

POLICIES AND PROCEDURES

of the

INSTITUTIONAL REVIEW BOARD

at

Trinity Health Of New England

TABLE OF CONTENTS

PAGE

GENERAL FUNCTIONS AND JURISDICTION OF THE IRB	1
International Research.....	5
Case Reports.....	5
IRB Chair and Members, and IRB Program Coordinator.....	5
Applicable Regulations, Hospital Policies and Definitions.....	7
Determination of Human Subjects Research.....	9
RELATIONSHIP OF THE IRB TO OTHER INSTITUTIONAL COMMITTEES	11
Research Committees.....	11
Ethics Committee.....	11
TRAINING IN THE PROTECTION OF HUMAN SUBJECTS	12
Investigators, Study Coordinators, and Research Staff.....	12
IRB Members.....	13
Signatory Officials of the FWA.....	13
SUBMISSION AND REVIEW OF APPLICATIONS	14
Initial Contact.....	14
Submission of Application.....	14
Application Fee.....	14
Initial Review and Submission Checklists.....	14
IRB Protocol Checklist.....	15
Checklist for Advertisements.....	16
Checklist for Contracts.....	16
Consent Form Checklist.....	16
HIPAA Authorization Checklist.....	19
Recruitment of Research Subjects and Advertisements.....	19
Data Safety and Monitoring for Interventional Protocols.....	23
THE REVIEW PROCESS	25
Full Board Review.....	25
Expedited Review.....	25
Criteria for Expedited Review.....	26
Exempt Review.....	30
Criteria for Exempt Review.....	30
The Review.....	33
Approval of a New Study.....	33
Approval Term.....	34
THE CONSENT PROCESS	36
Consent and Consent Forms.....	34
Consent Form, Individual Authorization Form and Waivers.....	39
Waiver of Informed Consent.....	39
Waiver or Alteration of the Consent Process/Waiver of Parental Permission.....	39
Waiver of Documentation of Informed Consent.....	40

TABLE OF CONTENTS (Cont.)

	PAGE
Exception from Informed Consent in Planned Emergency Research.....	41
Obtaining Consent for HIV Testing in Human Research Participants.....	41
Obtaining Permission of the Parent(s) / Assent of the Child.....	42
SHORT FORM WRITTEN CONSENT DOCUMENT.....	44
Use of a Short Form for English Speaking Subjects.....	44
Use of a Short Form for Non-English Speaking Subjects.....	44
NON-ENGLISH SPEAKING/READING POPULATIONS.....	46
Non-English Speaking/Reading Populations.....	46
MEETINGS OF THE IRB.....	47
Meetings and Quorum.....	47
Review Process.....	47
IRB Member Conflicts of Interest.....	50
Minutes of IRB Meetings.....	51
Documentation and Retention of IRB Records.....	53
Retention of Investigator Records.....	55
REVIEW OF RESEARCH INVOLVING VULNERABLE POPULATIONS.....	57
Additional Protections for Research Involving Pregnant Women, Fetuses or Neonates.....	57
45 CFR 46.201 to 46.207 (Subpart B).....	57
Additional Protections for Children Involved as Subjects in Research.....	63
45 CFR 46.401 to 46.409 (Subpart D).....	63
Prisoners.....	68
Cognitively Impaired Subjects in Research.....	68
PRIVACY AND CONFIDENTIALITY IN RESEARCH.....	70
HIPAA Compliance.....	70
Categories of Health Information.....	71
Identifiable Information and HIPAA Authorization.....	71
Waiver of Individual Authorization.....	71
De-Identified Information.....	72
Limited Data Sets.....	73
Preparatory to