- The consent does not include language through which the participant or their representative is made to waive the participant's legal rights or releases the investigator, the sponsor, the institution or its agents from liability for negligence
- Appropriate documentation of consent takes place
- All other requirements as outlined in Section 16, "*Informed Consent*" and IRB SOP 2.02, "*Informed Consent*" are followed.

In community-based research, additional issues should be considered and, as appropriate, included in the consent document and process. The informed consent might specifically address the risk of harm and potential benefit of the research for the individuals and the community. For example, any physical or psychosocial risks of harm to an individual's well-being or agency should be described, including risks of harm to individuals by virtue of their association with the group or community participating in the research involvement (Ross LF, Loup A, Nelson RM, et al. Empir Res Hum Res Ethics. 2010 Mar;5(1):5-17). Furthermore, in addition to describing a participant's right to withdraw from the research, the consent might also state, if true, that an individual's choice to withdraw will not affect their relationship or standing within the community.

Recruitment in CBPR

The IRB provides guidance for investigators on identifying relevant community members for research studies (ref. RM 05 Recruitment of Research Subjects and Patients). Guidance may also be provided via consultation with the IRB office/chairman, specific to the individual research study and resources available through The Christ Hospital Health Network. (ref. SOP 1.14 *Community Outreach on Human Subjects Researc*h)

NOTE: Engaging the community early in the process, before a study begins, can promote trust in the research study and may help facilitate successful recruitment.

IRB Review of Community-Based Participatory Research

IRBs face unique challenges in reviewing research that involves collaborations between academic researchers and community member partners. Federal regulations governing the review and conduct of human subjects research are not explicitly designed to protect

the rights and welfare of communities involved in research, nor are they written to protect against risks to the rights and welfare of individuals (with respect to their roles in the community) as a consequence of their research involvement (Ross LF, Loup A, Nelson RM, et al. Empir Res Hum Res Ethics. 2010 Mar;5(1):5-17). When preparing an initial application, investigators should include appropriate details allowing the IRB to apply the federal criteria for approval, yet when describing operational procedures, the descriptions should be general enough to allow flexibility.

Community Consultation Regarding Risks

The traditional IRB review paradigm is to assess both risk of harm and potential benefit from the individual participant's perspective. However, in community-engaged research, the focus widens as including community members as part of the research team poses additional challenges to maintaining privacy and confidentiality during the recruitment process and during the study. For example, community members who serve as researchers or staff and who are recruiting or otherwise interacting with study participants may know, or may be familiar with, the individuals they are recruiting. Additionally, researchers should work with the community members to identify any risks and potential issues (e.g., literacy, language barriers, local or cultural beliefs and attitudes) which the community researcher may not have considered.

To the extent feasible and allowable, researchers and IRBs should consider risk of harm for both individuals (e.g., social stigma or loss of status within the community) and the community (e.g., economic, political, educational, cultural, or adverse effects on the group's cohesiveness or function). Appropriate measures to minimize any foreseeable risks may be taken through consultation with the community members. Strategies to mitigate risk may include:

- Ensuring privacy so that groups are not singled out as research participants
- Working with a local, trusted partner who can help classify and discuss stereotypes of the community/population and advise on how best to approach these groups
- Informing participants about the potential research results and the risk that these may reinforce negative stereotypes or harm the group
- Referring participants to local support services
- Ensuring that all risks and benefits to the community will be discussed in the consent process, as well as any future use of data, tissue, or samples

Collaborative IRB Review

Some groups, agencies or entities (e.g., tribes, retirement communities, and school districts) may have their own ethical review process for research. In such cases, researchers should apply to the local ethics review body for review and approval of their research. Institutional and/or investigator agreements may also be necessary.

Additional Considerations for CBPR

The Christ Hospital IRB is comprised of members with multidisciplinary expertise and backgrounds including a non-affiliated community member(s), as required by federal policy and FDA regulations: (1) the IRB shall be sufficiently qualified through the

experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes; 2) regarding regular reviews of research involving a vulnerable category of subjects, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects; and (3) the IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. (Ref. IRB SOP *3.20 "Periodic Review and Assessment of IRB Members, Chair, and Staff"*; 21 CFR 56.107)

When reviewing studies involving community-based research, the IRB may, in the absence of a member with expertise in such research, invite consultants to assist in the review process. (Ref. SOP 3.01 "*Scientific/Scholarly Review of Protocols - Minimizing Risks to Subjects"*)

Section 2 Regulatory History
Effective Date: 01/07
Revised/Reviewed Date: 4/26
AAHRPP Element: I.4.C, II.2.A, II.2.B, II.2.E, II.2.F

SECTION 03 – MODIFICATIONS TO AND CONTINUING IRB REVIEW OF EXISTING RESEARCH

MODIFICATIONS TO EXISTING RESEARCH

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 (ref. 45 CFR 46.108(a)(3)(iii); 21 CFR 56.108(a)(4)).

The IRB is authorized to suspend or terminate approval of research that is not being conducted in accordance with the TCH IRB requirements (ref. 45 CFR 46.113; 21 CFR 56.113).

Refer to IRB SOP 2.03 "*Amendments"* for more details.

Categories of Modification Review

IRB approval of modifications to existing research protocols 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 Christ Hospital (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 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.

Minor Modifications: The IRB Chair or his/her designee can expedite the review and approval of minor modifications to an IRB-approved research protocol. 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:

An increase or decrease in proposed human research subject enrollment (should be supported by 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 that 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 and other key research personnel
- The addition or deletion of study sites
- Minor changes specifically requested by the IRB or Radiation Safety Committee

Major Modifications: Major modifications to an IRB-approved research protocol 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 of 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

NOTE: Modifications to the informed consent document must account for 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.

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 Institutional Review Board (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.

Submission Requirements for Modifications

The request for approval of the amendment or modification must be submitted in Mentor IRB. The request should include the following:

- Complete description of the nature of the changes
- A clean and tracked changes copy of the amended research protocol, if applicable
- A copy of the sponsor's summary of changes document addressing the respective modification(s), if applicable
- A clean and tracked changes copy of the revised consent form, if applicable
- New study materials
- A clean and tracked changes copy of the revised study material(s), if applicable

Modification Turnaround Time

- Minor Modifications: 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: Major modifications require full board review and investigators will receive correspondence from the IRB within approximately 5 working days of the scheduled meeting.

IRB Review Fee for Modifications

Substantial modifications to research which require review, (such as protocol amendments, revised protocols, updates to consent forms) may incur a review fee, which covers the cost associated with reviewing the materials and the related administrative responsibilities of preparing review documents. The Christ Hospital IRB only charge this fee for industry-sponsored research. Please contact the IRB Office for the current IRB Fee Schedule.

CONTINUING REVIEW OF RESEARCH AND STATUS UPDATES

TCH IRB is responsible for Continuing Review of ongoing research to ensure that the rights, safety, and wellbeing of human subjects are protected. However, certain applicable expedited studies approved on or after January 21, 2019 that are not subject to FDA regulation no longer require Continuing Review due to changes associated with the revised 2018 Common Rule. While Continuing Review is no longer mandatory for these research studies, TCH IRB requires the PI to submit a Status Update for the study. Biennial Status Updates are required for research in which TCH IRB serves as the IRB

of Record. Annual Status Updates are required for research in which TCH relies on an external IRB (Reliance Agreements).

Review Periods

Research ***requiring*** Continuing Review in which TCH IRB provides oversight (IRB of Record)

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 IRB SOP 1.01 "*Continuing Review"*). For ease of tracking, the expiration date of applicable studies is set for the first day of the month of the year following the date that approval was granted (i.e., if approval is granted on June 14, 2026, the expiration date will fall on June 1, 2027). The expiration date will be noted on the letter of approval and on subsequent Continuing Review approval letters. The expiration date is the first date that the protocol is no longer approved. TCH IRB also indicates in the letter of approval (on both initial and Continuing Review approval whether the study requires review more often than annually and whether the study requires verification from sources other than the investigator that no material changes have occurred since the previous TCH IRB review (ref. 45 CFR 46.108(a)(3)(ii); 21 CFR 56.108(a)(2)).

Research ***not requiring*** Continuing Review in which TCH IRB provides oversight (IRB of Record)

Research that presents no more than minimal risk to the participants and does not require full IRB Committee review is eligible for Expedited Review. Examples include blood draws within certain allowable volumes or non-invasive collection of biological specimens, such as a saliva swab. Expedited studies that are not subject to FDA regulation, approved on or after January 21, 2019, do not require Continuing Review. However, in certain circumstances, the IRB may determine it necessary to require Continuing Review of some research and will document the rationale for the decision to conduct Continuing Review using the expedited procedure.

When Continuing Review is not required, the IRB has implemented a brief "Study Status Update" process to ascertain the status of each protocol that does not require formal Continuing Review to verify that no unapproved changes or unreported problems have occurred. The status check occurs biennially (every two years). Researchers receive notification of an upcoming status check in advance of the biennial period end-date. At the time of initial review, The Christ Hospital IRB sets an expiration date in the Mentor IRB system for two years following the date of approval for each approved study (see IRB SOP 1.01 "*Continuing Review*"). For ease of tracking, this expiration date is set for the first day of the month that falls two years following the year that approval was granted (i.e., if approval is granted on January 9, 2026, the expiration date will fall on January 1, 2028). The expiration date is noted as the "Next Check-In Date" on the letter of approval and on subsequent Status Update approval letters. A grace period may be given on a case-by-case basis for these research studies.

Research Exempted by TCH IRB

Research determined to meet the criteria for exemption from IRB review in accordance with federal regulations, does not require continuing review; however, the IRB requires a formal notification of study closure once all research activities—including data analysis and destruction of identifiers—are complete.

Upon exemption, TCH IRB Office sets an expiration date in the Mentor IRB system for three years following the date of exemption. For ease of tracking, this expiration date is set for the first day of the month that falls two years following the year that approval was granted (i.e., if exemption is granted on January 9, 2026, the expiration date will fall on January 1, 2029). The expiration date is noted as the "Next Check-In Date" on the letter of exemption.

Prior to the expiration date, the researcher should either submit a closure request in Mentor IRB or contact the IRB Office for an extension.

Research in which TCH relies on an **External IRB** for oversight

For research in which The Christ Hospital relies on an External IRB for oversight, TCH IRB has implemented a brief "**Study Status Update**" process to ascertain the status of each protocol to:

- verify that the research still maintains IRB approval
- verify that no unapproved changes or unreported problems have occurred
- ensure there have been no changes to any key research personnel's financial conflict of interest (FCOI) disclosures, and
- ensure all key research personnel remain current on their required CITI training.

This status check occurs annually. Researchers receive notification of an upcoming status check in advance of the annual period end-date. At the time of initial review, The Christ Hospital IRB sets an expiration date in the Mentor IRB system that falls approximately six weeks after the expiration date provided on the external IRB approval letter. For ease of tracking, this expiration date is set for the first day of the month that occurs approximately six weeks after the approval period (i.e., expiration date on external IRB letter is January 15, 2026, the expiration date will fall on March 1, 2027). The expiration date is noted as the "Next Check-In Date" on the letter of approval and on subsequent Status Update approval letters. A grace period may be given on a case-by-case basis for these research studies.

Submission Requirements for Continuing Review and Status Updates

Prior to the deadline, the request for continuation must be submitted in Mentor IRB under the *Cont Rev* or *Status Update* submissions tab on the main protocol page of the study. All key personnel on sponsored/funded research must have a current Annual Financial Conflict of Interest (FCOI) Disclosure Form on file with the IRB.

Process for Continuing Review

Purpose: The purpose of Continuing Review is to review the progress of the entire study, not solely the modifications, for research in which TCH IRB serves as the **IRB of Record**.

For FDA-regulated studies and all studies subject to the pre-2018 Common Rule Requirements, Continuing Review may not be conducted through an expedited review process unless:

- the study was eligible for and initially reviewed by an expedited review procedure, or
- the research is closed to enrollment of new subjects, all subjects have completed all research related interventions, and collection and analysis of private identifiable information has been completed.

For research that is subject to the revised Common Rule, unless the IRB determines otherwise, Continuing Review is not required in the following circumstances:

- Research eligible for expedited review in accordance with 45 CFR 46.110
- Research reviewed by the IRB in accordance with the limited IRB review in accordance with 45 CFR 46.109(a)
- Research reviewed by the IRB in accordance with the limited IRB review described in 45 CFR 46.111(a)(7).
- Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
    - Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
    - Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

Refer to IRB SOP 1.01 "*Continuing Review*" and SOP 1.17 "*Expedited Review*" for more details.

Criteria for Approved Research

Federal and FDA regulations establish the criteria for TCH IRB approved research (ref. 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 the data collected to ensure safety and privacy of subjects and confidentiality of the data
- When appropriate, additional safeguards have been included to protect vulnerable subjects

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, 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 review report.

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 meet criteria for a one-year review cycle, the IRB issues the expiration date for the first day of the month of the following year that approval was granted.

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 January 9, 2026. Continuing Review must occur within 1 year of the date of the meeting and the expiration date is set for January 1, 2027 to allow it to be reviewed by the monthly convened IRB meeting that occurs in December 2026.

Scenario 2: The IRB reviews a protocol at a convened meeting on January 9, 2026 and approves the protocol contingent on minor modifications the IRB Chair or his/her designee can verify. On January 15, 2026, the IRB Chair or designee approves the required minor modifications. 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 January 1, 2027.

Scenario 3: The IRB reviews a study at a convened meeting on January 9, 2026 and has serious concerns, or lacks significant information, that required subsequent IRB review of the study at the convened meeting on February 13, 2026. At the February 13, 2026 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 February 13, 2026, and the expiration date is set for February 1, 2027 to allow it to be reviewed by the monthly convened IRB meeting that occurs in January 2027.

PI Responsibility: The PI is responsible for prompt reporting to the IRB. This includes Continuing Review reports by the stated date in the approval letter. Mentor IRB will send a courtesy reminder 4 weeks before the submission deadline date. A Continuing Review submission must be submitted into Mentor IRB by the due date indicated (three weeks

prior to the convened IRB meeting scheduled immediately preceding the approval expiration date) to allow adequate IRB review at the next regularly scheduled meeting. This form must be submitted until a study closure request has been submitted into Mentor IRB (see SOP 2.07 "*Notice of Study Closure" for more details*). Mentor IRB sends notifications to the PI and research coordinators if the submission has not been submitted by the due date. The IRB Office also will follow up with a phone call and/or email message.

Scenario: A study has an expiration date of 10/01/2026. This study must be reviewed by the full board at the September convened IRB meeting. The deadline for submission of the report to the IRB is 3 weeks prior to the meeting date in August 2026.

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 study expiration letter is generated through Mentor IRB and will be sent to the PI and any research coordinators. 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. 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.

Expedited Review: TCH IRB uses the expedited review procedure to review (1) some or all research studies appearing on the list in Section 2.3 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 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.

Full Board Review: Each Continuing Review report (non-expedited) will be presented to the 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.

Process for Status Updates for research in which TCH IRB provides oversight (IRB of Record) that does not require Continuing Review

Purpose: Study Status Updates serve multiple functions. They ensure that the institution is aware of all research that is currently ongoing within the institution. It also allows a

mechanism for study-specific FCOI disclosures and review of investigator and research personnel training requirements (i.e., CITI HSR and GCP training). Status Updates are submitted through Mentor IRB and have been designed to collect a very limited amount of information from the study team. The completed biennial status report must be received by the due date. If the researcher does not submit a Status Update, the IRB may consider this noncompliance. The Status Update is reviewed and approved through the expedited mechanism by the IRB Chair or experienced person delegated by the Chair to review from TCH IRB.

Frequency/Extent: Status Updates occur biennially. The Next Check-In Date is indicated in the approval letter. The Next Check-in Date serves as the expiration date in Mentor IRB.

Determining Next Check-In Date: The IRB issues the Next Check-In Date for the first day of the month two years after that approval was granted. The due date for submission is four weeks prior to the Next Check-In Date.

Example: The IRB Chair or designee reviews and approves the Status Update on June 8, 2026. The next study Status Update Check-In Date is June 1, 2027. The due date for the Status Update is May 1, 2027.

PI Responsibility: The PI is responsible for prompt reporting to the IRB. This includes Status Updates by the stated date in the approval letter. Mentor IRB will send a courtesy reminder 2 weeks before the due date. A Status Update submission must be submitted into Mentor IRB by the due date indicated to allow adequate time for review. Status Updates must be submitted annually until a study closure request has been submitted through Mentor IRB. Mentor IRB sends notifications to the PI and research coordinators if the submission has not been submitted by the due date. The IRB Office also will follow up with a phone call and/or email message.

Study Expiration: If TCH IRB has not received, reviewed, and approved a research study by the study's current expiration date in Mentor IRB, the IRB is authorized to suspend or terminate the research. A notice of study expiration will be sent to the PI and any research coordinators through Mentor IRB. The IRB may extend a grace period on a case-by-case basis.

Process for Status Updates for research with a Reliance Agreement in which TCH relies on an external IRB for oversight

Purpose: Study Status Updates serve multiple functions. They ensure the institution is aware of all research that is currently ongoing within the institution. This update also (1) verifies that the research still maintains IRB approval, (2) verifies that no unapproved changes or unreported problems have occurred, (3) ensures there have been no changes to investigator FCOI disclosures, and (4) ensures all key research personnel remain current on their required CITI training. These Status Updates are submitted via the Mentor IRB system and have been designed to collect a very limited amount of information from the study team. The IRB requests that the current re-approval letter, consent form(s) and

protocols are submitted into the Mentor system at the time of the Status Update. The completed annual status report must be received by the due date. If the researcher does not submit a Status Update, the IRB may consider this noncompliance. The Status Update is reviewed and approved through the expedited mechanism by the IRB Chair or experienced person delegated by the Chair to review from TCH IRB.

See SOP 1.01 *"Continuing Review"* and 1.17 "*Expedited Review"* for more details.

At the time of initial review, The Christ Hospital IRB sets an expiration date in the Mentor IRB system. For ease of tracking, this expiration date is set for the first day of the month that occurs approximately six weeks after the approval period (i.e., expiration date on external IRB letter is January 15, 2026, the expiration date will fall on March 1, 2027). The expiration date is noted as the "Next Check-In Date" on the letter of approval and on subsequent Status Update approval letters. A grace period may be given on a case-by-case basis for these research studies.

Frequency/Extent: Status Updates occur annually. The Next Check-In Date is indicated in the approval letter. The Next Check-in Date serves as the expiration date in Mentor IRB.

Determining Next Check-In Date: The IRB issues the Next Check-In Date for approximately six weeks after the expiration date provided on the external IRB approval letter for the first day of the month of the following year that approval was granted. The due date for submission is four weeks prior to the Next Check-In Date.

Example: The IRB Chair or designee reviews and approves the Status Update on February 8, 2026. The study expiration date provided on the external IRB approval letter is January 15, 2027. The Next Check-In Date/expiration date in Mentor IRB will fall on March 1, 2027. The Next Check-In Due Date is February 1, 2027.

PI Responsibility: The PI is responsible for prompt reporting to the IRB. This includes Status Updates by the stated date in the approval letter. Mentor IRB will send a courtesy reminder 2 weeks before the due date. A Status Update submission must be submitted into Mentor IRB by the due date indicated to allow adequate time for review. Status Updates must be submitted annually until a study closure request has been submitted into Mentor IRB (see SOP 2.07 *Study Closure*). Mentor IRB sends notifications to the PI and research coordinators if the submission has not been submitted by the due date. The IRB Office also will follow up with a phone call and/or email message.

Study Expiration: If TCH IRB has not received, reviewed, and approved a research study by the study's current expiration date in Mentor IRB, the IRB is authorized to suspend or terminate the research. A notice of study expiration will be sent to the PI and any research coordinators through Mentor IRB. The IRB may extend a grace period on a case-by-case basis.

Reporting Unanticipated Problems Involving Risks to Human Subjects

Federal and FDA regulations at 45 CFR 46.108(a)(4)(i) and 21 CFR 56.108(b)(1) 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 08. See SOP 2.05 "*Reporting Unanticipated Problems (UAPs) Involving Risks to Subjects or Others"* for reporting requirements.

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. The term "violation," 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 yet should be documented in the study file to be reviewed at specific intervals by the PI to determine if it constitutes continuing non-compliance and becomes reportable. Protocol violations must be reported to the IRB in Mentor IRB in the Reportable Event tab. See SOP 3.09 "*Protocol Violation, Deviation, and Non-Compliance Reporting"* for more details.

Research Protocol Suspension or Termination (Study Closure)

TCH IRB considers a study open until a study closure report is received in Mentor IRB. A report may be submitted when all the criteria meeting the definition of "Study Closure" below have been met.

Definitions

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

Sponsor/Investigator-Initiated Suspension: This 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.

Sponsor/Investigator-Initiated Termination/Closure: This 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 subjects research that, in the judgment of TCH IRB,

seriously compromises human research subjects protection or the integrity of TCH IRB's human research protection program. Examples of serious non-compliance include, but are not limited to:

- Performing non-exempt human subject research without obtaining TCH IRB approval
- Failing to obtain TCH IRB approval of substantial modifications implemented in a TCH IRB-approved research study
- Failing to systematically obtain the required written or, when previously approved by TCH IRB, verbal informed consent of research subjects
- Material failure of TCH IRB (including TCH IRB Office staff) to comply with federal regulations governing human subject protections

Study Closure: Study Closure is defined by TCH IRB as *all* the following having been accomplished:

- All participants have finished all protocol related interventions, interactions, final visits and follow-up; and
- The sponsor or its representative has indicated closure at the research site,
- If the study was conducted under a Federal Wide Assurance, all data analysis at the site is completed.

IRB-Initiated Suspension or Termination of a Research Protocol

The IRB has the authority to suspend or terminate 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. Suspension or termination of IRB approval initiated by the IRB shall be reported to the Institutional Official and Department Chair 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.

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

Suspension or termination 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 receipt of the sponsor suspension/termination notice) to the IRB Office and in Mentor IRB if the suspension/termination 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). Suspension/termination of a research study for other reasons (e.g., administrative) shall be reported in Mentor IRB within 10 working days of receipt of the suspension/termination notice. IRB notification shall include:

- The reason for study suspension or termination (e.g., subject accrual complete and data analyzed; demonstrated absence of benefit based on interim data analysis; serious adverse event)
- 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 enrolled subject
- A description of the procedures that will be used to notify active participants of the study suspension/termination; the procedures that will be undertaken to ensure their orderly and safe withdrawal from the study; follow-up care, if applicable
- A description of the procedures that will be used to notify participants who previously participated in the study of the study suspension/termination, if determined to be important to their rights or welfare

For terminated research protocols, a study closure should be requested in Mentor IRB within 10 working days of notification of closure by the sponsor. This request will be reviewed and acknowledged by the IRB Chair or Designee. The acknowledgment will be documented in the protocol record and assigned to the Expedited/Exempt Report for review, consideration, discussion, and acknowledgment by the convened IRB. The PI and any research coordinators will receive an acknowledgment notification through Mentor IRB after chair review.

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:

- The outcome of investigations on the causality of the serious adverse event(s)
- The frequency of occurrence of the serious adverse event(s) at TCH IRB or external sites, if applicable
- Modification of the protocol and consent form to address the serious adverse event(s)

Research Protocol Suspension or Termination - Human Research Subject Notification and Withdrawal

Human subjects currently participating in a research study must be notified of its suspension or termination due to safety issues and/or other problems (e.g., unanticipated problems, failure to obtain continuing IRB approval, investigator non-compliance) and the reasons, thereof. 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, 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.

IRB Record Retention Following Study Termination

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

See SOP 2.07 "*Study Closure"* for more details.

Study Audits

The IRB conducts audits of research studies annually. A minimum of two audits will be performed annually. Refer to SOP 1.09 **"***Quality Improvement Activities in Human Research Protection/Audits"* for more details.

Selection of Studies to Review

Research studies will be chosen for Quality Assurance (QA)/Quality Improvement (QI) review primarily from among studies meeting one or all the following characteristics:

- Does not receive study monitoring by the study sponsor or another organization
- Presents greater than minimal risk to participants
- Involves investigator-initiated research
- Enrolls vulnerable populations, including TCH employees and students, cognitively impaired participants, pregnant women/fetuses/neonates and children
- Has potential for conflict of interest
- Are requested by the IRB or institutional official

Section 3 Regulatory History
Effective Date: 12/06
Revised/Reviewed Date: 05/26
AAHRPP Element: II.2.E.2, II.2.E.3, II.2.F.2, II.2.F.3, II.2.G, II.2.H

SECTION 04 – INVESTIGATOR COMMUNICATIONS

IRB Submissions

The IRB utilizes a web-based IRB management system, Mentor IRB, for all submissions. Mentor IRB can be accessed through the following links:

TCH SSO Users: https://www.axiommentor.com/login/shibLogin.cfm?i=thechristhospital
External Users: https://www.axiommentor.com/login/axlogin.cfm

IRB Office Communications

Investigators and research staff with active TCHHN credentials may log in using their single sign-on (SSO) credentials. The IRB Office can be reached for questions or consultation by any of the following:

Email:	IRB_Office@thechristhospital.com
Telephone:	(513) 585-2298
Fax:	(513) 585-2107
In Writing:	The Christ Hospital IRB Office 2139 Auburn Ave., Room 3140 (3 North) Cincinnati, OH 45219

Written Communications of IRB Decisions

Decisions of the IRB will be communicated to the Principal Investigator (PI) and research coordinator through Mentor IRB in a notification letter outlining the approval status and/or the concerns, questions and/or comments of the IRB. Decisions from a full board meeting will be available the day following the meeting via verbal communication; however, written communications are not released until meeting minutes are reviewed and approved by the IRB chair. Written communication typically necessitates a period of three (3) working days from the IRB meeting date. **Initiation of the research study may not proceed until a written notification of final IRB approval has been received from the IRB office.**

Decisions of the IRB fall into one of the following categories:

Full Approval

The Principal Investigator may initiate the study upon written notification of full approval of the research protocol and (if applicable) the informed consent document by the IRB chair.

Approval with Minor Modifications

The Approval with Minor Modifications decision is conveyed when the protocol is recommended for approval by the IRB pending the investigator's response to IRB-directed changes. The PI must provide a response to the IRB's recommendations in

Mentor IRB including any modified protocol and/or consent forms with the respective changes tracked. The response will be reviewed by the IRB chair or his/her designee. If the response is acceptable, the PI will receive written notification of IRB approval and may then initiate the study. Such notification is typically received within 5-7 working days following receipt of the PI's response to the IRB's recommendations by the IRB Office. The date of approval is the date the modifications are determined to be met. If the research expires before the modifications are reviewed and approved, all research activities must stop until approval is obtained.

Approval Withheld Pending Major Clarifications and/or Modifications

When the IRB requests any additional information, clarifications or modifications which cannot be described as specific revisions requiring simple concurrence by the investigator, the investigator is sent a letter which includes a description of such revisions or clarifications requested by the IRB. For some studies, one or more members of the IRB may be designated to discuss reasons for the requests with the investigator. The convened IRB must then review the responsive materials subsequently submitted in Mentor IRB by the PI, or by the research coordinator on the PI's behalf. If the convened IRB approves the research based on the responsive materials, the approval date is issued as of the date of the IRB meeting in which the study was approved.

Tabled

This decision is made when the IRB has significant questions and concerns regarding the research protocol which could not be resolved at the IRB meeting. The Principal Investigator may not initiate the study until a response is received, and the protocol reviewed at a subsequent full board meeting. The Principal Investigator must respond to the IRB's concerns/comments, recommendations and/or questions in Mentor IRB. If the protocol and/or consent form is modified, the changes must be tracked. Unless otherwise requested by the Principal Investigator (e.g., timeframe necessitates review prior to next scheduled meeting), the reconsideration response will be scheduled for review by the full board committee that originally reviewed the research protocol. The Principal Investigator or designee may request to be present at the IRB convened meeting wherein his/her research protocol is being reconsidered for approval. If approval is granted after the reconsideration, the approval date will be the date of the IRB meeting during which the study was reconsidered (not the date of the meeting where the study was originally reviewed).

Disapproval

The IRB may disapprove a research protocol based on its identification of major scientific or ethical problems which, in the committee's opinion, cannot be readily resolved by the Principal Investigator. When a research protocol is disapproved by the IRB, the Principal Investigator is not authorized to initiate the study. In the case of IRB disapproval, a statement detailing reasons for the decision, as well as an opportunity for the investigator to respond in title of person or in writing, is provided through Mentor IRB. The Principal

Investigator can respond to the IRB's concerns/comments, recommendations and/or questions in Mentor IRB. If the protocol and/or consent form is modified, the changes must be tracked. Unless otherwise requested by the Principal Investigator (e.g., timeframe necessitates review prior to next scheduled meeting), the reconsideration response will be scheduled for review by the full board committee that originally reviewed the research protocol. The Principal Investigator or designee may request to be present at the IRB convened meeting wherein his/her research protocol is being reconsidered for approval. If approval is granted after the reconsideration, the approval date will be the date of the IRB meeting during which the study was reconsidered (not the date of the meeting where the study was originally reviewed).

Section 4 Regulatory History
Effective Date: 01/07
Revised/Reviewed Date: 04/26
AAHRPP Element: II.2.E, II.5.B

SECTION 05 - RECRUITMENT OF RESEARCH SUBJECTS

The Christ Hospital IRB is responsible for reviewing study recruitment procedures and materials to ensure protection of the rights and welfare of human subjects and equitable subject selection into research. Any method of advertisement must be approved by the IRB before it is implemented. All advertisements must align with subject selection and informed consent regulations pursuant to 45 CFR 46.111 and CFR 46.116.

Investigators must submit recruitment materials, as they will be implemented, to the IRB for review along with the initial protocol submission or as an amendment for review through an expedited mechanism.

All advertisements must not be coercive, must not promise a possibility of benefit beyond what is outlined in the consent and the protocol, must portray accurate information, and must direct potential subjects to appropriate personnel for further information. This is particularly important when a study involves subjects who may be vulnerable to undue influence.

Refer to IRB SOP 2.10 "*Recruitment of Subjects in Research"* for more information.

Recruitment Materials and IRB Approval

Types of Advertisements and Recruitment Materials Requiring IRB Approval:

- Printed materials (i.e., newspaper, posters, flyers, pamphlets)
- Direct recruitment scripts (e.g., telephone scripts)
- Audio and video recruitment materials (scripts may be accepted)
- National ad campaigns
- Internet advertising (postings on federally maintained sites such as clinicaltrials.gov do not need prior IRB approval)

Types of items NOT requiring IRB approval:

- Communication to be seen or heard by health professionals (e.g., letters from physician to physician)
- News stories
- Publicity intended for other offices

Content of Recruitment Materials

Recruitment materials SHOULD include:

- Name and location of the institution and center/department conducting the research

- Name of PI or department, if appropriate
- The word “research”
- Statement or condition under study and brief description of the purpose of the research
- Brief list of the procedures involved
- Brief summary of the eligibility criteria
- Statement of approximate time commitment required, if appropriate
- Brief description of the compensation/reimbursement
- Contact for further information including telephone number

Recruitment materials should NOT include:

- Any language that would contribute to therapeutic misconception (research subject’s belief that enrolling in study will contribute to direct therapeutic benefit)
- Claims about the efficacy, safety or superiority of an investigational agent
- Claims about the security of confidential information
- Enticing or inducing terms such as “free,” “new,” “exciting,” “opportunity,” “limited opportunity,” or “you deserve to feel better”
- Inducing phrases such as “limited enrollment,” “call today” or “study ends soon”
- Overemphasis on compensation; should not emphasize the payment or the amount to be paid by such means as larger or bold type. If the payments will be prorated, the ad should make this clear. For example, instead of stating “$300 compensation,” the ad should state that subjects will receive $50 for each of six completed visits.
- Links to sites/resources that are not IRB approved

Telephone Communications to Potential Subjects

Initiating telephone contact with the subject based on knowledge of confidential information (e.g., medical record information) regarding the subject and without prior introduction to the subject is prohibited by the IRB.

The investigator should NOT contact the patients of any particular clinic, physician, or other caregiver unless the patient’s physician or caregiver has previously notified the potential research subject (or the parent or Legally Authorized Representative of the potential research subject) and obtained his/her approval for such contact. This notification may be either verbal or in the form of a letter of introduction.

The investigator should NOT contact, based on knowledge of confidential information, the members of any community-, work-, school-, trade- or union-based program unless a program representative has previously notified the potential research subject (or the parent or Legally Authorized Representative of the potential research subject) and obtained his/her approval for such contact. This notification may be either verbal or in the form of a letter of introduction.

Internet Listings of Clinical Trials

IRB review and approval of listings of clinical trials on the internet would provide no additional safeguard and is not required when the system format limits the information

provided to basic trial information such as the study title, purpose of the study, protocol summary, basic eligibility criteria, study site location(s), and how to contact the site for further information. Examples of clinical trial listing services that do not require prospective IRB approval include the U.S. National Library of Medicine's database, ClinicalTrials.gov, the National Cancer Institute's cancer clinical trial listing (PDQ), and the government-sponsored AIDS Clinical Trials Information Service (ACTIS). However, when the opportunity to add additional descriptive information is not precluded by the database system, IRB review and approval may assure that the additional information does not promise or imply a certainty of cure or other benefit beyond what is contained in the protocol and the informed consent document.

Screening Tests and Interviews Prior to Subject Enrollment

Screening procedures (including interviews) that are performed solely for the purpose of determining eligibility for participation in a research protocol are subject to IRB oversight including the requirement for written informed consent. With respect to screening interviews/surveys, written informed consent must be obtained prior to conducting the interview/survey if (1) the interview/survey is being performed for research purposes, (2) the individual's responses to the interview/survey could place him/her at risk of civil or criminal liability or be potentially damaging to his/her employability or reputation, and (3) subject identifiers are recorded with the interview/survey responses.

Incentives for Participation in Research Studies

Subjects may be paid or otherwise rewarded for their time and inconvenience associated with participation in a research study. Remuneration of human research subjects is not, however, considered a benefit; it is a recruitment incentive. Financial or other incentives are frequently used when the benefit of study participation is remote or non-existent.

The amount of payment, if any, should be reasonable based on the complexities and inconveniences of the study, and the subject population. The amount of payment should NOT be based on the risk of study participation.

The amount of payment or reward and the proposed method and timing of its disbursement must not be coercive or present undue influence over initial or continued participation in the study.

It is acceptable for students to be offered course credits for their participation in a research study. However, the student must be provided with alternate, equitable ways to earn the credits if they decide not to participate in the research study.

IRB Review and Approval of Incentives for Participation in Research Studies

Information concerning the remuneration of human research subjects, including the amount of payment or nature of the reward, and the schedule of its disbursement is subject to initial and continuing review by the IRB. This information should appear in the Compensation and Reimbursement section of the application in Mentor IRB, as well as any informed consent document(s). It should not be included as a benefit of study participation.

Payment Disbursement Guidelines

Any payment or reward should accrue as the study progresses and not be contingent upon the human research subject completing the entire study. Disbursement of a proportion of the total payment or reward contingent upon study completion is acceptable, provided that the amount of this incentive is not so large as to unduly induce subjects to remain in the study when they might otherwise withdraw voluntarily.

Community-Based Participatory Research (CBPR) Considerations

Community-based participatory research (CBPR) is a collaborative approach to research involving stakeholders outside of academic research organizations, equitably involving all partners in the research process and recognizing the unique strengths that each may bring. CBPR can be advantageous in that contact with community members may raise participation rates. Engaging with the community early in the process can also promote trust in the research study and may help facilitate successful recruitment.

However, CBPR also presents distinct challenges not addressed in traditional research paradigms. Community residents participating in the full spectrum of the research, including recruitment of potential research subjects, raises issues of privacy and confidentiality requiring additional considerations. Such considerations include acknowledging, evaluating, and minimizing any foreseeable risks to potential research subjects, especially when community members serving as researchers or staff may be recruiting or otherwise interacting with potential subjects they may know or may be familiar with.

Issues surrounding privacy and confidentiality may include:

- Community members participating in recruitment may be friends or neighbors of those approached in the recruiting process.
- Participants' willingness to reveal information, particularly if that information is sensitive or stigmatizing, may create the potential to inadvertently and unknowingly impact the quality of data collection.
- Study recruitment that occurs in community settings such as meeting halls and libraries may experience increased risk when such recruitment includes postings that proclaim the intent of the meeting and/or sensitive topics.

Investigators working with a community-member research team should identify such risks as noted above, and other potential issues (e.g., literacy, language barriers, local or cultural beliefs and attitudes) which the community-member researcher may not have considered.

Institutional Review Board

The IRB provides guidance for investigators on identifying relevant community members for research studies. Guidance may also be provided via consultation with the IRB office/chairman, specific to the individual research study and

resources available through The Christ Hospital Health Network (ref. IRB SOP 1.14 "*Community Outreach on Human Subjects Research"*).

When evaluating the recruitment process in a CBPR study, the IRB (to the extent feasible and allowable) shall consider risk of harm for both individuals *and* the community. For additional information, see Section 02 *IRB Review of Proposed Research Studies*.

Section 05 Regulatory History
Effective Date: 02/07
Revised/Reviewed Date: 04/26
AAHRPP Element: I.4.C, II.3.C, II.4.A, III.1.E

SECTION 06 - VULNERABLE POPULATIONS

The Christ Hospital IRB (TCH IRB) shall apply additional protections as necessary to protect research participants who could potentially be vulnerable to coercion in regard to autonomy, present conditions that may affect risk/benefit determinations, or bear unequal burden in the research. Not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. The extent of additional protection afforded should depend upon the risk of harm and the likelihood of benefit conferred by the research. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations. In addition, when an IRB regularly reviews research involving a vulnerable population, consideration will be given to the inclusion of one or more IRB member(s) knowledgeable about and experienced in working with these research participants to be present at the meeting. The IRB chair may defer the review to another IRB or obtain consultation if there is not appropriate scientific or representational expertise represented on the board.

Groups or individuals recognized under federal law as having diminished autonomy entitling them to additional protection include: minors, prisoners, and pregnant women, fetuses and neonates. Although The Christ Hospital does not engage in research involving prisoners, there may be situations where a research participant becomes a prisoner after enrollment in a research study. Refer here for information on the unexpected incarceration of a research participant.

References: The Belmont Report, 45 CFR 46.111(b), 21 CFR 56.111(b), 45 CFR 46 Subpart B, 45 CFR 46 Subpart C and 45 CFR 46 Subpart D

Pregnant women, fetuses and in-vitro fertilization: additional requirements for participation in research

Definitions

1. *Fetus*: Product of conception from implantation until delivery
2. *Dead fetus*: Fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement
3. of voluntary muscles, nor pulsation of the umbilical cord
4. *Delivery*: Complete separation of the fetus from the woman by expulsion or extraction or any other means
5. *Neonate*: Newborn
6. *Viable*: As pertaining to the neonate, being able to, after delivery, survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration

7. *Nonviable neonate*: A neonate after delivery that, although living, is not viable
8. *Pregnancy*: encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery

Pregnant women and fetuses (45 CFR 46.204, Subpart B) – General Requirements

Pregnant women or fetuses may be involved in research only if all the following conditions are met:

1. Where scientifically appropriate, preclinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.
2. The risk to fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.
3. Any risk is the least possible for achieving the objectives of the research.
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of the pre-2018 Requirements or the 2018 Requirements, as applicable.
5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of the pre-2018 Requirements or the 2018 Requirements, as applicable, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Each individual providing consent under (d) or (e) above shall be fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
7. For children as defined in 45 CFR 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part.
8. No inducements, monetary or otherwise, shall be offered to terminate the pregnancy.
9. Individuals engaged in the research shall have no part in any decisions as to the timing, method or procedures used to terminate a pregnancy.
10. Individuals engaged in the research shall have no part determining the viability of the neonate.
11. The informed consent of the pregnant woman shall be obtained in accord with the standard regulatory provisions for informed consent if the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit to both the pregnant woman and the fetus, or no prospect of direct benefit for the

pregnant woman nor fetus when the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means. (Ref. 45 CF 46.204(b))

12. The informed consent of the pregnant woman and the father shall be obtained in accord with the standard regulatory provisions for informed consent if the research holds out the prospect of direct benefit solely to the fetus; except the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity, or if the pregnancy resulted from rape or incest. (Ref. 45 CF 46.204 (e))

Neonates (45 CFR 46.205, Subpart B) – General Requirements

1. Neonates of uncertain viability and nonviable neonates may be involved in research only if all the following conditions are met:
    a. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
    b. Each individual providing consent (see 3(c) and #5 below) is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
    c. Individuals engaged in the research will have no part in determining the viability of the neonate.
    d. The requirements outlined under this section, items (b.) and (c.) below, have been met, as applicable.
2. Requirements for research involving neonates of uncertain viability: Until it has been determined whether or not a neonate is viable, a neonate may not be involved in research unless the following additional conditions are met:
3. The IRB determines that:
    a. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving the objectives of the research, or
    b. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
    c. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with the standard regulatory provisions for informed consent; except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. (NOTE: For research involving viable neonates, the IRB is permitted to grant a waiver or alteration of such informed consent in accord with applicable regulatory provisions.)

Nonviable neonates – General Requirements

A nonviable neonate may not be involved in research unless all the following additional conditions are met:

1. Vital functions of the neonate will not be artificially maintained.
2. The research will not terminate the heartbeat or respiration of the neonate.
3. There will be no added risk to the neonate resulting from the research.
4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.
5. The legally effective informed consent of both parents of the neonate is obtained in accord with the standard regulatory provisions for informed consent. However, the IRB is not permitted to grant a waiver or alteration of such informed consent for (1) research involving nonviable neonates, and (2) the consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph. If either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph; except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest.

Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

Research involving, after delivery, the placenta, the dead fetus or fetal material (45 CFR 46.206, Subpart B) – General Requirements

1. Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus shall be conducted only in accord with any applicable Federal, State, or local laws and regulations regarding such activities.
2. If information associated with the dead fetus; macerated fetal material; or cells, tissue or organs excised from a dead fetus is recorded in such a manner that living individuals (e.g., the parent(s)) can be identified, directly or through identifiers linked to such individuals, those individuals are “human subjects” of the research study and the requirement for their informed consent applies.

Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates (45 CFR 46.207, Subpart B) – General Requirements

Research that does not meet the preceding general requirements as outlined in the three (1, 2, and 3) sections above may be approved only if:

- The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and welfare of pregnant women, fetuses or neonates; and
- The Secretary, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the Federal Register, has determined either:

- The research in fact satisfies the conditions as outlined in the three (1, 2, and 3) sections above, as applicable, or
- All of the following:
  - The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates;
  - The research will be conducted in accord with sound ethical principles; and
  - Informed consent will be obtained in accord with the standard regulatory provisions for informed consent unless the IRB has approved a waiver or alteration of the standard informed consent requirements.

Refer to IRB SOP 3.17 "*Additional Safeguards for Pregnant Women and Fetuses and Neonates in Research"* for more details.

Unexpected Incarceration of a Research Participant

The Christ Hospital does not engage in research involving prisoners. However, it may happen that an individual becomes incarcerated while enrolled in a research study. Upon discovery of a participant's incarceration, the all-research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must cease.

The principal investigator (PI), or designee, must immediately provide written notification to the IRB regarding the incarceration. The notification should include an assessment of whether continuing in the study would be in the best interests of the prisoner-participant, and the PI's plans for either continuation or cessation of the intervention during the participant's incarceration.

If the participant is incarcerated temporarily, and the temporary incarceration may affect the prisoner-participant's health or safety, the principal investigator must assess risks to the prisoner-participant resulting from cessation of the research intervention during the temporary incarceration and may consider requesting temporary continuation of the intervention.

If research activities are curtailed during the research participant's incarceration, meaning no interaction or intervention with, nor obtaining data from the participant while incarcerated, the participant does not have to be formally withdrawn as Subpart C is not invoked. Research activities may resume when the participant is no longer incarcerated.

If the investigator solicits or obtains information from the incarcerated participant's parents or spouse, rather than the incarcerated participant, for information regarding the participant's behavior and attitudes about the research project, such activity would constitute "obtaining identifiable private information about" the incarcerated participant, and this would invoke subpart C, and therefore require review and approval from the IRB.

If an investigator determines that temporary continued intervention is in the best interests of the incarcerated participant, the convened IRB, in consultation with a legal representative from the hospital's Risk Management Department, will review the submitted amendment in accordance with the requirements of 45 CFR 46, Subpart C, to ensure that the rights and wellbeing of the now-incarcerated participant are not in jeopardy. The Committee should take special consideration of the conditions of being a prisoner as set forth in. Upon this review, the IRB can either a) approve the involvement of the prisoner-subject in the research in accordance with this policy or b) determine that this subject must be withdrawn from the research. Additionally, the IRB should confirm that, when appropriate, the informed consent process includes information regarding when subsequent incarceration may result in termination of the subject's participation by the investigator without regard to the subject's consent.

Refer to IRB SOP 3.23 "*Unexpected Incarceration of a Research Participant*" for more details.

Adults with impaired decision-making capacity

Decisionally impaired adults are individuals who have a diminished capacity for judgment and reasoning due to a psychiatric, organic, developmental, or other disorder that affects cognitive or emotional functions. Other individuals may be considered decisionally impaired or have limited decision-making ability because they are under the influence of or dependent on drugs or alcohol, suffering from degenerative diseases affecting the brain, are terminally ill or have severely disabling physical handicaps.

There are no regulations specific to research involving adults with impaired decision-making capacity. The IRB takes special care to consider issues such as the selection of participants, privacy and confidentiality, coercion and undue influence, and risk-benefit analysis. Decisions should be made with the utmost deference to the ethical principles underlying human research as set forth in the Belmont Report.

The National Bioethics Advisory Commission (NBAC) has issued 21 recommendations for IRBs, the research community, and Federal regulators to consider regarding the decision-making capacity of particularly vulnerable subjects.

The following criteria should be taken into consideration for adult participants with impaired decision-making capacity involved in a research protocol:

- The objectives of the research cannot be met by conducting the research in a population that does not have the disorder that may affect decision-making capacity.
- The research is designed for a disease or condition relevant to the vulnerable population under study.
- The research is either minimal risk, more than minimal risk with a prospect of direct benefit, or more than minimal risk without a prospect of direct benefit, but of vital importance to the vulnerable population.

- Adequate provisions are made for obtaining consent from the participant's legally authorized representative.
- Adequate provisions are made for obtaining assent from the participant, unless the IRB determines that assent is not appropriate as a condition of participation or that some or all participants are not capable of providing assent.

The protocol must describe when and how the participants will be assessed for capacity for formal consent or assent and understanding of the proposed research, and the process for a second confirming assessment. Competency should be evaluated on an individual basis to avoid incorrect assumptions as to an individual's ability to make decisions. Criteria for determining competence might vary according to the degree of risk or discomfort presented by the research procedures and the extent to which therapeutic gain can be anticipated.

The IRB will consider additional safeguards to protect participants. Such decisions may be based on the amount of risk involved in the research and the likelihood that participants will derive health benefits from their participation. These include:

- Requiring the involvement of participant advocates
- Requiring independent monitoring
- Requiring waiting periods
- Appointing a monitor to supervise the informed consent process

Refer to IRB SOP 3.18 "*Additional Safeguards for Individuals Without Decision-making Capacity"* for more details.

Children as research participants

When a proposed research study involves children and is supported or conducted by HHS, the IRB must take into consideration the special regulatory requirements that provide additional protection for the children who would be involved in the research. If the proposed research involves FDA-regulated products, then FDA's parallel regulations apply.

When reviewing research with children as subjects, in addition to ensuring adherence to the general regulatory requirements of 45 CFR part 46, Subpart A, the IRB also must consider the potential benefits, risks, and discomforts of the research to children and assess the justification for their inclusion in the research. In assessing the risks and potential benefits, the IRB should consider the circumstances of the children to be enrolled in the study; for example, their health status, age, and ability to understand what is involved in the research, as well as potential benefits to subjects, other children with the same disease or condition, or society as a whole.

Refer to IRB SOP 3.22 "*Additional Protections for Children Involved as Subjects in Research"* for more details.

Definitions

1. *Children* are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.
2. *Assent* means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.
3. *Permission* means the agreement of parent(s) or guardian to the participation of their child or ward in research.
4. *Parent* means a child's biological or adoptive parent.
5. *Guardian* means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

Risk/benefit categories

The IRB considers the following risk/benefit categories when evaluating research involving children for approval:

a) Research not involving greater than minimal risk (Minimal Risk)
b) Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual participants
c) Research involving greater than minimal risk and no prospect of direct benefit to individual participants but likely to yield generalizable knowledge about the participant's disorder or condition
d) Research not otherwise approvable through categories (a) through (c) above

Risk Category	Risk Level	Provisions
a. Research not involving greater than minimal risk (45 CFR 46.404 and 21 CFR 50.51)	The risks of the research are no more than minimal.	• Permission from one parent/guardian may be sufficient, unless the requirement to obtain parental/guardian permission is waived. • Adequate provisions are made for soliciting the assent of child-participants, unless the requirement to obtain child assent is waived. (Ref. §46.408)
b. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects	• More than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject or by a monitoring procedure that is likely to contribute to the subject's well-being;	• Permission from one parent/guardian may be sufficient, unless the requirement to obtain parental/guardian permission is waived. • Adequate provisions are made for soliciting the

(45 CFR 46.405 and 21 CFR 50.52)	• The risk is justified by the anticipated benefit to the subjects; and • The relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches.	assent of child-participants, unless the requirement to obtain child assent is waived. (Ref. §46.408)
c. Research involving greater than minimal risk and no prospect of direct benefit to individual participants but likely to yield generalizable knowledge about the participant's disorder or condition (45 CFR 46.406 and 21 CFR 50.53)	• More than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual participant, or by a monitoring procedure that is not likely to contribute to the well-being of the child; • The risk represents a minor increase over minimal risk; • The intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations; and, • The intervention or procedure is likely to yield generalizable knowledge about the participants' disorder or condition which is of vital importance for the understanding or amelioration of the participants' disorder or condition.	• Permission from both parents or guardians, unless: a. one parent is deceased, unknown, incompetent, or not reasonably available, b. when only one parent has legal responsibility for the care and custody of the child, or c. the IRB waives the requirements for obtaining parental or guardian permission. • Assent of child participants, unless the requirement to obtain child assent is waived. • Enrolling wards of the state or any other agency, institution, or entity (e.g., orphans) with the appropriate documentation that: o Recognizes the status of the individual child as a ward; o Ensures communication of that status to the IRB; and o Confirms the IRB appointment of an advocate for the child/ward, in addition to any other individual acting as guardian or in loco parentis.

		Ref. 45 CFR 46.409 and 21 CFR 50.56 for additional information on the role of the advocate.
d. Research not otherwise approvable (45 CFR 46.407 and 21 CFR 50.54)	This category designation is only given for research which does not meet the conditions under 45 CFR 46.404, 46.405, or 46.406, but finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.	• The research will be conducted in accordance with sound ethical principles and informed consent will be obtained in accordance with the informed consent provisions of 45 CFR 46, including all applicable subparts including adequate provisions for soliciting the assent of children and the permission of their parents or guardians, as set forth in § 46.408. • Research also subject to FDA regulations under 21 CFR 312 (or 812), FDA regulatory requirements at 21 CFR 50.54 must be met.

Requirements for permission by parents or guardians assent by children (Ref. 45 CRF 46)

In addition to the determinations required under other applicable sections of Section 06, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with 45 CFR 46.116 of Subpart A.

In addition to the determinations required, the IRB shall determine, in accordance with and to the extent that consent is required by 45 CFR 46.116 of Subpart A, that adequate

provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under §46.404 or §46.405. Where research is covered by §46.406 and §46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

In addition to the provisions for waiver contained in 45 CFR 46.116, Subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A and the paragraph above, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

Permission by parents or guardians shall be documented in accordance with and to the extent required by §46.117, Subpart A.

When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

Wards (Ref. 45 CFR 46.409)
Children who are wards of the state or any other agency, institution, or entity can be included in research approved under §46.406 or §46.407 only if such research is:

- Related to their status as wards; or
- Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

The IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigators(s), or the guardian organization.

Other vulnerable groups

Although the federal regulations do not list all vulnerable groups, the IRB considers vulnerable groups to include:

- mentally impaired or disabled persons

- employees of the sponsor or investigator or The Christ Hospital
- terminally ill patients; and the very elderly

The IRB will determine special protections for these groups on a case-by-case basis, considering the risks and benefits and other protections afforded by institutional policies and state and federal law.

Refer to IRB SOP 3.19 "*Additional Safeguards for Vulnerable Populations Other Than Decisionally Impaired, or Pregnant Women, Fetuses or Neonates"* for more details.

Section 06 Regulatory History
Effective Date: 02/07
Revised/Reviewed Date: 05/26
AAHRPP Element: II.1.A., II.1.E., II.3.E., II.3.F., II.4.A., II.4.B.

SECTION 07 - RESEARCH PROTOCOL AND CONSENT - FORMAT AND REQUIREMENTS

When submitting a study to The Christ Hospital (TCH) Institutional Review Board (IRB) for approval, it is necessary to adhere to the following guidelines carefully and completely. Non-conformance may result in unnecessary delays in IRB review and approval, and initiation of research.

All submission forms and templates are available on Mentor IRB or can be obtained by contacting the IRB Office by email at IRB_Office@thechristhospital.com. The forms are also located on the IRB page of The Christ Hospital website and the IRB SharePoint site.

Full Board Review Submission Documents

Full Board Review submissions must include the following documents, completed and/or uploaded in Mentor IRB, as applicable to the research:

- Full Board Review e-application in Mentor IRB, which may include the following (as applicable):
  - Request for Full or Partial Waiver of HIPAA Authorization
  - Waiver of Informed Consent Request
  - Waiver of Documentation of Informed Consent Request
  - Investigational Drug Information
  - Investigational Device Information
- Informed Consent documents, such as:
  - Informed Consent using the TCH template
  - The HHS-approved sample consent document (when available)
- Protocol/Clinical Investigation Plan (CIP), when applicable, such as:
  - Sponsor-approved protocol
  - Complete HHS-approved protocol (when available)
- Electronic Signature Affidavit for submitter (one signature is required, either principal investigator or research coordinator)
- Annual Financial Conflict of Interest (FCOI) Disclosure form for all investigators and other key research personnel on sponsored/funded research
- Documentation for FDA-regulated products
- Recruitment/Advertising materials
- Investigator's Brochure
- Instructions for Use
- Data collection materials
- Key Research Personnel Qualification Documentation, including:

    - Certificates of completion for the required CITI courses for all investigators and other key research personnel including
    - Training in Human Subjects Research (HSR) and Good Clinical Practice (GCP), or approved alternative
    - Transcripts of required CITI training reflecting completion within the most recent three years
    - Most recent CV for all investigators and other key research personnel
    - Medical or nursing license for all investigators and other key research personnel, as applicable

For studies requiring Full Board review, all submission documents must be provided to the IRB office 21 days prior to the monthly convened IRB meeting.

Expedited Review Submission Documents

Expedited Review submissions must include the following documents, completed and/or uploaded in Mentor IRB, as applicable to the research:

- Expedited Review e-application in Mentor IRB, which may include the following (as applicable):
    - Request for Full or Partial Waiver of HIPAA Authorization
    - Waiver of Informed Consent Request
    - Waiver of Documentation of Informed Consent Request
    - Investigational Drug Information
    - Investigational Device Information
- Informed Consent documents, such as:
    - Informed Consent using the TCH template
    - The HHS-approved sample consent document (when available)
- Protocol/Clinical Investigation Plan (CIP), when applicable, such as:
    - Sponsor-approved protocol
    - Complete HHS-approved protocol (when available)
- Electronic Signature Affidavit for submitter (one signature is required, either principal investigator or research coordinator)
- Annual Financial Conflict of Interest (FCOI) Disclosure form for all investigators and other key research personnel on sponsored/funded research
- Documentation for FDA-regulated products
- Recruitment/Advertising materials
- Data collection materials
- Key Research Personnel Qualification Documentation, including:
    - Certificates of completion for the required CITI courses for all investigators and other key research personnel including
    - Training in Human Subjects Research (HSR) and Good Clinical Practice (GCP), or approved alternative

- Transcripts of required CITI training reflecting completion within the most recent three years
- Most recent CV for all investigators and other key research personnel
- Medical or nursing license for all investigators and other key research personnel, as applicable

Expanded Description of Required Documentation

Application

The Christ Hospital IRB requires an application be completed in Mentor IRB for any proposed research project. The Mentor IRB system automatically generates the appropriate e-application depending on the submission/review type requested at the time of initial registration, and generation of the IRB reference number. This number will be the reference number throughout life of the project. The application must be completed in its entirety prior to submission to the IRB. Upon submission, a request for approval to proceed through IRB review will be automatically forwarded to the appropriate department director.

Informed Consent

Informed consent is one of the primary ethical requirements underpinning research involving humans. Informed consent reflects the basic principle of respect for persons.

Informed consent is an *ongoing process*, not a single event, designed to give individuals all relevant information needed to make the decision whether to participate in the research study or to continue participation in the research study. The informed consent process should permit the potential research subject to ask questions and to exchange information freely with the study investigators. Moreover, investigators have an ethical and contractual responsibility to keep research subjects fully informed of any new information that may affect their willingness to continue study participation. Thus, rather than an endpoint, the consent document should be the basis for an ongoing meaningful exchange between the investigator and the potential research subject or study participant.

Unless the IRB has waived the requirement for consent to the research study or has specifically waived the requirement for a signed consent form, **an investigator may NOT involve an individual in a research study unless he/she has prospectively obtained the legally effective, written informed consent of the individual or the individual's legally authorized representative.** Note that verbal or telephone consent is not acceptable unless the IRB has specifically waived the requirement for a signed consent form; nor is deferred consent (i.e., obtaining consent after the initiation of study procedures).

A thoroughly written consent document is crucial to any research study. Very specific guidelines for the informed consent have been developed for studies at The Christ Hospital. Refer to the TCH IRB *Informed Consent template* for specific guidelines.

The Principal Investigator of the research study is ultimately accountable for assuring that all aspects of the study are, at all times, in compliance with applicable federal regulations and IRB policies, including but not limited to the entire informed consent process and the instruction and oversight of individuals who may be involved in the process. (Ref. Section 16 Informed Consent; IRB SOP *2.02 Informed Consent*)

Research Protocol or Clinical Investigation Plan (CIP)

A research protocol or Clinical Investigation Plan (CIP) is the key document in a trial. It is a document developed by the research sponsor that describes the background, rationale, objectives, design, methodology, statistical considerations, and organization of a clinical research project. It should be designed in such a way as to optimize the scientific validity and reproducibility of the results of the study in accordance with current clinical knowledge and practice to fulfil the objectives of the investigation.

Electronic Signature Affidavit

The electronic signature affidavit is required by the submitter, either principal investigator or designated research coordinator, to document responsibility for the submission.

Annual Financial Conflict of Interest (FCOI) Disclosure

All investigators and key research personnel directly involved in research activities and/or interacting with research subjects must submit an Annual FCOI Disclosure to the IRB Office to disclose whether any of the financial interests/arrangements listed below apply to themselves or an immediate family member (e.g., a spouse, dependent child, or [other] members of their household) in relation to any research study. The reporting period for any of the following financial interests/arrangements is 12 months preceding the date of disclosure.

- Having been an executive, director, or employee of the sponsor of the study
- Having received remuneration from a sponsor/funding agency when the aggregated value received during the 12-month period preceding the disclosure exceeds $5,000.
- Having received reimbursed or sponsored travel that is related to investigator's responsibilities for this study
- Having equity interests (e.g. stocks, stock options, or other ownership interests) of any value for a non-publicly traded company or that exceeds $5,000 for a publicly traded company during the 12-month period preceding the disclosure.
- Having income related to intellectual property rights and interests (e.g., patents, trademarks, service marks, and copyrights)
- Having agreed to or plan to accept recruitment bonuses for enrolling subjects into the research
- Receiving any significant payments of other sorts not aforementioned including monetary values more than $5,000 which may be in forms such as grants to fund

ongoing research, compensation in the form of equipment or retainers for ongoing consultation, or honoraria

If a significant financial conflict exists, the IRB will approve a plan to manage the conflict, as appropriate, to minimize the risk of imparting bias into the research. Management plans are typically tailored to the specific study and/or sponsor and the researcher's financial interests.

This disclosure must be updated at least annually and following a material change which may create an actual or perceived conflict of interest. The research should contact the IRB Office with any questions or to request a new form.

A one-time institution-specific FCOI training is required when a researcher is new to the organization. This training is sent to each new Mentor User by the IRB Office. Re-training with the institution-specific FCOI training is required immediately when financial conflict of interest policies are revised in a manner that changes researcher requirements, or a researcher is non-compliant with financial conflict of interest policies and procedures.

A COI refresher is required at least every three years through a CITI course module when the researcher is up for renewal.

Refer to IRB SOP 2.13 "*Financial Conflict of Interest*" for more information.

Documentation for FDA-Regulated Products

For studies involving investigational drugs, biologics and food supplements, the IRB requires submission of documentation from either (1) the sponsor or FDA verifying the Investigational New Drug (IND) number or (2) the investigator providing the reason why an IND is not required.

For studies involving investigational medical devices, the IRB requires submission of documentation from (1) the FDA granting the Investigational Device Exemption (IDE), (2) the sponsor stating that the study is a non-significant risk device study and the basis for that determination, or (3) the sponsor as to why the investigation is exempt from the IDE requirements under 21 CFR § 812.2(c) (e.g., the PMA approval letter/number or 510(k) clearance letter/number).

Recruitment/Advertising Materials

All recruitment materials (e.g., advertisements, posters, flyers) must be reviewed and approved by the IRB prior to distribution. As part of sound study design, investigators should assess enrollment and recruitment practices for fairness and equitable selection. Investigators will provide information to the IRB to make these determinations. (Ref. SOP *2.10 "Recruitment of Subjects in Research"*)

Investigator Brochure

The Investigator's Brochure is a comprehensive compilation of clinical and nonclinical data on the investigational product (drug, supplement, device, or other product) that are relevant to the study and maintained by a drug developer or investigator. The Investigator Brochure contains the body of information about the investigational product obtained before and during a trial, is of critical importance throughout the development process, and updated with new information as the information becomes available.

Instructions for Use

The Instructions for Use is a device manual that is provided by the sponsor for device studies.

Data Collection Materials

Data collection materials must be reviewed and approved by the IRB prior to use. Common data collection materials include interview questions, focus group questions, observation sheets, surveys, questionnaires, and participant diaries.

Investigator Qualifications

To ensure investigators and research personnel are appropriately qualified, investigators and research staff must submit their current professional license showing the expiration date, curriculum vitae (CV) or resume, and CITI transcripts. The IRB requires CITI Human Subjects Research (HSR) and Good Clinical Practice (GCP) training, or approved alternative. Transcripts of required CITI training must reflect completion within the most recent three years. (Ref. SOP *3.12 "Education of IRB Staff/Board Members/Investigators/Research Staff"*)

Section 07 Regulatory History
Effective Date: 02/07
Revised/Reviewed Date: 05/26
AAHRPP Element: Not Applicable.

SECTION 08 - REPORTING UNANTICIPATED PROBLEMS INVOLVING RISKS TO HUMAN SUBJECTS OR OTHERS AND ADVERSE EVENTS

Federal regulations at 45 CFR 46.108(b)(1) and 21 CFR 56.108(b) require Institutional Review Boards (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 (UAPs) involving risks to human subjects or others following the procedures outlined below. A UAP is any incident, experience or outcome that is (1) unexpected, (2) related (or possibly related) to participation in the research study, and (3) poses a greater risk of harm to subjects or others. UAPs are considered Reportable Events. Events that do not meet all three criteria do not require immediate reporting to the IRB but should be documented in the study records and may require reporting to the sponsor or other applicable agencies. (Ref. DHHS guidance publication: Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events)

Examples of Reportable Events/UAPs include, but are not limited to:

- Adverse events that are related, or possibly related, to study participation and unanticipated
- Any accidental or unintentional deviation from the IRB-approved protocol that involved risks or has the potential to recur
- Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a given research subject
- 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
- Any complaint made by a subject that indicates an unanticipated risk or which cannot be resolved by the research staff
- 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
- Enrollment which is greater than what was approved by the IRB
- Information indicating a change in risks or benefits
- Breach in confidentiality (e.g., laptop stolen)
- Change in FDA labeling
- Changes for an apparent immediate hazard
- Incarceration
- Event that requires prompt reporting to the sponsor

- Unresolved complaint
- Protocol violation

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 quality or type that suggests a failure to understand and consistently comply with federal regulations and The Christ Hospital (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 or 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 Problem (UAP): TCH IRB (based on the Office for Human Research Protections definition) considers unanticipated problems, in general, to include any incident, experience or outcome that meets ALL the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (1) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (2) 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 that 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 UAPs

(The following list of examples representing unanticipated problems involving risks to subjects or others is not exhaustive.)

- Information that indicates a change to the risks of the research, in terms of severity or frequency, such as:
- 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
- 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
- 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 (Ref. SOP 3.08 "*Complaints and Inquiries for Research Participants, Investigators, Research Staff, and the Community*")
- Violation: 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 (Ref. SOP 3.09 "*Protocol Violation, Deviation, and Non-Compliance Reporting"*)
- Incarceration of a participant when the research was not previously approved under 45 CFR 46 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 (Ref. 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 or recommendations which alter the risks and/or benefits
- New information which indicates 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
- 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.

General Reporting Requirements for UAPs

Reporting to the IRB

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

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 "Reportable Event" tab in Mentor IRB. These reports are initially reviewed by the IRB chairman or designee. If determined to represent an "unanticipated problem involving risks to human subjects or others," "serious noncompliance," or "continuing non-compliance," the event will be referred by the IRB chair or designee to a convened IRB for consideration.

Communication of IRB Action

Following IRB review, the IRB`s action shall be reported promptly to the investigator, appropriate institutional officials, and any applicable regulatory bodies by the IRB Office staff.

Reporting to Regulatory Bodies

HHS conducted or supported research:

Following IRB and institutional review, the IRB Office submits any reports of unanticipated problems involving risks to subjects or others (UAPs) involving HHS conducted or supported research to the Office for Human Research Protection (OHRP) using the OHRP Incident Reporting Online Form. UAPs involving research that is not covered by HHS regulations do not require reporting to OHRP.

Food and Drug Administration (FDA) regulated research:

Following IRB and institutional review, as applicable, the IRB Office submits any reports of unanticipated problems involving risks to subjects or others (UAPs) involving FDA-

regulated research to the Food and Drug Administration. UAPs involving research that is not covered by FDA- regulations do not require reporting to FDA.

For Drug Products:
Email: CDER-OSI-GCPReferrals@fda.hhs.gov
Phone: (301) 796-3150

For Biologic Products:
Email:CBERBIMONotification@fda.hhs.gov

For Medical Devices:
Email: bimo@cdrh.fda.gov
Phone (301) 796-5490

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 Reportable Events requiring prompt reporting to the IRB. It is the investigator's responsibility to report the event within 10 business days utilizing the "Reportable Event" tab in Mentor IRB. Exceptions to the 10-day reporting timeline are (1) the death of a human subject, and (2) an event which poses an immediate threat to the subject or others. 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, the IRB must be notified within one (1) business day utilizing the "Reportable Event" tab in Mentor IRB. 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.

Section 08 Regulatory History
Effective Date: 02/07
Revised/Reviewed Date: 05/26
AAHRPP Element: I.5.D, II.2.G, III.2.D

SECTION 09 - RESPONSIBILITIES OF INVESTIGATORS AND KEY RESEARCH PERSONNEL

Principal Investigator Responsibilities

The Principal Investigator (PI) is the primary individual responsible for the preparation, conduct, and administration of the research study in compliance with applicable laws and regulations and institutional policy governing the conduct of research. The PI undertakes the primary responsibility for protecting the rights and welfare of research participants and must be familiar with the ethical principles of human subject protection requirements per federal regulations (ref. 45 CFR 46), Federal Wide Assurance, and IRB policy and procedures.

Certification of Principal Investigator Responsibilities

The principal investigator must agree to:

1. Review protocol submissions in their entirety and be fully cognizant of, and in agreement with, all submitted statements
2. Be familiar with clinical research regulations and comply with these regulations during the conduct of the study
3. Read the Belmont Report and understand the three ethical principles outlined therein: (1) respect for persons, (2) beneficence, and (3) justice; the PI must adhere to these principles during the conduct of the study
4. Have adequate resources and facilities available to carry out the proposed research projects
5. Identify and disclose financial interests according to organizational policies and regulatory requirements and, with the organization, manage, minimize, or eliminate financial conflicts of interest
6. Conduct research in strict accordance with all statements submitted except where a change may be necessary to eliminate an apparent immediate hazard to a given research subject(s) or others
7. Notify the IRB promptly of any change in the research procedures necessitated in the interest of the safety of a given research subject(s)
8. Request and obtain IRB approval of any proposed modifications to research protocol(s) or informed consent document(s) prior to implementing such modifications
9. Ensure that all sub-investigators and other personnel assisting in the conduct of research have been provided with a copy of the entire, current version of the research protocol and are fully informed of the current:
    - Study procedures including procedure modifications
    - Informed consent requirements and process

- Potential risks associated with the study participation and the steps to be taken to prevent or minimize these potential risks
- Adverse event reporting requirements
- Data and record-keeping requirements
- IRB approval status of the research study

10. Not enroll any individual into a research study:
    - Until such a time that the conduct of the study has been approved in writing by the IRB
    - During any period wherein IRB renewal approval of a research study has lapsed
    - During any period wherein IRB approval of a research study or research study enrollment has been suspended or wherein the sponsor has suspended research study enrollment
    - Following termination of IRB approval of a research study or following sponsor/principal investigator termination of research study enrollment
11. Understand the criterion per state or other law regarding situations in which consent will be obtained from a Legally Authorized Representative (LAR) rather than the subject, and that the LAR must meet on behalf of the subject to consent to the subject's participation in the procedures involved in the study
12. Respond promptly to all requests for information or materials solicited by the IRB or IRB office
13. Submit continuing reviews (for applicable research) for IRB review and approval within the established timeframe listed on the study approval letter, thus avoiding study expiration
14. Ensure that a final Continuing Review to close the study is submitted to the IRB upon completion of the research
15. Recruit participants in a fair and equitable manner
16. Not enroll any individual into a research study until such time his/her written informed consent is obtained, or, if applicable, the written informed consent of his/her authorized representative, except in instances where the IRB has granted a waiver of the requirement to obtain written informed consent
17. Employ and oversee an informed consent process which ensures that potential research subjects fully understand the purpose of the research study, the nature of the research procedures they are being asked to undergo, the potential risks of the research procedures, and their rights as a research study volunteer
18. Ensure that research subjects are kept fully informed of any new information which may affect their willingness to continue to participate in the research study
19. Maintain adequate, current, and accurate records of research data, outcomes and adverse events, thus permitting an ongoing assessment of the risk/benefit ratio of research study participation
20. Be cognizant of, and comply with, current federal regulations and IRB requirements governing human subject research including adverse event reporting, protocol deviations and violations, subject complaints and conflict of interest

21. Make a reasonable effort to ensure that subjects who have suffered an adverse event associated with research participation receive adequate care to correct or alleviate the consequences of the adverse event to the extent possible
22. Ensure that the conduct of the research study adheres to Good Clinical Practice guidelines
23. Ensure that all listed investigators have the appropriate credentials to conduct the portion of the study in which they are involved
24. Ensure that the privacy of research subjects and the confidentiality of the study data will be appropriately maintained at the study site
25. Understand that payments in exchange for referrals of potential participants (i.e., finder's fees) are prohibited by The Christ Hospital
26. Inform and obtain approval of the attending physician prior to approaching and seeking enrollment of a hospitalized patient

Key Research Personnel Responsibilities

The principal investigator is responsible for determining key research personnel; individuals who are directly involved in conducting research with study participants or who are directly involved in using study participants' identifiable private information during the course of the research. All key research personnel are responsible for protecting the rights and welfare of research participants and must be familiar with the ethical principles of human subject protection requirements per federal regulations outlined in 45 CFR 46, Federal Wide Assurance, and IRB policy and procedures.

Certification of Key Research Personnel Responsibilities

Key research personnel must accept responsibility for protecting the rights and welfare of human research participants and agree to:

1. Have sufficient training and experience to conduct the research in accord with the protocol, including, but not limited to any cultural sensitivities, cultural norms, and/ or dialect spoken
2. Have fulfilled the human subject research training requirement (CITI) and understand the ethical standards and regulatory requirements governing research activities with human participants
3. Ensure the proposed research complies with the ethical principles outlined in the Belmont Report, human subject research regulations including 45 CFR 46, HIPAA (45 CFR 164), FDA (21 CFR 50 & 56), institutional policies, and other applicable federal or state laws
4. Report any real or potential conflicts of interests in compliance with the conflict-of-interest policies.
5. Ensure all research activities have IRB approval and other ancillary approval required by the institution before human subjects are involved and implement the research activity as it was approved by the IRB.
6. Ensure that the confidentiality and security of all information obtained from and about human subjects, and that the privacy of subjects is maintained.

7. Ensure that any Prompt Reports, Monitoring Reports and Adverse Events are submitted to the IRB in a timely manner.

Additional Information
See HHS publication Investigator Responsibilities FAQs

Section 09 Regulatory History
Effective Date: 01/07
Revised/Reviewed Date: 04/26
AAHRPP Element: III.1.A-G, III.2.A-D

SECTION 10 - CONFLICTS OF INTEREST

Conflicts of interest and commitment in research can adversely impact the integrity of research results and the confidence of prospective volunteers in the research enterprise. Researchers are often faced with competing demands on time, effort and responsibilities. A conflict of interests occurs when a researcher must contend with two or more competing concerns, such as achieving publication, retaining outside funding or honestly reporting research results. A conflict of commitments occurs when a researcher engages in competing obligations, such as collaboration on another project, preparing a new grant application, teaching or peer review. (Ref. APA Conflicts of Interests and Commitments)

The Christ Hospital (TCH) Institutional Review Board (IRB) seeks to avoid these negative repercussions by identifying, disclosing, and avoiding or managing such conflicts.

The Christ Hospital has bylaws, policies, procedures and practices concerning staff members' outside financial or management interests which could form the basis of a conflict, and seeks to protect at least the following values:

- Objectivity and integrity in research
- Open publication of research results
- Appropriate use of sponsor or hospital funds
- Maintenance of appropriate relationships with and fulfillment of obligations to colleagues
- Fulfillment of administrative duties
- Integrity of academic decision making
- Avoidance of "pipelining" institutional intellectual property to an outside entity
- Protection of and appropriate informed consent with human subjects

Identification of Conflicts of Interest of Investigators and Research Staff

IRB Identified

All investigators and other key research personnel directly involved in research activities and/or interacting with research subjects on any federally-funded and/or FDA-regulated research project at The Christ Hospital must complete a Financial Conflict of Interest (FCOI) Disclosure prior to their participation in the research project. The reporting period is the 12-month period preceding the date of their disclosure. These key research personnel must also complete an annual FCOI disclosure thereafter for the duration of their participation in the research project.

This provides an opportunity for investigators to certify that neither they, nor their immediately families*, have any significant financial interest in the proposed research. When an investigator, or any other key personnel, on a proposed research project

discloses that they (or their spouse or dependent children) have significant financial or management interests in a sponsored project, further review by the IRB is required to determine what, if any, management plan is necessary to minimize the risk of imparting bias into the research. These disclosures are reviewed by the IRB COI Committee at the time of initial submission and during continuing review of the research. (Ref. SOP 2.13 "*Investigator Disclosure of Financial Interest"*)

* Immediate family is defined as a spouse, dependents or members of one's household.

Investigators and other key research personnel must report when they or an immediate family member:

- Are currently or have been an executive, director, or employee of the sponsor of this study.
- Have received remuneration from a sponsor/funding agency when the aggregated value received during the 12-month period preceding the disclosure exceeds $5,000.
- Have received reimbursed or sponsored travel that is related to investigator's responsibilities for this study.
- Have equity interests (e.g. stocks, stock options, or other ownership interests) of any value for a non-publicly traded company or that exceeds $5,000 for a publicly traded company during the 12-month period preceding the disclosure.
- Have income related to intellectual property rights and interests (e.g. patents, trademarks, service marks, and copyrights).
- Have agreed to or plan to accept recruitment bonuses for enrolling subjects into the research.
- Have received any significant payments of other sorts not aforementioned including monetary values more than $5,000. These may be in forms such as a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation, or honoraria.

<u>Institution Identified</u>

In compliance with The Christ Hospital conflict of interest policies, the Institutional Official may also receive certain disclosures of outside activities generated including disclosure of significant financial interest. The Institutional Official reviews the disclosures and will report any conflict of interest to the IRB Chair and appropriate administrative committee.

<u>Management Plans</u>

The convened IRB reviews any disclosures of significant financial interest upon receipt and at the time of initial and continuing review. The IRB develops and approves plans to manage the interest, as appropriate, to minimize the risk of imparting bias into the research. Management plans are typically tailored to the specific study and/or sponsor and the researcher's financial interests. Examples of special protections used in management strategies may include, but are not limited to:

- Disclosing the potential COI to the subjects in the informed consent form
- Reducing the researcher's role in the research (less interaction with subjects, less data analysis)
- Adding an independent monitor to the study team to make sure that the research procedures are transparent
- Precluding the conflicted research from obtaining informed consent from subjects
- Blinding the conflicted research to treatment arm(s)
- Requiring researchers to disclose their financial interest in presentations and publications related to the research

(Ref. IRB SOP 2.13 "*Investigator Disclosure of Financial Interest"*; IRB SOP *1.28 "Review of Financial Conflicts of Interest"*; TCH Policy 1.05.104 "*Human Research Protections Program Conflict of Interest"*)

Institutional Conflicts of Interest

Equities in Outside Organizations

When conducting reviews of research projects, the Institutional Official for Research receives and reviews information on any Hospital equity in an outside organization associated with the research and seeks to manage any conflict-of-interest risk associated with that equity including any significant financial or management interest in the outside entity by hospital administrators and manages those conflict in light of the special need for protections from research risks. In addition, the Hospital's equity in start-up companies is managed as part of the Institution's broader investment portfolio and therefore no different from other institutional investments. This helps avoid bias or favoritism. The Chief Financial Officer, not the Institutional Official for Research, coordinates hospital investments utilizing outside managers to assist with investment strategy. Thus, a determination to liquidate the Hospital's investment in a holding is never a research decision.

Gifts

Organizational financial conflicts of interest involving gifts are evaluated for potential institutional COIs when the donor has an interest in the research. (Ref. TCH Policy 4.21.116 *Conflict of Interest - Managers and Employed/Contracted Medical Staff Members*; TCH Policy 4.21.124 *Conflict of Interest – Board of Directors*)

Conflicts of Interest of IRB Members and Consultants

IRB members and consultants will not participate in any IRB action taken including the initial and continuing review of projects in which the member has a conflicting interest, except to provide information requested by the IRB. IRB members are expected to self-identify conflicting interests. Consultants with a conflicting interest are required to disclose their conflicting interests to IRB members reviewing the research, are excluded from discussion (except to provide information requested by the IRB), and must leave the meeting room during convened IRB meetings when discussion and voting take place.

An IRB member is considered to have a conflicting interest when the IRB member or an immediate family member* of the IRB member:

- Is the project director or another member of the research team
- who has a financial interest in the research which has a value that cannot be readily determined, or a value that may be affected by the outcome of the research
- Has a financial interest in the research with value exceeding the specified monetary threshold in The Christ Hospital Conflict of Interest policy
- Has received or will receive any compensation which has a value that may be affected by the outcome of the study
- Has a proprietary interest in the research: property or other financial interest in the research including, but not limited to, a patent, trademark, copyright or licensing agreement
- Has received payments from the sponsor that exceed the specified monetary threshold in The Christ Hospital Conflict of Interest policy
- Is an executive or director of the agency/company sponsoring the research
- In any other situation believes that an interest conflicts with his/her ability to deliberate objectively on a research protocol

Except when requested by the IRB to be present to provide information, IRB members with a conflict of interest will be absent from the convened meeting room while the IRB reviews the research associated with the member holding the conflict of interest. The IRB chair will allow board discussion only after the conflicted member has recused him/herself. The absent member is not counted toward quorum. His/her absence during the discussion and vote on the protocol will be noted in the IRB meeting minutes.

Section 10 Regulatory History
Effective Date: 01/07
Revised/Reviewed Date: 04/26
AAHRPP Element: I.6.A, I.6.B, II.1.C, II.1.D, II.2.A, III.1.B

SECTION 11 - CRITERIA FOR APPROVAL OF RESEARCH

The Christ Hospital Institutional Review Board (TCH IRB) shall determine that appropriate requirements are satisfied prior to approval of a research project. Research which meets exempt or expedited criteria may be reviewed by the IRB chairman or designee. Research involving greater than minimal risk must be reviewed by the convened "full" board. For these studies, TCH IRB strongly recommends that the Principal Investigator (PI) or designee attend the IRB meeting at which his/her research proposal is under review to present on the proposal and discuss potential issues with IRB members.

Review Criteria

In order to approve research covered by federal regulations the IRB shall determine that all of the following requirements are satisfied (ref: 21 CFR 56.111):

a) Risks to subjects are minimized:
   - By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and
   - Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes

b) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

   For the purpose of IRB consideration:
   - "Risk" is defined as the probability of harm or injury (physical, psychological, social or economic) occurring as a result of participation in a research study. In evaluating risk, the IRB is to consider the conditions that make this situation dangerous, per se (i.e., as opposed to those chances that specific individuals are willing to undertake for some desired goals).
   - "Benefit" is defined as a valued or desired outcome; an advantage.

c) Selection of subjects is equitable. In making this assessment, the TCH IRB should consider the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research

involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons. (For additional information, see Section 06.)

d) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by federal regulations, IRB policies and state law, unless a recognized exception or waiver applies.

e) Informed consent will be appropriately documented, unless a waiver of documentation applies, in accordance with and to the extent required by federal regulations (21 CFR 50.27) and IRB guidelines.

f) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. This plan should include a provision for reporting to the IRB any findings of a serious or adverse nature which impact human subjects.

g) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

Additional Safeguards

When some or all the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects. (Note: TCH IRB does not participate in research concerning prisoners.)

Research Involving Children

In order to approve research in which some or all of the subjects are children, the IRB must determine that all research is in compliance with 21 CFR 50, Subpart D.

Modifications/Amendments

TCH IRB may suggest modification or amendments to proposals based on consideration of human subject protection and adequate informed consent.

Section 11 Regulatory History
Effective Date: 01/07
Revised/Reviewed Date: 04/26
AAHRPP Element: II.3.A, II.3.B, II.3.C, II.3.D, II.3.F, II.3.G

SECTION 12 – INVESTIGATOR NONCOMPLIANCE

The Principal Investigator (PI) bears the ultimate responsibility for conduct of a research project. The PI must comply with the requirements of The Christ Hospital's Federalwide Assurance (FWA), the FDA, state laws, and the determinations of The Christ Hospital (TCH) Institutional Review Board (IRB) as outlined in IRB minutes, guidelines and other correspondence.

Conceptualizing Noncompliance, Serious Noncompliance, and Continuing Noncompliance

Noncompliance is a significant failure by an investigator or institution to abide by federal or state regulations or institutional policy governing the protection of human participants in research, including the requirements or determinations of the IRB.

Serious Noncompliance occurs when instances pose an actual or potential increased risk to the safety, rights and welfare of human research subjects because investigators fail to comply with federal regulations, state laws, TCH policies related to the protection of human subjects, and/or the requirements or determinations of the IRB. Serious Noncompliance can also occur because of a systemic failure of the institution to follow or implement practices described in TCH policies and/or federal regulations or state laws related to the protection of human subjects in research.

Continuing Noncompliance is repeated instances of noncompliance by the same investigator or by the institution. Repetition may be of the same instance or different instances. Regarding a single investigator, this repetition may be in the same or different protocols by the investigator and, if unaddressed, such repetition may affect the protection of human research subjects. Regarding the institution, repetition may be of the same or different policies, procedures, regulations and/or laws.

Conceptualizing Protocol Deviations and Violations

Protocol Deviations include, but are not limited to:

- Any emergent deviation from the IRB protocol made without prior IRB review to eliminate apparent immediate hazard to a research subject.
- Implementation of unapproved recruitment procedures
- Use of an incorrect version of informed consent
- Missing original signed and dated consent forms or missing pages from an executed consent form
- Inappropriate documentation of consent

- Subject visit/procedure falls outside of the window of time indicated by the protocol or is not done per protocol, and there is no increased potential for risk to the subject or any damage to the integrity or completeness of the data

Protocol Violations include, but are not limited to:

- Intentional deviation from the protocol or regulations in a non-emergency setting
- Any unintended or intended deviation from the IRB approved protocol that involves potential risks or has the potential to recur
- Enrollment of subjects not meeting the inclusion/exclusion criteria of an IRB approved protocol
- Failure to withdraw a subject meeting withdrawal criteria
- Inadvertent loss of samples or data
- Failure to obtain informed consent prior to initiation of study-related procedures
- Improper consent procedure
- Failure to follow federal and/or local regulations and policies
- Working under an expired professional license/certification, debarred or disqualified status
- Frequent minor deviations
- Any medication error involving dosing, administration and/or preparation of the study drugs
- Any lapse in study approval where there is a continuation of research activities (i.e., recruitment, enrollment, procedures, data analysis)
- Failure to report unanticipated problems to the IRB and/or the sponsor, or
- Any event that requires prompt reporting according to the protocol or the study sponsor

Note: Serious or Continuing Noncompliance may take the form of a protocol deviation or violation. However, some, but not all, protocol deviations and violations are not considered serious noncompliance. Contact the IRB Office if there is uncertainty in reporting requirements.

Notifications of Noncompliance to the IRB

Information regarding noncompliance in human subject studies may come to the attention of the IRB through several pathways. These include information contained in application forms, IRB reporting forms, monitoring reports, or reports from collaborators, employees, subjects or others not directly involved in the research. (Ref. SOP 3.06, "*Compliance with Human Subjects Regulations/IRB Requirements/Determinations"*.)

In cases involving allegations of research misconduct, an allegation of research misconduct may be made by anyone, whether associated with the institution or not, and may be made anonymously.

Allegations can be made through one of the following avenues:

1. Complaint or Concern Form
2. Email: IRB_Office@thechristhospital.com
3. Mail: IRB, 2139 Auburn Avenue, Room 3140, Cincinnati, Ohio 45219
4. Telephone:
    a. IRB Office at 513-585-2298
    b. Patient Relations at 513-585-1200
    c. TCH Compliance Hotline at 1-800-398-1496

In cases involving allegations of research misconduct, the IRB chair contacts the Institutional Official. This does not preclude the chair or any member of the IRB from independently contacting the Institutional Official about any allegation of scientific misconduct. Inquiries or investigations into research misconduct do not preclude IRB review and actions. Allegations of research misconduct are investigated according to IRB SOP 3.10 "*Misconduct in Research*".

Information Identified Outside a Full-Board Meeting

When information comes to the attention of the IRB apart from a convened full board meeting, the Chair of the IRB reviews the allegations of noncompliance and makes a determination as to whether the alleged practices appear to (1) cause injury or any other unanticipated problems involving risks to subjects or others, or (2) constitute serious or continuing noncompliance with IRB determinations or federal regulations. In such cases, the Chair may place a hold on the study procedures, taking into consideration the welfare of currently enrolled subjects, pending an investigation and review by the full IRB. If the Chair determines that the potential noncompliance did not involve any risk to subjects or others, and did not constitute serious or continuing noncompliance, the Chair may resolve the issue directly with the Principal Investigator and research team and render a report to the full IRB.

Information Identified During a Full-Board Review

When potential noncompliance is first identified during a full-board review, the full board makes a determination as to whether the alleged practices appear to (1) cause injury or any other unanticipated problems involving risks to subjects or others, or (2) constitute serious or continuing noncompliance with IRB determinations or federal regulations. In such cases, the full board may place a hold on the study procedures, taking into consideration the welfare of currently enrolled subjects, and determine how further investigation will be conducted.

REFERENCES:
21 CFR 56.108(b)(2); 21 CFR 56.113; 21 CFR 56.120; 21 CFR 312.23(a)(8)(iii); 21 CFR 812.27(b)(3); 21 CFR 812.27(b)(4)(i); 21 CFR 812.140(a)(4); 21 CFR 812.150(a)(4) 45 CFR 46.108(a)(4)(i)

Section 12 Regulatory History
Effective Date: 12/06
Revised/Reviewed Date: 04/26
AAHRPP Element: I.5.D

SECTION 13 - EXPANDED ACCESS ("COMPASSIONATE USE") TO INVESTIGATIONAL MEDICAL PRODUCTS

Expanded access (sometimes called "compassionate use") is a potential pathway for patients with a serious or immediately life-threatening disease or condition to gain access to an investigational medical product (medical device, drug, or biologic) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.

Expanded access may be appropriate when all the following apply:

1. The patient has a serious or immediate life-threatening disease or condition;
2. There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
3. Patient enrollment in a clinical trial is not possible;
4. Potential patient benefit justifies the potential risks of treatment;
5. Providing the investigational medical product will not interfere with investigational trials that could support a medical product's development or marketing approval for the treatment indication.

(Ref. U.S. Food & Drug Administration (FDA) Expanded Access)

INVESTIGATIONAL DEVICES

An unapproved medical device may normally be used on human subjects only through an approved clinical study in which the research subjects meet certain criteria and the medical product is used only in accordance with the approved protocol by a clinical investigator participating in the clinical trial. However, there may be circumstances under which a health care provider may wish to use an unapproved medical device (not approved or cleared by the FDA) to save the life of a patient or to help a patient suffering from a serious disease or condition for which no alternative therapy exists. Patients and physicians faced with these circumstances may have access to an investigational device through one of three mechanisms administered by the FDA:

1. Emergency use
2. Compassionate use
3. Treatment Investigational Device Exemption (IDE)
4. Continued Access

These mechanisms can be utilized during a certain timeframe in the IDE process if certain criteria are met. FDA approval is required for all mechanisms except in the case of emergency use.

Refer to IRB SOP 1.24 "*Expanded Access to Investigational Devices"* for more details.

Emergency Use

Emergency situations may arise in which an investigational medical device that has not received the FDA's approval, or clearance is needed for use (1) in a manner inconsistent with the approved investigational plan, and/or (2) by a physician who is not part of the clinical study investigating the device. In such cases, emergency use of an unapproved medical device may occur before the device is approved.

Criteria

1. Life-threatening or serious disease or condition
2. No comparable or satisfactory alternative
3. Because of the immediate need to use the device, there is no time to use existing procedures required for FDA approval for the use of the device.

Timeframe

1. Before initiation of the clinical trial
2. After initiation of the clinical trial

Documentation

The sponsor must submit a separate IDE application to the FDA within 5 business days after the sponsor learns of the use of the investigational medical device. The report should include circumstances of the case and measures followed for patient protection including

- Informed consent
- Institutional clearance
- Concurrence of IRB Chairperson
- Independent assessment from an uninvolved physician
- Authorization from the IDE sponsor (if an IDE exists) or manufacturer
- Monitoring plans and follow-up information.

Refer to IRB SOP 1.10 "*Emergency Use of An Investigational Drug, Biological Product, or Device"* for more details.

Expanded Access/Compassionate Use

The FDA recognizes that there are circumstances in which an investigational device is the only option available to a patient faced with a serious or life-threatening disease or condition. The compassionate use provision provides a path to accessing investigational devices that have not received FDA approval or clearance for patients for whom the treating physician believes the device may provide a benefit in diagnosing, monitoring, or treating their disease or condition. Compassionate use can be for devices that are being studied in a clinical trial under an IDE for patients who do not meet the requirements for inclusion in the clinical investigation but for whom the treating physician believes the device may provide a benefit in treating or diagnosing their disease or condition. It can also be used for devices that are not being studied in a clinical investigation (such as an IDE for the device does not exist). This provision is typically approved for individual

patients but may be approved to treat a small group, if the small group request is under an IDE. (Ref FDA Expanded Access for Medical Devices)

Criteria

1. Serious disease or condition
2. No comparable or satisfactory alternative treatment

Timeframe

During the clinical trial

Requesting Approval for Compassionate Use of a Device

For a device with no IDE: If there is **no IDE** for the device, a compassionate use request for a single patient may be submitted by the physician or manufacturer with the above information, along with a description of the device provided by the manufacturer, to the FDA at:

Food and Drug Administration
Center for Devices and Radiological Health
10903 New Hampshire Ave
Document Control Center
WO66 Rm G-609
Silver Spring, MD 20993

For assistance, physicians and manufacturers may contact CDRHExpandedAccess@fda.hhs.gov.

***For a device with an existing IDE*:** Prior FDA approval is needed before compassionate use occurs according to a 30-calendar-day review timeframe. In order to obtain FDA approval on **an existing IDE** to treat the patient(s), the sponsor (who may be the device manufacturer or a physician who has submitted the IDE to conduct the clinical study for the device) should submit an IDE supplement requesting approval for a protocol deviation under section 21 CFR 812.35(a). The IDE supplement must include:

1. A description of patient's (or patients') condition and circumstances necessitating treatment;
2. A discussion of why alternative therapies are unsatisfactory and why the probable risk of using the investigational device is not greater than the probable risk from the disease or condition;
3. Identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient, and
4. Patient protection measures that will be followed including:
   - informed consent,
   - concurrence of the IRB chair,
   - clearance from the institution,
   - independent assessment from uninvolved physician,
   - authorization from IDE sponsor.

The physician should not treat the patient identified in the IDE supplement until the FDA approves use of the device under the proposed circumstances. When there is an IDE for the device, compassionate use request IDE supplements have the same statutory 30-day review cycle as other IDE submissions; however, the patient need is considered when reviewing these requests as well as whether the preliminary evidence of safety and effectiveness justifies such use and whether such use would interfere with the conduct of a clinical trial investigating support of marketing approval.

If the request is approved, the attending physician should devise a schedule for monitoring the patient, taking into consideration the investigational nature of the device and the specific needs of the patient. The patient should be monitored to detect any problems arising which could be possibly associated with the use of the device. Following the compassionate use of the device, a follow-up report should be submitted to the FDA as an IDE supplement within 45 days of using the investigational device in which summary information regarding patient outcome is presented. If any problems occurred as a result of device use, these should be discussed in the supplement and reported to the reviewing IRB as soon as possible.

Treatment IDE Use

An approved IDE specifies the maximum number of clinical sites and the maximum number of human subjects that may be enrolled in a study. During the course of the clinical trial, if the data suggests that the device is effective, the trial may be expanded under a new IDE to include additional patients with life-threatening or serious diseases.

An "immediately life-threatening" disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. "Treatment use" of a device includes the use of a device for diagnostic purposes. (Ref. 21 CFR 812.36(a))

Criteria

The FDA shall consider the use of an investigational device under a treatment IDE if:

1. The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition
2. There is no comparable or satisfactory alternative device or other therapy available to treat or diagnose the stage of the disease or condition in the intended patient population
3. The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or such clinical trials have been completed, and
4. The sponsor of the investigation is actively pursuing marketing approval/clearance of the investigational device with due diligence

(Ref. 21 CFR 812.36(b))

Timeframe

During the clinical trial

A device that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease or condition in patients for whom no comparable or satisfactory alternative device or other therapy is available. During the clinical trial or prior to final action on the marketing application, it may be appropriate to use the device in the treatment of patients not enrolled in the trial under the provisions of the Treatment Use of an investigational device exemption (IDE). (Ref. 21 CFR 812.36)

The Treatment Use provision facilitates the availability of promising new devices to desperately ill patients as early in the device development process as possible, before general marketing begins, and to obtain additional data on the device's safety and effectiveness. In the case of a serious disease, a device ordinarily may be made available for treatment use under this section after all clinical trials have been completed. In the case of an immediately life-threatening disease, a device may be made available for treatment use under this section prior to the completion of all clinical trials.

Applications for Treatment Use

A treatment IDE application shall include, in the following order (ref. 21 CFR 812.36(c)):

1. Name, address and telephone number of the sponsor of the treatment IDE;
2. The intended use of the device, criteria for patient selection, and a written protocol describing the treatment use;
3. An explanation of the rationale for use of the device, including, as appropriate, either a list of the available regimens that ordinarily should be tried before using the investigational device or an explanation of why the use of the investigational device is preferable to the use of available marketed treatments;
4. A description of clinical procedures, laboratory tests, or other measures that will be used to evaluate the effects of the device and to minimize risk;
5. Written procedures for monitoring the treatment use and the name and address of the monitor;
6. Instructions for use for the device and all other labeling as required under § 812.5(a) and (b);
7. Information that is relevant to the safety and effectiveness of the device for the intended treatment use (information from other IDE's may be incorporated by reference to support the treatment use);
8. A statement of the sponsor's commitment to meet all applicable responsibilities under federal regulations 21 CFR 812.36(c)(1)(vii) and 21 CFR 56, and to ensure compliance of all participating investigators with the informed consent requirements of 21 CFR 50;
9. An example of the agreement to be signed by all investigators participating in the treatment IDE and certification that no investigator will be added to the treatment IDE before the agreement is signed; and
10. If the device is to be sold, the price to be charged and a statement indicating that the price is based on manufacturing and handling costs only.

A licensed practitioner who receives an investigational device for treatment use under a treatment IDE is an "investigator" under the IDE and is responsible for meeting all applicable investigator responsibilities under 21 CFR 812, 21 CFR 50, and 21 CFR 56. (Ref. 21 CFR 812.36(c)(2))

Address for IDE Correspondence

If you are sending an application, supplemental application, report, request for waiver, request for import or export approval, or other correspondence relating to matters covered by this part, you must send the submission to the appropriate address as noted in 21 CFR 812.19.

Applications should be identified on the outside envelope as a treatment IDE application and Reference the IDE number. The original and two copies should be mailed to:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center (DCC) – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Additional information for submission of applications and most IDE supplements, amendments and reports may be found at IDE Application | FDA including instructions for electronic submission.

FDA Action on Treatment IDE Applications

Approval of Treatment IDEs

Treatment use may begin 30 days after FDA receives the treatment IDE submission at the address specified in 21 CFR 812.19, unless FDA notifies the sponsor in writing earlier than the 30 days that the treatment use may or may not begin. FDA may approve the treatment use as proposed or approve it with modifications.

Disapproval/Withdrawal of Approval of Treatment IDEs

FDA may disapprove or withdraw approval of a treatment IDE if:

1. The required criteria 812.36(b) are not met or the treatment IDE application does not contain the required information 812.36(c);
2. FDA determines that any of the grounds for disapproval or withdrawal of approval apply 812.30(b)(1) through (b)(5);
3. The device is intended for a serious disease or condition and there is insufficient evidence of safety and effectiveness to support such use;

4. The device is intended for an immediately life-threatening disease or condition and the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the device:
    a. May be effective for its intended use in its intended population; or
    b. Would not expose the patients to whom the device is to be administered to an unreasonable and significant additional risk of illness or injury
5. There is reasonable evidence that the treatment use is impeding enrollment in, or otherwise interfering with the conduct or completion of, a controlled investigation of the same or another investigational device;
6. The device has received marketing approval/clearance or a comparable device or therapy becomes available to treat or diagnose the same indication in the same patient population for which the investigational device is being used;
7. The sponsor of the controlled clinical trial is not pursuing marketing approval/clearance with due diligence;
8. Approval of the IDE for the controlled clinical investigation of the device has been withdrawn; or
9. The clinical investigator(s) named in the treatment IDE are not qualified by reason of their scientific training and/or experience to use the investigational device for the intended treatment use.

Notice of Disapproval or Withdrawal

If the FDA disapproves or proposes to withdraw approval of a treatment IDE, the FDA will follow the procedures set forth in the IDE regulations 812.30(c).

Safeguards (ref. 21 CFR 812.36(e))

Treatment use of an investigational device is conditioned upon the sponsor and investigators complying with the safeguards of the IDE process and the regulations governing informed consent at 21 CFR 50 and IRB's at 21 CFR 56.

Reporting Requirements (ref. 21 CFR 812.36(f))

The sponsor of a treatment IDE shall submit progress reports on a semi-annual basis to all reviewing IRBs and FDA until the filing of a marketing application. These reports shall be based on the period of time since initial approval of the treatment IDE and shall include the number of patients treated with the device under the treatment IDE, the names of the investigators participating in the treatment IDE, and a brief description of the sponsor's efforts to pursue marketing approval/clearance of the device. Upon filing of a marketing application, progress reports shall be submitted annually in accordance with § 812.150(b)(5). The sponsor of a treatment IDE is responsible for submitting all other reports required under §812.150.

Additional Information

Type of Expanded Access	Brief Definition	FDA approval required?	Follow-up Reports to the FDA
Emergency use	Use of an investigational device when an **individual patient is in a life-threatening situation**	No	Yes

	and needs immediate treatment (there are no alternative options and no time to use existing procedures to get FDA approval for the use)		
Compassionate use	Use of an investigational device to **treat or diagnose an individual patient or a small group of patients** with a serious disease or condition when there are no available alternative options	Yes	Yes
Treatment IDE	Use of an investigational device to **treat or diagnose a group of patients** with a serious or immediately life-threatening disease or condition when the device is also being studied for the same use under an approved Investigational Device Exemption.	Yes	Yes

(Ref. FDA Expanded Access for Medical Devices)

Continued Access

In order to allow access to an investigational medical device while the marketing application is being prepared by the sponsor or reviewed by the FDA, the FDA may allow continued enrollment of subjects after the controlled clinical trial under an IDE has been completed.

Criteria

1. Public health need for the device, or
2. Preliminary evidence that the device is likely to be effective and no significant safety concerns have been identified for the proposed indication.

Timeframe

After completion of the clinical trial

The continued enrollment of subjects in an investigation while a marketing application is being prepared by the sponsor and/or reviewed by ODE is known as an "extended investigation." Extended investigations permit patients and/or physicians continued access to investigational devices while also allowing the collection of additional safety and effectiveness data to support the marketing application or to address new questions regarding the investigational device. The Continued Access mechanism may be applied to any clinical investigation that meets the identified under **13.1.4** (a) above. However, continued access is intended to be applied late in the device development process (i.e., after the controlled clinical trial has been completed).

IDE Supplement Guidelines

A sponsor's request for an extended investigation should be submitted as an IDE supplement and include:

1. Justification for the extension;
2. Summary of the preliminary safety and effectiveness data generated under the IDE;
3. A brief discussion of the risks posed by the device;
4. The proposed rate of continued enrollment (the number of sites and subjects);

5. The clinical protocol, if different from that used for the controlled clinical trial, as well as the proposed objectives for the extended study; and
6. A brief discussion of the sponsor's progress in obtaining marketing approval/clearance for the device.

Determining Continued Access or Treatment Investigational Device Exemption

There is significant overlap between the mechanisms Continued Access and Treatment IDE. Both Continued Access and the Treatment IDE are intended to provide additional access to an unapproved device once preliminary evidence regarding safety and effectiveness is available to the FDA. However, because a Treatment IDE can be submitted earlier in the IDE process (i.e., once promising evidence of safety and effectiveness has been collected under the IDE but while the clinical study is ongoing), Treatment IDE could provide access to a wider group of patients at an earlier stage in the IDE process. However, the Treatment IDE regulation has a narrower application than the Continued Access policy in that treatment used is intended to address only those patients who have an immediately life-threatening or serious disease or condition whereas Continued Access, applied after completion of the clinical trial, may be considered for any clinical investigation.

INVESTIGATIONAL DRUGS AND BIOLOGICS

The FDA describes three distinct categories of expanded access to investigational drugs and biologics based on the number of people who need access and the level of risk:

1. Expanded access for individual patients (including for emergency use)
2. Expanded access for intermediate-size patient groups
3. Expanded access for widespread treatment use

An expanded access IND submission is required for each of the three types of expanded access. The submission may be a ***new IND*** or a protocol amendment to an ***existing IND***. Ref. FDA Guidance Expanded Access Categories for Drugs (Including Biologics)

Refer to IRB SOP 1.11 "*Expanded Access to Investigational New Drugs*" for more details.

Individual Patient Access

Commonly held by the treating physician or investigator for treatment of an individual patient. (Ref. 21 CFR 312.310)

Individual Patient Expanded Access IND (Single Patient IND)

Requests access to an investigational drug (including a biologic) for use by a single patient submitted as a protocol ***under a new IND***. The investigational product may or may not be under development. Unless FDA notifies the sponsor that treatment may begin earlier, there is a 30-day waiting period before treatment with the drug may begin.

Individual Patient Expanded Access Protocol (Single Patient Protocol)

Access to an investigational drug (including biologics) for use by a single patient submitted as a new protocol *to* ***an existing*** **IND** ***by the sponsor of the existing IND***. Typically, several patients may follow the same protocol. The investigational product may or may not be under development. There is no 30-day waiting period before treatment with the investigational product may begin, but the protocol must be received by the FDA and have approval by the IRB before treatment may begin.

Individual Patient Access in an Emergency

Emergency IND

Access to an investigational drug (including biologics) for use by a single patient in an emergency situation (i.e., a situation that requires a patient to be treated before a written submission can be made) submitted as a protocol under a ***new IND***. Treatment is initially requested and authorized by telephone or other rapid means of electronic communication and may start immediately upon FDA authorization. The written submission (i.e., the individual patient expanded access IND) must be submitted within 15 business days of the telephone authorization.

Emergency Protocol

Individual Patient Expanded Access Protocol for Emergency Use providing access to an investigational drug (including a biologic) for use by a single patient in an emergency situation (i.e., a situation that requires a patient to be treated before a written submission can be made) submitted as a new protocol to an ***existing IND*** by the sponsor of the existing IND. Treatment is initially requested and authorized by telephone or other rapid means of communication, and treatment may start immediately upon FDA authorization. The written submission (i.e., the individual patient expanded access protocol) must be submitted within 15 business days of the telephone authorization.

In an emergency situation where there is not sufficient time to secure IRB review prior to beginning treatment, the emergency use of the investigational drug must be reported to the IRB within 5 working days, as required under 21 CFR 56.104(c).

Note: If a physician has determined that an emergency exists, instructions can be followed on FDA's Expanded Access Contact Information. For additional information regarding emergency requests (phone submissions, other forms of rapid communication such as e-mail) made by a licensed physician after receiving agreement from industry to provide the investigational medical product for expanded access use, refer to FDA publication Emergency Use of an Investigational Drug or Biologic.

Ref. FDA guidance: Expanded Access | Information for Physicians

Refer to IRB SOP 1.10 "*Emergency Use of An Investigational Drug, Biological Product, or Device*" for more details.

Intermediate-Size Patient Population Access (ref. 21 CFR 312.315)

Intermediate-size Patient Population Expanded Access IND
Access to an investigational drug (including a biologic) for use by more than one patient, but generally fewer patients than are treated under a typical treatment IND or protocol, submitted as a protocol under a new IND. The investigational product may or may not be under development for marketing. Unless FDA notifies the sponsor that treatment may begin earlier, there is a 30-day waiting period before treatment may begin.

Intermediate-size Patient Population Expanded Access Protocol
Access to an investigational drug (including biologics) for use by more than one patient, but generally fewer patients than are treated under a typical treatment IND or protocol, submitted as a protocol to an existing IND by the sponsor of the existing IND. The investigational product may or may not be under development for marketing. There is no 30-day waiting period before treatment with the investigational product may begin, but the protocol must be received by FDA and have IRB approval before treatment may begin.

An intermediate-size patient population protocol may also be requested to allow access to treatment with an approved drug (including a biologic) or a related product that is not available through marketing channels because of failure to meet the conditions of approval or a drug shortage, provided the drug and the patient meet the general criteria for expanded access as well as the criteria specific to use in an intermediate-size patient population.

Expanded Access for Widespread Use (Ref. 21 CFR 312.320)

Treatment IND
Access to an investigational drug (including biologics) for treatment use by a large (widespread) population, submitted as a protocol ***under a new IND***. The investigational product must be under active development for marketing. Unless FDA notifies the sponsor that treatment may begin earlier, there is a 30-day waiting period before treatment may begin.

Treatment Protocol
Access to an investigational drug (including biologics) for treatment use by a large (widespread) population, submitted as a protocol ***to an existing IND by the sponsor of the existing IND***. The investigational product must be under development for marketing. Unlike other access protocols submitted to existing INDs, there is a 30-day waiting period before treatment may begin, unless FDA notifies the sponsor that treatment may begin earlier.

REFERENCES:

- IRB SOP 1.10 “Emergency Use of An Investigational Drug, Biological Product, or Device” for more details.
- IRB SOP 1.11, Expanded Access - Investigational New Drugs

- IRB SOP 1.24 Expanded Access - Investigational Devices
- FDA Regulation, 21 CFR 312.305, Requirements for All Expanded Access Uses

Section 13 Regulatory History
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SECTION 14 - SPONSOR REQUIREMENTS FOR INVESTIGATORS WHO ARE SERVING AS SPONSORS (SPONSOR-INVESTIGATORS) FOR FDA REGULATED RESEARCH

INVESTIGATIONAL DRUG OR BIOLOGIC STUDIES

A *sponsor* is an individual, pharmaceutical company, governmental agency, academic institution, private organization, or other organization which takes responsibility for and initiates a clinical investigation. Sponsors of Investigational New Drugs (INDs) are responsible for reviewing the federal regulations before performing any sponsor's duties including, but not limited to, selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the Investigational New Drug authorization (IND), maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. (Ref. 21 CFR 312.50)

Sponsors who also serve as investigators of a drug/biologic are individuals who both initiate and conduct an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A *sponsor-investigator* must meet the requirements for both the sponsor *and* the investigator. Regulatory responsibilities for investigators and sponsors are detailed in Subpart D of 21 CFR 312.

IND Requirements

When research involves the use of a drug other than the use of a marketed drug in the course of medical practice, the IRB must confirm that either:

A. The drug has an IND, or

B. The protocol meets one of the FDA exemptions from the requirement to have an IND (ref. 21 CFR 312.2(b)):

1. Exemption 1
   The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements if all the following apply:
   a. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

b. If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
c. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
d. The investigation is conducted in compliance with the requirements for institutional review set forth in 21 CFR 56 and with the requirements for informed consent set forth in 21 CFR 50; and
e. The investigation is conducted in compliance with the requirements of 21 CRF 312.7.

2. Exemption 2
   a. A clinical investigation involving an in vitro diagnostic biological product listed in 14.1.2(b)(ii)(2) below is exempt from the requirements of this part if (a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure, and (b) it is shipped in compliance with 21 CFR 312.160.
   b. In accordance with 14.1.2(b)(ii)(1) above, the following products are exempt from the requirements of this part: (*a*) blood grouping serum; (*b*) reagent red blood cells; and (*c*) anti-human globulin.

3. Exemption 3
   A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped in accordance with 21 CFR 312.160.

4. Exemption 4
   FDA will not accept an application for an investigation that is exempt under the provisions of Exemption 1 above.

5. Exemption 5
   A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.

6. Exemption 6
   A clinical investigation involving an exception from informed consent under 21 CFR 50.24 is not exempt from the requirements of this part.

Responsibilities of Sponsors with IND Studies

1. IND Application: Submits an IND application including Form FDA-1571 and other required documentation to the FDA (ref. 21 CFR 312.23)

2. Labeling: Labels the investigational drug in accordance with FDA regulations (ref. 21 CFR 312.6)

3. Promotion and Distribution: Promotes and distributes the drug in accordance with FDA regulations (ref. 21 CFR 312.7)

4. Selection of Investigators: Selects qualified investigators based on training and experience (ref. 21 CFR 312.53(a))

5. Control of Drug: Ships investigational drugs only to investigators participating in the investigation (ref. 21 CFR 312.53(b))

6. Form FDA 1572: Obtains FDA Form 1572 from the investigator(s) (ref. 21 CFR 312.53(c)(1))

7. Commitment of Investigator: Obtains a written statement that the investigator(s) will conduct the study as outlined in the protocol (ref. 21 CFR 312.53(c)(1)(vi)(a))

8. Financial Disclosure: Obtains relevant financial information from the investigator(s) (ref. 21 CFR 312.53(c)(4))

9. Selection of Monitor(s): Selects a qualified monitor to oversee the progress of the investigation (ref. 21 CFR 312.53(d))

10. Emergency Research: Complies with FDA regulations regarding emergency use (ref. 21 CFR 312.54)

11. Informing Investigators: Keeps each participating investigator informed on the safety and effectiveness of the drug (ref. 21 CFR 312.55)

12. Review of Ongoing Investigations:
    a. Monitors the progress of all IND investigations (ref. 21 CFR 312.56(a))
    b. Terminates investigator(s) participation when investigator(s) fails to follow protocol (ref. 21 CFR 312.56(b))
    c. Reviews and evaluates the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator (ref. 21 CFR 312.56(c))
    d. Discontinues the study if the investigational drug presents an unreasonable and significant risk to subjects, and notifies the FDA, IRB and the investigator(s) if the study is discontinued (21 CFR 312.56(d))

e. Safety Reporting: Sends safety reports to the FDA (ref. 21 CFR 312.56(c); 21 CFR 312.32)

13. Sponsor Recordkeeping and Retention (ref. 21 CFR 312.57)
    a. Maintains adequate records showing the receipt, shipment or other disposition of the investigational drug
    b. Maintains complete and accurate records of payments made to clinical investigator(s).

14. Disposition of Unused Supply: Assures that investigator(s) return all unused investigational drugs (ref. 21 CFR 312.59)

15. Investigator Recordkeeping and Retention (ref. 21 CFR 312.62):
    a. Requires investigator(s) to maintain adequate drug records.
    b. Requires investigator(s) to keep case histories on each individual administered the investigational drug or employed as a control in the investigation.

16. Assurance of IRB Review**:** Requires investigator(s) to meet local IRB requirements (ref. 21 CFR 312.66)

17. Investigator Reports**:** Collects reports (progress, safety, financial and final reports) from investigator(s) (ref. 21 CFR 312.64)

18. Handling of Controlled Substances**:** Requires investigator(s) to store the investigational drug in a secure area (ref. 21 CFR 312.69)

INVESTIGATIONAL DEVICE OR TEST ARTICLE STUDIES

A sponsor of an investigational medical device is an individual, pharmaceutical company, governmental agency, academic institution, private organization, or other organization which takes responsibility for and initiates a clinical investigation of an investigational device. Sponsors are responsible for reviewing the federal regulations before performing any sponsor's duties. Sponsors who also serve as investigators of the investigational device are individuals who both initiate and conduct an investigation, and under whose immediate direction the investigation is carried out. A sponsor-investigator must meet the requirements for both the sponsor *and* the investigator.

The following is an overview of the FDA requirements for sponsors, intended to assist sponsors in identifying and complying with their responsibilities in connection with the conduct of clinical investigations of medical devices that are deemed "significant risk" by the reviewing IRB or by the FDA.

A *significant risk device* is an investigational device that:

1. is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

2. is for use in supporting or sustaining human life and represents a potential for serious risk to the health, safety, or welfare of a subject;
3. is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4. otherwise presents a potential for serious risk to a subject.

In addition, sponsors should be aware that a clinical investigation must be conducted in accordance with any requirements imposed by the reviewing IRB, by institutional policies, or by state law.

Responsibilities of Sponsors with IDE Studies

1. General Responsibilities (Ref. 21 CFR 812.40): Sponsors are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an Investigational Device Exemption (IDE) application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation.

   An Investigational Device Exemption (IDE) refers to the regulations under 21 CFR 812 Subchapter H. An approved IDE means that the IRB (and FDA for significant risk devices) has approved the sponsor's study application and all the requirements under 21 CFR 812 are met. Additional responsibilities of sponsors are described in subparts B and G.

2. Application:

   a. A sponsor shall submit an application to FDA if the sponsor intends to use a significant risk device in an investigation, intends to conduct an investigation that involves an exception from informed consent (ref. 21 CFR 50.24), or if FDA notifies the sponsor that an application is required for an investigation.
   b. A sponsor A sponsor shall not begin an investigation for which FDA's approval of an application is required until FDA has approved the application.
   c. A sponsor shall submit a signed "Application for an Investigational Device Exemption" (IDE application), together with accompanying materials in electronic format, to one of the addresses in 21 CFR 812.19, and if eCopy by registered mail or by hand. Subsequent correspondence concerning an application or a supplemental application shall be submitted in electronic format and if eCopy by registered mail or by hand.
   d. A sponsor shall submit a separate IDE for any clinical investigation involving an exception from informed consent under 21 CFR 50.24 of this chapter. Such a clinical investigation is not permitted to proceed without the prior written authorization of FDA. FDA shall provide a written determination 30

days after FDA receives the IDE or earlier. If the investigation involves an exception from informed consent under 21 CFR 50.24 of this chapter, the sponsor shall prominently identify on the cover sheet that the investigation is subject to the requirements in 21 CFR 50.24.

e. **Other Contents and Information:** An IDE application shall include all content, additional information, and information previously submitted as outlined under 21 CFR 812.20(b), (c) and (d).

3. FDA and IRB Approval: A sponsor shall not begin an investigation or part of an investigation until an IRB and FDA have both approved the application or supplemental application relating to the investigation or part of an investigation. (Ref. 21 CFR 812.42)

4. Selecting Investigators and Monitors: A sponsor shall select investigators qualified by training and experience to investigate the device. A sponsor shall select monitors qualified by training and experience to monitor the investigational study in accordance with this part and other applicable FDA regulations. (Ref. 21 CFR 812.43)

5. Informing Investigators: A sponsor shall supply all investigators participating in the investigation with copies of the investigational plan and the report of prior investigations of the device. (Ref. 21 CFR 812.45)

6. Control of Device: A sponsor shall ship investigational devices only to qualified investigators participating in the investigation. (Ref. 21 CFR 812.43(b))

7. Obtaining Agreements: A sponsor shall obtain from each participating investigator a signed agreement that includes:
   a. The investigator's curriculum vitae
   b. Where applicable, a statement of the investigator's relevant experience, including the dates, location, extent, and type of experience.
   c. If the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination.
   d. A statement of the investigator's commitment to: (1) conduct the investigation in accordance with the agreement, the investigational plan, this part and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA; (2) supervise all testing of the device involving human subjects; and (3) ensure that the requirements for obtaining informed consent are met (ref. 21 CFR 50).
   e. Sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement as required under 21 CFR 54. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant

changes occur during the course of the investigation and for 1 year following completion of the study. This information shall not be submitted in an investigational device exemption application, but shall be submitted in any marketing application involving the device.

8. Monitoring (ref. 21 CFR 812.46):
   a. Securing Compliance**:** A sponsor who discovers that an investigator is not complying with the signed agreement, the investigational plan, the IDE requirements, any other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA must promptly either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation. A sponsor must also require that the investigator dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.

   b. Unanticipated Adverse Device Effects (UADEs)**:** The sponsor must immediately conduct an evaluation of any unanticipated adverse device effect. A sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects must terminate all investigations or parts of the investigations presenting that risk as soon as possible. Termination must occur no later than 5 working days after the sponsor makes this determination and no later than 15 working days after the sponsor first received notice of the effect.

   c. Resumption of Terminated Studies**:** For significant risk device investigations, a sponsor may not resume a terminated investigation without IRB and FDA approval. For a nonsignificant risk device investigation, a sponsor may not resume a terminated investigation without IRB approval. If the nonsignificant risk study was terminated for unanticipated adverse device effects, the sponsor must also obtain FDA approval.

9. Controlling Distribution and Disposition of Devices: Although investigators are responsible for ensuring that investigational devices are made available only to persons who are legally authorized to receive them (ref. 21 CFR 812.110(c)), sponsors also bear responsibility for taking proper measures to ensure that devices are not diverted outside of legally authorized channels. Sponsors may ship investigational devices only to qualified investigators participating in the clinical investigation (ref. 21 CFR 812.43(b)). Sponsors must also maintain complete, current and accurate records pertaining to the shipment and disposition of the investigational device (ref. 21 CFR 812.140(b)). Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark. Records of disposition shall describe the batch number or code marks of any devices returned to the sponsor,

repaired or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal.

To ensure further compliance with these requirements, sponsors should take appropriate measures to instruct investigators regarding their responsibilities with respect to recordkeeping and device disposition. The specific recordkeeping requirements for investigators are set forth at 21 CFR 812.140(a). Upon completion or termination of a clinical investigation (or the investigator's part of an investigation), or at the sponsor's request, an investigator is required to return to the sponsor any remaining supply of the device or otherwise to dispose of the device as the sponsor directs. (ref. 21 CFR 812.110(e)).

10. Prohibition of Promotion and Other Practices (ref. 21 CFR 812.7): The IDE regulations prohibit the promotion and commercialization of a device that has not been cleared or approved for marketing by the FDA. A sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator shall not:

    a. Promote or test market an investigational device, until after FDA has approved the device for commercial distribution;
    b. Commercialize an investigational device by charging the subjects or investigators for a device a price larger than that necessary to recover costs of manufacture, research, development, and handling;
    c. Unduly prolong an investigation; If data developed by the investigation indicate in the case of a class III device that premarket approval cannot be justified or in the case of a class II device that it will not comply with an applicable performance standard or an amendment to that standard, the sponsor shall promptly terminate the investigation, or
    d. Represent that an investigational device is safe or effective for the purposes for which it is being investigated.

11. Supplemental Applications: Supplemental applications are required to be submitted to, and approved by, the FDA in the following situations:

    a. Changes in the investigational plan, changes requiring prior approval including any change that may affect the scientific soundness of the investigation or the rights, safety or welfare of the subjects. IRB approval is also required for changes that may affect the rights, safety or welfare of subjects. The change in the investigational plan may not be implemented until FDA approval (and IRB approval, if required) is obtained.
    b. Addition of New Institutions: IRB approval is also required for new institutions. The investigation at the new institution may not begin until both FDA and IRB approvals are obtained, and certification of IRB approval is submitted to the FDA. Ref. 21 CFR 812.35 for additional information.

12. Records

a. Sponsor Records (ref. 21 CFR 812.140(b)): A sponsor shall maintain the following accurate, complete and current records relating to an investigation:

1) All correspondence with another sponsor, a monitor, an investigator, an IRB, or FDA, including required reports
2) Records of shipment and disposition. Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark. Records of disposition shall describe the batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal.
3) Signed investigator agreements including the financial disclosure information required to be collected under 21 CFR 812.43(c)(5) in accordance with 21 CFR 54.
4) For each investigation subject to 21 CFR 812.2(b)(1) of a device other than a significant risk device, the records described in 21 CFR 812.140(b)(5) and the following records, consolidated in one location and available for FDA inspection and copying:
   - The name and intended use of the device and the objectives of the investigation;
   - A brief explanation of why the device is not a significant risk device:
   - The name and address of each investigator:
   - The name and address of each IRB that has reviewed the investigation:
   - A statement of the extent to which the good manufacturing practice regulation in 21 CFR 820 will be followed in manufacturing the device; and
   - Any other information required by FDA.
5) Records concerning adverse device effects (whether anticipated or unanticipated) and complaints; and
6) Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

b. **Investigator Records** (21 CFR 812.140(a)): A participating investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:

1) All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.
2) Records of receipt, use or disposition of a device that relate to:

- The type and quantity of the device, the dates of its receipt, and the batch number or code mark.
- The names of all persons who received, used, or disposed of each device.
- Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.

3) Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:

   - Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
   - All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
   - A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.

4) The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

5) Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

Sponsor/Investigator Responsibilities - Records

Records	Maintained by Sponsor	Maintained by Investigator
All correspondence pertaining to the investigation	X	X
Shipment, receipt, disposition	X	X
Device administration & use	-	X
Subject case histories	-	X
Informed consent	-	X
Protocols and reasons for deviations from protocol		X

Adverse device effects and complaints	X	X
Signed investigator agreements	X	-
Conflicts of interest	X	-

13. Reports

a. Sponsor Reports: A sponsor shall prepare and submit the following complete, accurate and timely reports (ref. 21 CFR 812.150(b)):

1) Unanticipated Adverse Device Effects: A sponsor who conducts an evaluation of an unanticipated adverse device effect under 21 CFR 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit additional reports concerning the effect as FDA requests.
2) Withdrawal of IRB Approval: A sponsor shall notify FDA and all reviewing IRB's and participating investigators of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the withdrawal of approval.
3) Withdrawal of FDA Approval: A sponsor shall notify all reviewing IRB's and participating investigators of any withdrawal of FDA approval of the investigation and shall do so within 5 working days after receipt of notice of the withdrawal of approval.
4) Current Investigator List: A sponsor shall submit to FDA, at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. The sponsor shall submit the first such list 6 months after FDA approval.
5) Progress Reports: At regular intervals, and at least yearly, a sponsor shall submit progress reports to all reviewing IRBs. In the case of a significant risk device, a sponsor shall also submit progress reports to FDA. A sponsor of a treatment IDE shall submit semi-annual progress reports to all reviewing IRB's and FDA in accordance with 21 CFR 812.36(f) and annual reports in accordance with this section.
6) Recall and Device Disposition: A sponsor shall notify FDA and all reviewing IRBs of any request that an investigator return, repair, or otherwise dispose of any units of a device. Such notice shall occur within 30 working days after the request is made and shall state why the request was made.
7) Final Report: In the case of a significant risk device, the sponsor shall notify FDA within 30 working days of the completion or termination of the investigation and shall submit a final report to FDA and all reviewing the IRB's and participating investigators within 6 months after completion or

termination. In the case of a device that is not a significant risk device, the sponsor shall submit a final report to all reviewing IRBs within 6 months after termination or completion.

8) Informed Consent: A sponsor shall submit to FDA a copy of any report by an investigator under 21 CFR 812.150(a)(5) of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.
9) Significant Risk Device Determinations: If an IRB determines that a device is a significant risk device, and the sponsor proposed that the IRB consider the device not to be a significant risk device, the sponsor shall submit to FDA a report of the IRB's determination within 5 working days after the sponsor first learns of the IRB's determination.
10) Other: A sponsor shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

b. Investigator Reports **(**21 CFR 812.150(a)): An investigator shall prepare and submit the following complete, accurate, and timely reports:

1) Unanticipated adverse device effects: An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
2) Withdrawal of IRB approval: An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
3) Progress: An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the Reviewing IRB at regular intervals, but in no event less often than yearly.
4) Deviations from the investigational plan: An investigator shall notify the sponsor and the reviewing IRB (see 21 CFR 56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB in accordance with 21 CFR 812.35(a) also is required.
5) Informed consent: If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

6) Final report: An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.
7) Other: An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

Sponsor/Investigator Responsibilities - Reporting

Report Type	Sponsors prepare for:	Investigators prepare for:
Unanticipated adverse device events	FDA, IRBs and Investigators	Sponsors and IRBs
Withdrawal of IDE approval	FDA, IRBs and Investigators	Sponsors
Progress Report	FDA and IRBs	Sponsors, Monitors and IRBs
Final Report	FDA, IRBs and Investigators	Sponsors and IRBs
Withdrawal of FDA approval	IRBs and Investigators	N/A
Current Investigator List	FDA	N/A
Recall and device disposition	FDA and IRBs	N/A
Records maintenance transfer	FDA	FDA
Significant risk determinations	FDA	N/A

14. Inspections (ref. 21 CFR 812.145):

a. Entry and Inspection**:** A sponsor or an investigator who has authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).
b. Records Inspection**:** A sponsor, IRB, or investigator, or any other person acting on behalf of such a person with respect to an investigation, shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.
c. Records Identifying Subjects**:** An investigator shall permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

Additional Guidance: Significant (SR) and Nonsignificant Risk (NSR) Investigational Device Studies

FDA guidance for Sponsors of Nonsignificant Risk Device Studies, Investigators of Significant Risk Device Studies and Investigators of Nonsignificant Risk Device Studies can be found in FDA publication "IDE Responsibilities."

Section 14 Regulatory History
Effective Date: 10/09
Revised/Reviewed Date: 04/26
AAHRPP Element: I.7.A, I.7.B, 1.7.C, III.2.B

SECTION 15 - INVESTIGATIONAL MEDICAL PRODUCTS

Background

The U.S. Food and Drug Administration (FDA) defines a medical device, in part, as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part or accessory which is intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes" (Food, Drug and Cosmetic Act [2012], Chapter 2, Section 201[h]).

Examples of medical devices include, but are not limited to, surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts or stents, intraocular lenses, orthopedic pins, and radiographic imaging equipment. Medical devices also include diagnostic aids such as reagents and test kits for in vitro diagnosis of disease or other medical conditions such as pregnancy.

Except for certain low risk devices (Class I and Class II devices), device manufacturers who wish to bring new medical devices to the market must register their intent by submitting pre-market notification to the FDA. The FDA reviews pre-market notifications to determine if the new device is "substantially equivalent" to a device that was marketed prior to the passage of the Medical Device Amendments of 1976 (i.e., a "pre-amendments device") to the Federal Food, Drug and Cosmetics Act. If the new device is deemed to be substantially equivalent to a pre-amendment's device, it may be marketed immediately and is regulated in the same regulatory class as the pre-amendments device to which it is equivalent. Devices determined by FDA to be "substantially equivalent" are often referred to as "510k devices" (i.e., the pre-market notification requirement for new devices is set forth in section 510(k) of the Federal Food Drug and Cosmetic Act). If a new device is deemed not to be equivalent to a pre-amendment's device, clinical studies of its safety and effectiveness must be performed and FDA approval granted before the device can be marketed.

If the objective of the clinical investigation is to assess the safety and/or effectiveness of a medical device, then the study is a device study and is subject to regulatory oversight by the US Food and Drug Administration as defined in 21 CFR 812 (Investigational Device Exemption). If the objective of the study is not to test the safety or effectiveness of the device, then the study would not fall within the scope of 21 CFR 812.
Such a device is used as a "tool". One example of this would be when an MRI is used to collect data in an oncology drug trial to evaluate tumor response or a thermometer used to check temperature as an inclusion criterion for a study.

When research involves a device with an IDE, the IRB Chair or Primary Reviewer confirms that the IDE number is valid. Validation can occur by confirming the IDE number on the sponsor protocol, communication from the sponsor, or communication from the FDA. In cases of investigators who hold the IDE, validation can occur by confirming the number on the communication from the FDA. Note: Investigator brochures should not be used as confirmation that an IDE exists for the trial since one brochure may be used for multiple IDEs.

Regulatory Requirements for Clinical Studies

An investigational device is any unapproved medical device undergoing clinical trials to provide evidence to regulatory authorities that the product is safe and effective. Clinical studies of investigational devices must comply with FDA Investigational Device Exemption (IDE) regulations. See the decision tree in Section 15 Appendix 1 to determine whether a proposed investigation will require IDE submission and FDA oversight. Research involving investigational medical devices is reviewed by the IRB Chair or Primary Reviewer to confirm that either (1), (2) or (3) is true:

1. The device has an IDE issued by the FDA
2. The device fulfills the requirements for an abbreviated IDE if the device is not a banned device and the sponsor (ref. 21 CFR 812.2(b)(1)):
    a. Labels the device in accordance with 21 CFR 812.5;
    b. Obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;
    c. Ensures that each investigator participating in an investigation of the device obtains consent from each subject under the investigator's care (ref. 21 CFR 50) and documents it, unless documentation is waived by an IRB under 21 CFR 56.109(c);
    d. Complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations;
    e. Maintains records required under 21 CFR 812.140(b)(4) and (5) and makes the reports required under 21 CFR 812.150(b)(1) through (3) and (5) through (10);
    f. Ensures that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 21 CFR 812.150(a) (1), (2), (5), and (7); and
    g. The sponsor complies with the prohibitions in 21 CFR 812.7 against promotion and other practices, OR

3. The device fulfills one of the IDE exemption categories (ref 21 CFR 812.2(c)):
    a. A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time
    b. A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately

before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence

c. A diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
   - Is noninvasive
   - Does not require an invasive sampling procedure that presents significant risk
   - Does not by design or intention introduce energy into a subject
   - Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure

d. A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk

e. A device intended solely for veterinary use

f. A device shipped solely for research on or with laboratory animals and labeled in accordance with § 812.5(c)

g. A custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution

Significant Risk and Non-significant Risk Medical Device Studies

Significant Risk Device Studies

IDE regulations (21 CFR part 812.3(m)) describe a significant risk device as an investigated device that:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject.
2. Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Note that risk determination should be based not only on the nature of the device, but also on the proposed use of the device in the research study. Two examples:

1. The research evaluation of a pacemaker that is a modification of a commercially available pacemaker is a "significant risk" device study because the use of any pacemaker involves the potential for serious harm to patients involved. This is true even though the modified pacemaker may pose less risk, or only slightly greater risk, in comparison with the commercially available product.

2. The research evaluation of contact lens wherein the proposed study involves its extended wear constitutes "significant risk." Although the contact lens, itself, poses minimal risk, wearing it continuously for several days/nights presents a potential for injuries not normally seen with limited daily use.

Significant risk device studies must be conducted in accordance with the complete requirements of the IDE regulations and necessitate the prospective approval of an IDE application by the FDA and approval by the IRB.

Non-significant Risk Device Studies

A non-significant risk device study is an investigation of a device that does not pose a significant risk to human subjects. Examples include most daily wear contact lenses, ultrasonic dental scalers, and Foley catheters.

Non-significant risk device studies are conducted in accordance with abbreviated requirements of the IDE regulations and may be approved by the IRB and commence without the requirement of submission of an IDE application or other notification to the FDA (i.e., the IRB serves as the FDA's surrogate with respect to study review and approval of non-significant risk device studies).

Sponsor/Investigator and IRB Responsibilities

The sponsor/investigator initially makes the determination of whether a device study falls under non-significant risk or significant risk. If the sponsor/investigator considers the device study to be of non-significant risk, the sponsor/investigator must provide the IRB with an explanation of this determination and copies of the respective research protocol and informed consent document. The sponsor should inform the IRB of the FDA's assessment of the risk status of the proposed device study, if such an assessment has been made. The IRB may question whether other IRBs have reviewed the proposed device study and what determination the IRBs made, or the IRB may consult with the FDA for its opinion.

The IRB may agree or disagree with the sponsor's/investigator's initial non-significant risk assessment as follows:

1. IRB Agreement with Non-significant Risk
   If the IRB agrees with the determination that the device study presents "non-significant risk" and approves the research study and informed consent document(s), the study may proceed without further notification of the FDA. Under this scenario, the sponsor and principal investigator are required to comply with the abbreviated requirements of the IDE regulations (21 CFR 812.2(b)).

2. IRB Disagreement with Non-significant Risk
   If the IRB disagrees with the determination that the device study presents non-significant risk, the sponsor/investigator must notify the FDA that the device study has been determined to be of significant risk and, if electing to proceed with the study, must submit an IDE application. The device study may not commence until

the FDA approves the IDE and the IRB approves the device study and informed consent document(s). Under this scenario, the sponsor and principal investigator are required to comply with the complete IDE regulations under 21 CFR 812.

If a sponsor/investigator submits an IDE to the FDA because it is presumed to be a significant risk study, but the FDA classifies it as a non-significant risk, the FDA will return the IDE application with the recommendation that it be presented to the IRB as a non-significant risk device study.

FDA's Final Authority for Determination

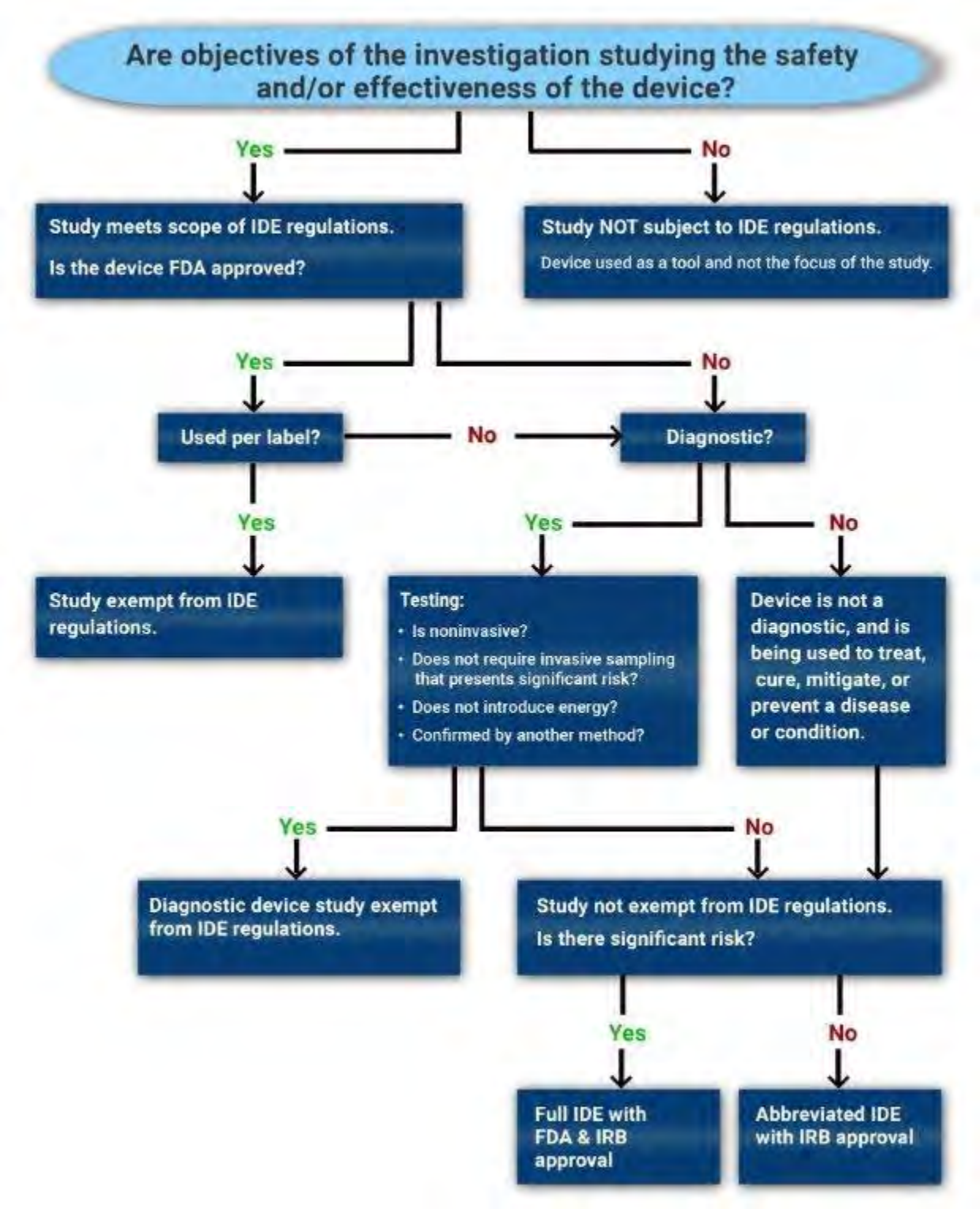
The FDA has the ultimate authority in determining whether a device study presents as non-significant risk or significant risk. If the FDA, upon review of IRB activities, disagrees with the IRB's decision that a device study presents a non-significant risk, an IDE application must be submitted to the FDA.

On the other hand, if a sponsor/investigator submits an IDE to the FDA because it is presumed to be a significant risk study, but the FDA classifies it as a non-significant risk, the FDA will return the IDE application with the recommendation that it be presented to the IRB as a non-significant risk device study.

Unanticipated Device Effect (UADE) Reporting

See Section 08 "*Reporting Unanticipated Problems Involving Risks to Human Subjects/Adverse Events*".

Appendix 1: Decision Tree for IDE Submission and FDA oversight



Reference: https://www.cc.nih.gov/orcs/ide/exemption-criteria-study-risk-determination

Section 15 Regulatory History
Effective Date: 02/07
Revised/Reviewed Date: 04/26
AAHRPP Element: I.7.A

SECTION 16 - INFORMED CONSENT

Ethical Foundation

Informed consent is one of the primary ethical considerations in research involving human participants. **The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research** describes the purpose of consent as the mechanism to ensure that participants understand the research study and voluntarily agree to participate.

The Principal Investigator (PI) and study team members should consider that *consent is a process;* not simply a form that potential study participants must sign. The process of informed consent does not end at the time of obtaining initial informed consent, rather than a one-time event, it is a dynamic and ongoing process throughout a subject's participation in the research study.

General Requirements for Informed Consent

Federal requirements mandate the type of consent that may be obtained, the elements that should be present in a consent explanation, and who may obtain and give consent for research purposes. Federal requirements for informed consent must meet the regulatory requirements of the U.S. Department of Health and Human Services (HHS) 45 CFR 46.116 and the US Food and Drug Administration (FDA) 21 CFR 50.20. Under these regulations there are six general requirements for informed consent:

1. **Consent Obtained Prior to Research Involvement:** Investigators may involve human participants in research only with the consent of the participant or the participants' legally authorized representative (LAR), unless the requirement for consent is waived. There are exceptions for waiver of consent, but waivers are highly regulated and must be justified.
2. **Voluntary Participation:** The potential study participant must be given enough time to consider whether or not to participate in the research, and the possibility of coercion or undue influence should be minimized.
3. **Understandable Language:** Consent explanations must be in language understandable to the potential study participant or the individual's legally authorized representative.
4. **Waiver of Rights Prohibited:** The consent may not include language through which the participant or their representative is made to waive the participant's legal rights or releases the investigator, the sponsor, the institution or its agents from liability for negligence.
5. **Key Information:** Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might

or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension.

6. **Organized to Assist Understanding:** Informed consent must present information in sufficient detail relating to the research and must be organized and presented in a way that does not merely provide lists of isolated facts, but, rather, facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate.

Note on Broad Consent: While 45 CFR 46.116(a) permits a broad consent (which may be obtained with respect to the storage, maintenance, and secondary research uses of identifiable private information and identifiable biospecimens), The Christ Hospital (TCH) Institutional Review Board (IRB) will not approve a broad consent process.

Mechanisms for Obtaining Informed Consent

Federal regulations provide two possible mechanisms for obtaining informed consent from a research participant:

1. A process with consent documented by having the appropriate person sign a written IRB-approved consent document, or
2. A process involving a waiver of documentation of consent that has been approved by the IRB. See Waiver of Documentation of Consent for more information.

The Informed Consent Process

Under the federal regulations, investigators must obtain "legally effective" informed consent in order to enroll a person into a research study. The Principal Investigator is responsible for devising a process for obtaining informed consent that outlines how the investigator plans to communicate the details about the research study to potential subjects. It should include a detailed description of from whom informed consent may be obtained, including who will obtain informed consent and when, where and how the consent process will take place.

Informed consent is legally effective if the consent is:

1. Obtained from the subject or the subject's legally authorized representative, and
2. Documented in a manner that is consistent with the federal HHS and FDA regulations on protection of human subjects and with the applicable laws of the jurisdiction in which the research is conducted, and
3. Obtained under circumstances that:
4. Provide the prospective subject or the legally authorized representative sufficient opportunity to consider whether to participate in the research,
5. Minimize the possibility of coercion or undue influence, and
6. Respect the privacy of the potential participant by taking place in a setting that is not open to the public.

The information provided should be in language that is understandable to the subject or the legally authorized representative. No informed consent may include any exculpatory language (language that waives or appears to waive any of the participant's legal rights or releases, or appears to release, the investigator, the sponsor, the institution or its agents from liability for negligence).

Who May Obtain Informed Consent?

The Principal Investigator of an IRB-approved research study is ultimately responsible for the conduct of the study. Both the consent process and the consent form must be approved by the IRB. The Principal Investigator must ensure that informed consent from each potential research participant is:

1. Obtained by an IRB-approved consent designee, and
2. Documented (if required) using the method approved by the IRB. Unless the IRB has approved a waiver of the requirement to obtain consent, informed consent must be obtained before the participant takes part in any aspect of the research study. See Waiver or Alternation of Consent for more information.

The investigators or other key research personnel listed in the IRB application may obtain consent only after the IRB grants approval of each key research personnel. As part of the application process, each individual who interacts with potential research participants in order to obtain consent must complete Human Subjects Research (HSR) training through CITI. The Principal Investigator must also confirm that individuals who will be obtaining consent from research participants have been trained by the PI. Each of the consenters must be knowledgeable about the study and capable of answering study-related questions posed by the potential research study participant. Additionally, consenters must not have a conflict of interest, financial or otherwise, associated with the research. Investigators and other key research personnel with conflicts of interest must report those conflicts to the IRB.

When May Informed Consent be Obtained?

The informed consent process description must include details about the timing of informed consent. Potential participants should have adequate time to review the consent form, ask questions about the research, and consult with family, friends, or others (if desired) before signing the consent depending on the type of study and the risk(s) associated with it. For example, in research involving elective procedures or scheduled therapy, potential participants should be given ample time to consider participation and should not be solicited immediately before beginning the procedure. However, in certain types of research involving emergent procedures this may not be feasible.

Where May Informed Consent be Obtained?

In-person communication between investigators and study candidates is always the preferred scenario, with ample time to discuss issues and answer questions. At times, however, this may not be necessary nor feasible, e.g., when conducting a straightforward minimal risk survey study which may be readily explained in a consent without the need

for much education or interaction. However, consenting for a greater than minimal risk interventional study, even if done remotely, must allow for education, questioning and dialogue.

Methods other than an “in person” consent discussion may be acceptable if those methods (1) allow for an adequate exchange of information, (2) ensure that the signee of the consent form is the person who plans to enroll as a subject or is the legally authorized representative (LAR) of the subject, and (3) unless waived, document consent including the signature and date obtained from the subject or LAR.

No single set of recommendations fit all research needs. Options vary with the risk level and applicable regulations. Investigators should consider what would be feasible or preferable for the subject population and propose multiple or contingency plans to meet situational or individual participant needs.

From Whom May Consent/Assent be Obtained?

Adults: The ethical principle described in the Belmont Report, “Respect for Persons,” directs that individuals should be treated as autonomous agents, meaning that potential research study participants must be given sufficient information to assure an informed decision about participation. In the U.S., adults (as defined by state law) may provide consent for themselves. In Ohio, adults are defined as persons aged 18 years or older.

NOTE: Investigators who conduct research in which adult participants are recruited at sites outside of the state of Ohio must follow laws applicable in the local jurisdiction which determine who is an adult, who may give legal consent, and how consent from adults who lack capacity should be obtained.

Considerations for Vulnerable Populations in Research

Refer to Section 06 for detailed information on Vulnerable Populations.

1. Adults who Lack Capacity to Provide Informed Consent: Individuals may lack capacity as a result of a range of cognitive disorders or conditions, which may result in the inability of individuals to protect themselves by freely-given informed consent. This vulnerable population is entitled to special protection in research.

   An individual’s consent capacity is not simply present or absent; capacity is best understood as occurring along a continuum. The term “incompetence” is similar to “incapacity”, although incompetence has to do with legal matters while incapacity has to do with medical matters. Most states use "legally incapacitated" to refer to a person who cannot take care of his or her own physical safety and health.

   PIs seeking to enroll adults who may lack capacity to make an informed decision must make clear in the IRB application how capacity to provide informed consent

will be assessed. If participants are expected to lose the ability to consent while the study progresses, the research plan should address procedures for reassessing participants' ability to (1) understand protocol procedures, and (2) provide ongoing informed consent.

Incompetence may be a temporary result of the participant's condition (e.g., the participant is unconscious or sedated) or may result from cognitive impairment produced by a disease or medical condition that impairs mental capacity. Whenever a participant lacks capacity to provide informed consent for him/herself, federal regulations require that the participant's legally authorized representative must give consent before the incapacitated person may participate in a research study.

For purposes of research conducted at The Christ Hospital, a legally authorized representative is an individual, judicial or other body authorized under applicable law to consent on behalf of a prospective subject in regard to the subject's participation in procedures involved in research. Usually, the law of the jurisdiction in which the research is conducted will be the state law where the research procedures will be performed.

Such consent may be obtained from:

- A health care agent appointed by the potential subject in a Durable Power of Attorney for Healthcare (DAHC) or similar document
- A court-appointed guardian
- Next-of-kin in the following order of priority (unless otherwise specified in applicable law):
- Spouse
- Adult child (18 years of age or older)
- Parent
- Adult sibling (18 years of age or older)
- Grandparent
- Adult grandchild (18 years of age or older)

NOTE: The preceding list contains the only surrogate entities who are allowed to provide consent for research purposes.

For individuals who know that they may lose capacity to provide consent during the course of the study, PIs should provide participants the opportunity to appoint a "research agent" who may provide consent on the participant's behalf after the participant loses capacity to consent for him/herself.

Refer to IRB SOP 3.18 "*Additional Safeguards for Individuals Without Decision-making Capacity*" for additional details.

2. Pregnant Women, Fetuses, and Neonates: Under federal regulations 45 CFR 46, Subpart B there are special conditions regarding involvement of pregnant women, fetuses or neonates in research. A pregnant woman must give her informed consent, and, if the research holds out the prospect of direct benefit only to the fetus, then the father must also give informed consent (unless he is unable to consent because of unavailability, incompetence, temporary incapacity, or the pregnancy resulted from rape or incest). Each individual providing consent must be informed of the impact of the research on the fetus.

3. Children: All research projects involving children, regardless of funding source, will be reviewed and approved in accordance with 45 CFR Part 46, Subpart D, as applicable. Four categories of human research involving children may be approved by an Institutional Review Board (IRB). The four categories differ from one another according to the level of risk involved, the prospect of direct benefit to research subjects, and the anticipated research findings. In all four categories, the proposed research activity must satisfy the requirements for parental or guardian permission and child assent (ref. HHS Research with Children FAQs). Depending on the category, additional conditions must be met in order for the IRB to approve the research activities.

4. Non-English Speakers: Federal regulations require that researchers obtain the legally effective informed consent of the research subject or their legally authorized representative (if the subject is not able to consent for his/herself), and that informed consent shall be in language understandable to the subject or the representative *(45 CFR 46.116(a)(3))*. TCH IRB allows two means by which these requirements can be accomplished:
   - Written translation of IRB-approved documents, or
   - Use of a Short Form and request for an exception (45 CFR 46.117(b)(2); 21 CFR 50.27(b)(2))

5. Other Vulnerable Adult Populations: TCH IRB recognizes that the ability of adult populations to give voluntary informed consent may be compromised by circumstance. Those circumstances range from economic or educational disadvantage, physical handicap, sedation, and drug abuse to the terminally ill. The research study protocol should take into account any of these issues and address them in the consent process.

Determining a Participant's Understanding

In order for participation in a study to be truly voluntary, the participant must understand what he/she is agreeing to. The information should be presented to the participant in a way that is understandable to that participant. The investigator must ensure that the participant understands all elements of the consent form at the time the consent is signed, and also have means to assess the participant's continued understanding throughout the

duration of the research study. It is important that the participant also understands that participation is voluntary, and that he/she can withdraw from the study at any time.

Remote Consent Process

The *remote consent* process must be prospectively reviewed and approved by the IRB. The proposed process should be outlined in the Mentor application (Informed Consent Process sub-section) and should include how (1) the consent form will be presented/reviewed, (2) signatures will be obtained, (3) copies will be provided to subjects. If applicable, screenshots showing the final formatting and features that the subjects would see should be provided. The remote consent process may vary depending upon the risk level. The intent is to receive a signed and dated document for research unless a waiver of consent or a waiver of documentation of consent has been approved by the IRB.

Note: The process for each individual research type should be followed as outlined below:

1. *Minimal Risk Research with a Waiver of Documentation of Consent*: Research conducted using a Waiver of Documentation of Informed Consent requires a consent form (e.g., cover letter, verbal script) and an outline of the informed consent process. However, the investigator does not have to collect a signed document. The process is as follows:
   - If consent is not built into the data collection instrument, mail, fax, or email the consent form to the subject in advance.
   - After the potential subject/LAR has received the form, verify him/her/them as the correct individual(s) through phone or video, talk through the consent, answer questions, and ensure that the subject/LAR understands the consent and that consent is voluntary.
   - Document the conversation by noting the date, names of individuals present, how the process was conducted, discussion points, and whether the person agreed to enroll.

2. *Minimal Risk Research or Greater Than Minimal Risk Research Not Subject to FDA Regulation:* Written informed consent must be documented using a written informed consent form approved by the IRB and signed and dated (including in an electronic format) by the subject or the subject's legally authorized representative. A written copy shall be given to the person signing the informed consent form. The process is as follows:
   - Mail, fax or email the consent form and HIPAA Authorization (if applicable) to the potential subject and/or LAR in advance of the remote discussion between the consent designee and the participant. The PI must obtain advance IRB approval if a LAR is involved.
   - After the potential subject/LAR has received the form, verify him/her/them as the correct individual(s) through phone or video, talk through the consent,

answer questions, and ensure that the subject/LAR understands the consent and that consent is voluntary.

- Document the conversation by noting the date, name(s) of individual(s) present, how the process was conducted, discussion points, and how the signed document is to be returned.
- The subject then returns the signed and dated document via a prepaid envelope, OR by scanning or photographing the signed and dated document and then sending the scan/photo to the investigator by email/fax/upload.
- When the investigator receives the signed and dated consent form, the person who conducted the consent conference signs his/her name and enters the current date on the form.
- Study procedures should not be initiated until the subject's signed consent document is received.
- Ensure that the subject is provided with a copy of the form(s) he/she signed.
- If added security is needed or if HIPAA applies to the research, employ cybersecurity precautions or secure/HIPAA video conferencing as applicable. Refer to Question 10 on HHS guidance FAQ's on Telehealth during COVID-19 during COVID-19 regarding "non-public facing" platforms that ensure only the intended parties participate in the video conferencing. Unacceptable public-facing products are also listed.

3. *Process for Greater Than Minimal Risk Research Subject to FDA Regulation:* Written informed consent must be documented using a written informed consent form approved by the IRB and signed and dated (including in an electronic format) by the subject or the subject's legally authorized representative. A written copy shall be given to the person signing the informed consent form. The process is as follows:
    - Mail fax or email the consent form and HIPAA Authorization (if applicable) to the potential subject and/or LAR in advance of the remote discussion between the consent designee and the participant. The PI must obtain advance IRB approval if a LAR is involved.
    - After the potential subject/LAR has received the form, verify him/her/them as the correct individual(s) through phone or video, talk through the consent, answer questions, and ensure that the subject/LAR understands the consent and that consent is voluntary
    - Document the conversation by noting the date, name(s) of individual(s) present, how the process was conducted, discussion points, and how the signed consent form is to be returned.
    - The subject then returns the signed and dated consent form via a prepaid envelope, OR by scanning or photographing the signed and dated consent form and then sending the scan/photo to the investigator by email/fax/upload.

- When the investigator receives the signed and dated consent form, the person who conducted the consent conference signs his/her name and enters the current date on the form.
- Study procedures should not be initiated until the subject's signed consent form is received.
- Ensure that the subject is provided with a copy of the form(s) he/she signed.
- If added security is needed or if HIPAA applies to the research, employ cybersecurity precautions or secure/HIPAA video conferencing as applicable. Refer to Question 10 on HHS guidance FAQ's on Telehealth during COVID-19 during COVID-19 regarding "non-public facing" platforms that ensure only the intended parties participate in the video conferencing. Unacceptable public-facing products are also listed.

Electronic Informed Consent

Electronic consent (e-consent) refers to the use of electronic systems and processes that may employ multiple types of electronic media including text, graphics, audio, video, podcasts, passive and interactive websites, biological recognition devices, and card readers to convey information related to the study and to obtain and document informed consent.

The e-consent process should have the capability to

1) Prove that the actual signer is the intended signer,
2) Allow the signer to deny the signature, and
3) Contain an assurance that neither the record nor the signature has been altered from the moment of signing; to achieve this, signatures executed to electronc records shall be linked to their respective electronic records to ensure that the document cannot be modified or otherwise tampered with. Ref 21 CFR 11.70

If using a PDF format to collect a signature, set verification preferences in advance. This helps ensure that Digital Signatures are valid when a PDF is opened and verification details appear with the signature. Refer to Adobe Validating Digital Signatures.

Refer to IRB SOP 2.17 "*Electronic Consent*" for more detailed information.

FDA Regulated Research: The process of e-consenting differs depending on regulation. FDA regulated research requires that software systems be compliant with all requirements under FDA Part 11 regulation (e.g., restricted access, administrative controls, training, identity verification, etc.). Ref. FDA guidance Part 11, Electronic Records; Electronic Signatures – Scope and Application; 21 CFR Part 11.

The FDA does not certify systems for Part 11 compliance. Sponsors may provide Part 11 compliant electronic consent. For investigator-initiated research, refer to Part 11 options such as DocuSign Part 11 or Adobe Sign Part 11.

Generally, there is no “out of the box” software solution as the customer is responsible for setting features, demonstrating compliance, providing/documenting training, and administering operational policies and procedures. It is the investigator’s responsibility to be able to demonstrate that the software is fit for its intended use and the system meets applicable regulations should your protocol be audited. A statement may be requested from the sponsor or vendor of the electronic system used for obtaining the electronic signature verifying that the system meets requirements contained in Part 11 and maintains documentation that your site has fulfilled applicable customer requirements such as training, password controls, etc.

Signatures: To capture consent on electronic systems, one may use:

1. Electronic Signatures
   A computer data compilation of any symbol(s) executed, adopted, or authorized by an individual to be a legally binding equivalent of the individual’s handwritten signature. Methods include computer readable ID cards, biometrics, digital (cryptographic) signatures, and user/password combinations. Electronic signatures must comply with 21 CFR Parts 11.50 and *11.70* requirements including:

   - The printed name of the signer;
   - The date and time when the signature was executed;
   - The meaning (such as review, approval, responsibility, or authorship) associated with the signature.

2. Handwritten Signatures Executed to Electronic Records
   Hand-scripted signatures executed to electronic records may be:

   - Obtained by signing with a stylus, finger, or cursor drawing;
   - Used in a hybrid process where the only electronic component is the documentation (signature) of informed consent.

   Handwritten signatures executed to electronic records must comply with 21 CFR 11.7 and should be linked to their respective electronic records to ensure that it cannot be excised, copied, or otherwise transferred (i.e., tampered with).

Additional Considerations for Subjects in Medical Isolation: FDA Covid-19 Guidance provides the process which would be considered to satisfy FDA’s informed consent documentation requirement when electronic informed consent is not available nor feasible:

1. An unsigned consent form, and HIPAA Authorization, if applicable, is provided to the patient or LAR by a healthcare worker who can enter the room.

2. If in-person communication with the patient in isolation is not feasible or safe, the investigator arranges a three-way call or video conference with the patient, an impartial witness, and, if desired and feasible, additional people as requested by the patient. To ensure that patients are approached in a consistent fashion, a standard process should be used that will accomplish the following:
    a. Identification of who is on the call
    b. Review of the informed consent document with the patient by the investigator/designee and response to any questions the patient may have
    c. Verbal confirmation by the patient that their questions have been answered, that they would like to participate in the trial, and that they have signed and dated the informed consent document which is in their possession
3. If the signed and dated paper consent document can be safely collected, the person who conducted the consent conference prints his/her/their name on the form, signs the form and enters the current date, then provides the subject with a copy of the form he/she/they signed.
4. If the signed informed consent document cannot be safely collected from the patient's location and included in the study records, the FDA considers the following two methods acceptable for providing documentation that the patient signed the informed consent document:
    a. A photograph of the signed and dated document may be transmitted to the investigator or research staff. The patient (or an individual in the room) takes a photograph of the signed informed consent document and sends it to the investigator/designee. A trial team member enters the photograph into the trial records along with an attestation that states how the photograph was obtained and that it is a photograph of the informed consent document signed by the patient.
    b. A witness can attest to the signature, but a photograph of the signed informed consent document cannot be transmitted. Steps 1 and 2 above must be followed. When using a witness, documentation in the study trial records includes:
        - a signed and dated attestation by the witness who participated on the call, that the patient confirmed their agreement to participate and signed and dated the informed consent document (or call recording); and
        - a signed and dated attestation by the investigator/designee stating why the informed consent document signed by the patient was not retained (e.g., due to potential contamination by infectious material).

        Alternatively, in lieu of using a witness during the three-way telephone call or video conference, a recording of the conversation can be made and retained in the study record. Documentation in the trial records includes:
        - the recording of the conference call; and
        - a signed and dated attestation by the investigator/designee who participated on the call stating why the informed consent document

signed by the patient was not retained (e.g., due to potential contamination of the document by infectious material).

When either method above is used to document informed consent, the resulting documentation should be: (1) collected and archived, as either original paper copies or appropriately certified electronic copies (e.g., using a validated process for scanning paper copies), and (2) retained according to applicable FDA record retention requirements as part of the trial record.

If the patient is unable to provide informed consent and there is a legally authorized representative, investigators must obtain written consent from the patient's legally authorized representative in accordance with 21 CFR 50.27(a).

Waiver or Alteration of Informed Consent

Per federal regulations 45 CFR 46.116, a waiver of one or more elements of consent is permitted provided that the research presents no more than minimal risk and meets specific criteria. Alteration of consent is appropriate if one or more of the required elements is not relevant to the research activity. Complete waiver of consent is also permitted and most frequently granted for retrospective research, but also possible for some types of prospective research. The investigator seeking permission for an alteration or waiver of consent should include the request for alteration or waiver in the study application.

Non-FDA Regulated Research: For non-FDA-regulated research, the IRB may waive or alter informed consent requirements only if it finds and documents that the criteria listed in 45 CFR 46.116(f) are satisfied as well as any other applicable regulations of sponsoring federal agencies and state and local laws and regulations. The IRB may approve a request for an alteration or waiver of informed consent for a non-FDA regulated study if the study meets the following criteria:

1) The research involves no more than minimal risk to the participants
2) The research could not practicably be carried out without the waiver or alteration
3) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format
4) The alteration or waiver will not adversely affect the rights and welfare of the participants, and
5) Whenever appropriate, the participants will be provided with additional pertinent information after participation

Public Demonstration Projects: A waiver or alteration of the consent process may be requested for a public demonstration project conducted or approved by state or local government officials. The following criteria apply:

1. The research is conducted by or approved by state or local government officials
2. The research or demonstration project is designed to study, evaluate, or otherwise examine:
    a. Public benefit or service programs
    b. Procedures for obtaining benefits or services under those programs
    c. Possible change in or alternatives to those programs or procedures
    d. Possible changes in methods or levels of payment for benefits or services under those programs
3. The research cannot practicably be carried out without the waiver or alteration
4. The research is not regulated by the FDA

Research Subject to FDA Requirements: The FDA has provided guidance on regulations governing informed consent for studies that involve no more than minimal risk to human subjects for which obtaining informed consent is not practicable. For investigations under the jurisdiction of the FDA, the IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent as set forth in 21 CFR 50.25, or waives the requirements to obtain informed consent when the IRB finds and documents that such approval is supported by requirements noted in 16.2.4(a) above. (Ref. FDA Guidance: IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More than Minimal Risk to Human Subjects, III. Discussion, page 3)

Emergency Research: There are special cases under emergency research in which the human research subject is in a life-threatening situation, in need of emergency medical intervention, and it is not feasible to obtain informed consent. Permitting certain clinical trials involving human subjects who are confronted by life-threatening situations and who are unable to give informed consent because of their medical condition, allows the individuals in these situations access to potentially life-saving therapies, potentially resulting in advancement in knowledge and improvement of treatments used in emergency medical situations that currently have poor clinical outcome (ref. FDA FDA Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research). In order to allow such research to proceed, special provisions for exception from informed consent requirements must be met. The conditions required to conduct this type of research with exception from informed consent are described in 21 CFR 50.24 including the IRB's approval (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation).

Documentation of the Informed Consent Process

Generally, the IRB requires consent to be documented (ref. 45 CFR 46.117; 21 CFR 50.27) by a written consent form that includes all the required elements and all appropriate optional elements approved by the IRB prior to use. An IRB-approved consent document will contain the date of IRB approval. Unless the requirement for consent is waived by the IRB, the written consent form must be reviewed with the potential research participant

(or the participant's legally authorized representative) and signed and dated by the participant or the participant's representative. Such actions must occur before any research procedures (including screening) or research data collection can begin. The consent form should also be signed and dated by the individual who obtains the participant's consent.

Waiver of Documentation of Informed Consent

A waiver of documentation of consent must meet the regulatory requirements of HHS 45 CFR 46.117 and FDA 21 CFR 56.109. This may include an oral consent process or an electronic consent process by which a legally effective signature will not be obtained. The investigator should submit this request for waiver of documentation of consent with the study application and must include a script that the consent designee will use with potential study participants or which will be made available electronically. The script must include all the required consent elements and, when private health information is to be collected, the elements required for HIPAA privacy authorization. Details about the consent (e.g., date, time, identity of consent designee) should be recorded in the study record by the consent designee. If the project involves clinical care, details about the consent should also be added to the clinical record. Note that since the HIPAA authorization provided in an oral or electronic consent process would not be in writing, investigators should request that the IRB grant an alteration to the HIPAA written signature requirement in the application submitted in Mentor IRB.

Non-FDA Regulated Research: The IRB may approve a request for a waiver of documentation of consent for non-FDA regulated studies under three circumstances:

1. The only record linking participants to the research would be the consent document and, the principal risk to the participant would be potential harm resulting from a breach of confidentiality. In this case, each participant will be asked if he/she wants documentation linking him/her to the research and the participant's wishes will govern; or
2. The research presents no more than minimal risk to the participants and involves no procedures for which written consent is normally required outside of the research context; or,
3. If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

Waiver of Documentation of the Consent Process: Screening, Recruiting, and Determining Eligibility

An IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject or the subject's legally authorized representative, if the following conditions are met:

1. The investigator will obtain information through oral or written communication with the prospective subject or legally authorized representative, or
2. The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

Ref. 45 CFR46.116(g)(1) and (2)

Research Subject to FDA Requirements

For FDA-regulated studies, waiver of documentation is only permitted if the study presents no more than minimal risk. The IRB shall require documentation of informed consent in accordance with 21 CFR 50.27 except as follows:

1. The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; - or -
2. The IRB may, for some or all subjects, find that the requirements in 21 CFR 50.24 for an exception from informed consent for emergency research are met. Ref. 21 CFR 56.109(c); IRB SOP 1.10 "*Emergency Use Exemption*".

Waiver of Documentation of the Consent Process – Consent Normally Not Required

In cases where documentation is waived where consent is normally not required outside the research context, the IRB shall require that:

1. The oral or written information provided to subjects includes all required and appropriate additional elements of consent disclosure.
2. The IRB determines whether the investigator should provide subjects with a written statement regarding the research (21 CFR 56.109(d)). Such a document requires IRB approval.

Informed Consent Document

Basic Elements of Informed Consent

The Christ Hospital Institutional Review Board requires investigators to include the consent requirements established by HHS 45 CFR 46.116 and FDA regulations 21 CFR 50.20, as applicable, including providing each subject or the LAR:

1. A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental;
2. A description of any reasonably foreseeable risks or discomforts to the Subject;
3. A description of any benefits to the subject or to others that may reasonably be expected from the research;

4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;
8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled, and
9. One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

    a) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or
    b) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

<u>Additional Elements of Informed Consent</u>

In addition, the consent document may contain the following items when appropriate:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable;
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's or the legally authorized representative's consent;
3. Any additional costs to the subject that may result from participation in the research;
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
5. A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject;

6. The approximate number of subjects involved in the study;
7. A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
8. A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and
9. For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

Statement Required for Research Subject to FDA Regulation

If the research is subject to FDA regulation, there must also be a statement noting the possibility that the FDA may inspect study records. Research is FDA regulated if it involves the use of any drugs or medical devices other than the use of approved drugs or medical devices in the course of medical practice, or if the data will be submitted to or held for inspection by the FDA. (Ref. 21 CFR 50.25(a)(5))

The above elements are included in the preprinted "boilerplate" text of the TCH IRB informed consent templates.

HIPAA Authorization

HIPAA requires a participant's prior written authorization before his or her identifiable health information can be used or disclosed by “covered entities.” HIPAA authorization for use and disclosure of health information is included in the "boilerplate" text of the TCH IRB informed consent template. When HIPAA authorization hasn’t been combined with an informed consent document (a compound or combined authorization), a stand-alone HIPAA authorization may be utilized.

IRB Approval of Informed Consent and HIPAA Authorization Documents

The IRB must review and approve all materials associated with obtaining informed consent prior to utilization.

Section 16 Regulatory History
Effective Date: 10/21
Revised/Reviewed Date: 05/26
AAHRPP Element: II.3.F, II.3.G, II.4.B, II.4.C., III.1.F

SECTION 17 - SURROGATE CONSENT IN RESEARCH

Background

All adults (including those with cognitive impairments) are presumed to have the capacity to consent unless legally judged to be incompetent or determined to lack decisional capacity by an appropriate provider. Cognitively impaired persons are considered a *vulnerable research population* because their mental disability may compromise their capacity to make reasoned decisions about participation in a study. People with Alzheimer's disease, dementia, mental illness and developmental disabilities may be considered cognitively impaired and may not be able to provide informed consent for participation in research.

In certain circumstances, when it is determined that a potential research participant is cognitively impaired, federal regulations and state statute permit researchers to obtain consent from a legally authorized representative (LAR) via surrogate consent.

Federal regulations permit investigators to obtain consent from a legally authorized representative (LAR) in research that involves enrollment of prospective research subjects who cannot provide consent on their own behalf. The Christ Hospital IRB Policy SOP 3.18 *Additional Safeguards for Individuals Without Decision-making Capacity* describe who may serve as an LAR in research.
For research studies involving subjects who have fluctuating or limited decision-making capacity or prospective incapacity, Principal Investigators should establish and maintain ongoing communication with involved caregivers, consistent with the subjects' autonomy and with medical confidentiality and privacy laws.

The ability of individuals to participate in research if they are unable to consent depends on state law state where the research is being conducted. In Ohio, adults who are unable to consent because of decisional impairment may only participate in research under the following circumstances:

- If the IRB waives the consent requirement under the federal regulations allowing for waiver of consent after consideration and comment by the local community on the research.
- If a Durable Power of Attorney for Healthcare names an individual who has authority to consent specifically for research, and the state where the research is conducted recognizes the legality of the document. The state of Ohio recognizes the legality of the Durable Power of Attorney for Healthcare.
- In emergency situations, if the researcher has obtained the consent of a family member of the participant. In states other than Ohio, the researcher must submit to the IRB a legal opinion supporting the validity of the surrogate consent.

Definitions

Legally Authorized Representative (LAR): Per Federal regulations, LAR means "an individual, or judicial, or other body authorized under applicable law to consent on behalf of a prospective research subject to the subject's participation in the procedure(s) involved in the research" (Ref. 45 CFR 46.102(i); 21 CFR 50.3(l)).

The 2018 Revised Common Rule provided clarification to supplement this definition. Specifically, "in jurisdictions where there is no applicable law for allowing an LAR to provide consent on behalf of a prospective research subject, LAR means an individual recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective research subject to the subject's participation in the procedure(s) involved in the research"

Surrogate Consent: In research, surrogate consent is the use of an LAR.

Advanced Healthcare Directive: Documents written in advance of serious illness in which a person states their choices for healthcare or names someone to make those choices. When a person is selected to make medical decisions, the document is called a Durable Power of Attorney and the designated person is called an Agent. In certain circumstances, the Agent can serve as an LAR to provide surrogate consent for participation in research.

Capacity to Consent (to Research): The ability of the individual to understand the choices presented, to appreciate the implications of choosing one alternative or another, and to make and communicate a decision (e.g., whether or not to participate in a study).

When is the Use of an LAR Required in Research?

An LAR is required to conduct human research with a person who is an adult incapable of making an informed decision at the time consent is required. The person's legally authorized representative may issue informed consent/permission and the signature shall be witnessed.

It is important to note that even though verbal consent, obtained over the phone may be obtained from the LAR for clinical care, verbal consent from the LAR is not allowed for research if written consent is required for the study.

The research participant should be invited to participate in the informed consent discussion and provide his/her assent.

Requesting the use of surrogate consent

The investigator must request the use of surrogate consent from the IRB. Preferably this is requested in the study application at the time of initial submission; however, it can be done as an amendment to the protocol. In certain limited circumstances, the IRB could approve the use of an LAR for a single subject on a case-by-case basis.

Investigators must use appropriate safeguards to protect the rights and welfare of these participants and those providing consent on their behalf if it determines that they may be vulnerable to coercion or undue influence. Sufficient justification for inclusion of participants who lack decision-making capacity and a plan to protect them and their surrogates from coercion and undue influence must be included in the research plan.

IRB Considerations for the Use of Surrogate Consent in Research

The IRB will review any requests to enroll adults who are not capable of providing consent using surrogate consent.

IRB Considerations may include:

- Whether all eligible subjects will require an LAR **OR** only some subjects may be able to provide assent or even consent for themselves
- Ensuring that the plan includes documents to assess capacity and solicit the consent for continued participation for adult subjects who will or may regain decision making capacity.
- Ensuring a written or script-supported consent document (or other information relevant to the research) will be provided to the research participant accompanied by a consent conversation, as applicable.
- The circumstances of the consent process provide the prospective participant or the LAR sufficient opportunity to consider whether to participate.
- The circumstances of the consent process minimize the possibility of coercion or undue influence.
- Ensuring the person communicating information to the participant or the LAR during the consent process will provide that information in language understandable to the participant or the representative.

The IRB must determine:

- whether the involvement of such individuals in the research is justified, and
- whether the proposed plan minimizes or eliminates the risks to vulnerable subjects.

The IRB may request additional safeguards to protect participants depending on the amount of risk involved in the research and the likelihood that participants will derive health benefits from their participation. Additional safeguards may include:

- requiring involvement of participant advocates,
- requiring independent monitoring,
- requiring waiting periods, and/or
- appointing a monitor to supervise the informed consent process.

When consent will be obtained from an LAR (surrogate), the IRB usually will require that the assent of the subject be obtained. Assent is defined as affirmative agreement to participate in research. Failure to object does not qualify as assent.

Conditions Limiting LAR Use

The ability of individuals to participate in research if they are unable to consent depends on the state law where the research is being conducted.

In Ohio, adults who are unable to consent because of decisional impairment may only participate in research under the following circumstances:

- If the IRB waives the consent requirement under the federal regulations allowing for waiver of consent after consideration and comment by the local community on the research.
- If a Durable Power of Attorney for Healthcare names an individual who has authority to consent specifically for research, and the state where the research is conducted recognizes the legality of the document. The state of Ohio recognizes the legality of the Durable Power of Attorney for Healthcare.
- In emergency situations, if the researcher has obtained the consent of a family member of the participant. In states other than Ohio, the researcher must submit to the IRB a legal opinion supporting the validity of the surrogate consent.

Use of LARs for research being conducted outside of Ohio

Different states may vary how they define:

- The age of children and/or minors, including emancipated minors,
- Which individuals can give permission for their participation in research and for the participation of children who are in court-appointed custody, and
- Which individuals are qualified to serve as legally authorized representatives.
- Determinations about who can serve as an LAR, that is, consent on behalf of someone else's participation in research, are based on the jurisdiction in which the research is being conducted.

The PI must understand the implications of state laws for the proposed research and describe how differing state requirements will be met in the research. Also note that research being conducted in foreign countries is subject to applicable laws for designating a legally authorized representative for the region or country in which the research is being conducted.

If the site of the research is outside Ohio, the researcher must provide a legal opinion acceptable to the IRB of the circumstances under which the law of the state where the research is conducted allows individuals who do not have the capacity to consent to participate in research. Also, the IRB or investigator may seek advice from The Christ Hospital Risk Management Department on the definition of a legally authorized representative for the applicable jurisdiction.

<u>Additional Considerations/Conditions</u>

- If two or more persons who qualify as legally authorized representatives and have equal decision-making priority inform the principal investigator or attending physician that they disagree (with each other) as to participation of the prospective subject in human research, the subject shall not be enrolled in the human research that is the subject of the consent.
- No informed consent form shall include any language through which the person who is to be the human subject waives or appears to waive any of his legal rights,

including any release of any individual, institution, or agency or any agents thereof from liability for negligence.

- Notwithstanding consent by a legally authorized representative, no person shall be forced to participate in any human research if the investigator conducting the human research knows that participation in the research is protested by the prospective subject.
- In the case of persons suffering from organic brain diseases causing progressive deterioration of cognition for which there is no known cure or medically accepted treatment, the implementation of experimental courses of therapeutic treatment to which a legally authorized representative has given informed consent shall not constitute the use of force, unless prior knowledge of participant refusal is known.
- Unless the research constitutes the best medical interests for the prospective participant and is not available outside of the research context, dissent or objection on the part of the participant ought to be respected regardless of the LAR's wishes.

DETERMINING DECISION-MAKING CAPACITY

A primary consideration when recruiting subjects with severe cognitive disorders is to establish procedures for determining which individuals are able to provide legally valid consent, and which are not.

The protocol reviewed by the IRB must detail a specific plan for the assessment of the decision-making capacity of the subject. The assessment will be conducted by the investigator for any subject who may qualify for Surrogate Consent. While there are no standardized measures for determining capacity to consent, subjects may be assessed on their ability to understand and to express a reasoned choice concerning the:

- Nature of the research and the information relevant to his/her participation;
- Consequences of participation for the subject's own situation, especially concerning the subject's health condition; and
- Consequences of the alternatives to participation.

The capacity to understand all these concepts may not be necessary to consent to participate in a particular research protocol -- greater capacity is required for higher-risk protocols.

In protocols in which surrogate consent has been approved by the IRB, assessment of the decision-making capacity of the surrogate should be implemented only when the investigator has reason to believe that the subject's decision-making capacity may be impaired.

If a study anticipates using surrogate consent from legally authorized representatives, the method of assessment must be specified in the IRB Application.

Assessment Methods

- Assessment tools: Various methods of assessment may be acceptable for differing studies. In general, a greater capacity to consent and more rigorous methods of assessing capacity are needed in studies that have higher risks for subjects.
- Review of consent documents with the subject: The assessor may review the IRB-approved consent form with the prospective subject in the normal manner used to obtain consent. A simplified study summary may be used as an aid to emphasize/remind subjects of major points.
- Capacity assessment: The assessor can ask the prospective subject to explain the main elements of this study and indicate a decision about taking part or not. The prospective subject may use a simplified study summary to answer the questions. Based on these responses, and whether the decision to participate or not appears to be a rational choice reflecting an appreciation of the facts, the assessor can then make a final determination about capacity for consent.
- Sample questions to assess consent capacity: These questions pick up at the point that consent form review has been completed. They are examples only — clinical judgment remains the best guide for what to ask.
    - Are we offering you your usual medical care, or asking you to be in a research study?
    - Do you have to take part in this study, or is it OK to say “no”?
    - What is the purpose of this study?
    - Tell me the main things that would happen to you in this study
    - Tell me the main risks to you of being in this study.
    - Will this study mainly help you or others?
    - If you want to drop out of the study, when can you do this?
    - Considering the risks and benefits we’ve discussed, what have you decided about taking part in this study?
- Educational procedures: For subjects scoring less than perfect on the initial presentation, educational procedures may be employed to raise understanding to sufficient levels for them to make a meaningful choice about participating. Potential measures include repetitive teaching, group sessions and audiovisual presentations.

Obtaining Surrogate Consent from an LAR

Initial Consent

If the research subject is responsive but lacks the capacity to consent, the investigator must make a reasonable effort to describe the research to the subject in a manner consistent with the standard consent process and indicate the intent to obtain surrogate consent. This communication should be documented in the research file. If, however, the research subject is non-responsive (e.g., unconscious due to trauma or medication administered to treat that trauma), the investigator will document this observation in the research file, and a note in the participant’s medical record that references the research file.

If the research subject expresses resistance or dissent to being in the research or to the use of the surrogate consent by word or gesture, they will be excluded from the research study.

Ongoing Consent

Consent in research is an ongoing process. If reconsent is ever required, the LAR should sign the amended consent on behalf of the subject if still incapacitated. In addition, researchers must also be prepared to re-evaluate a subject's ability to consent over time:

In cases where the subject regains the cognitive ability to consent, the research subject must be re-consented using the standard consenting process as soon as possible. After re-consent, the consent previously granted by the LAR is no longer considered valid. If in the re-consenting process, the research subject indicates that s/he no longer wish to continue participation, the subject must be withdrawn from study in a safe and respectful manner.

In the event that a research subject has been initially consented by an LAR, and a surrogate of higher priority subsequently notifies the investigator of that relationship to the research subject, the investigator must defer to the higher priority surrogate's decision regarding whether the research subject will continue to participate or to withdraw from the study.

Investigators must describe to potential surrogates the nature of ongoing decisions during the study, including decision to participate in certain procedures, changes to the study, etc., in order to ensure that the surrogate will be willing to undertake these ongoing responsibilities.

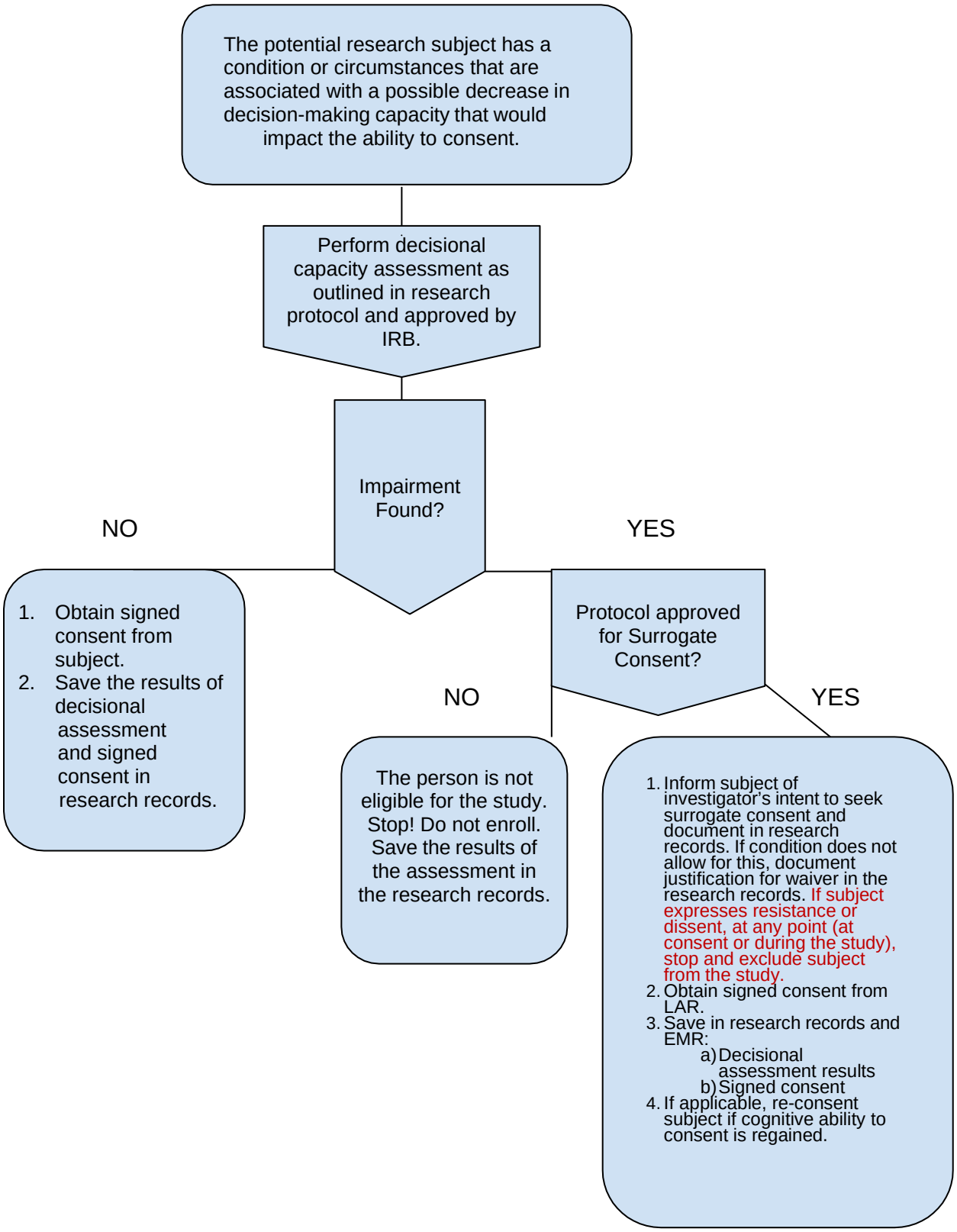
In the event that the LAR dies, the research subject or next available surrogate must be re-consented upon any event that would otherwise trigger re-consenting the research subject.

In conformance with the Common Rule, for research that is no more than minimal risk, the IRB may approve a request to waive some or all of the required elements of informed consent under specific criteria, and in such cases the need for surrogate consent may also be waived.

RESOURCES

- Revised Common Rule Q&As - Definition of Legally Authorized Representative
- FDA Regulation: 21 CFR 50.3(l)
- HHS Regulation: 45 CFR 46.102(i)
- IRB SOP 2.02 Informed Consent
- IRB SOP 3.18 Additional Safeguards for Individuals Without Decision-making Capacity
- IRB Reference Manual - RM 06 Vulnerable Populations
- IRB Reference Manual - RM 16 Informed Consent Process
- Ohio Revised Code 2317.54

Decision Tree for Assessment of Capacity to Consent



Section 17 Regulatory History
Effective Date: 10/21
Revised/Reviewed Date: 05/26
AAHRPP Element: II.3.F, II.3.G, II.4.B, II.4.C., III.1.F

APPENDIX 1: HRPP-RELATED TCHHN POLICIES AND PROCEDURES

Policy#	Title
-	Medical Staff Rules and Regulations - Research – Section 14
-	Medical Staff Bylaws, Policies, and Rules and Regulations - Medical Staff Credentials Policy
-	The Christ Hospital Code of Responsible Conduct
2.1.111	HIV Testing
2.34.139	Investigational Studies, Drugs, & Devices
2.47.121	Limited Data Set and Data Set Agreement
2.47.124	HIPAA Education and Training
2.47.132	HIPAA Privacy/Security Violation Sanction Guideline
4.14.123	Implementing New, Revised or Off Label Use Procedures, Services, Therapies, Implants, Devices, Supplies (including Vendor Inventory); Contracts or Offerings with Material Changes to Cost
4.20.102	Patient Advocate Process/Behavioral Medicine
4.20.122	Rights and Responsibilities of the Patient
4.20.171	Medical Ethics Committee - Philosophy, Functions, Consultations
4.20.172	Customer Complaint/Grievance
4.20.178	Research Involving Human Subjects
4.20.180	TCHHN Institutional Philosophy of Ethical Conduct
4.20.188	Reporting Adverse Medical Device Occurrences and Medical Device Tracking
4.20.198	Language Access and Interpreter Services
4.21.106	Code of Responsible Conduct and Certification

4.21.116 Conflict of Interest - Managers and Employed/Contracted Medical Staff Members

4.21.124 Conflict of Interest - Board of Directors

4.22.108 Consent for Hospital and Medical Treatment

4.28.106 Dispute Resolution

4.30.110 Release of Patient and Clinical Research Information to the News Media

7.4.100 Standard Operating Policy and Procedure Process Management

7.4.201 Protection of Human Subjects in Research

7.4.202 Investigator's Responsibilities

7.4.203 Responsibilities of the Research Team

8.4.108 Specialized Services

Appendix 1 Regulatory History
Effective Date: 05/26
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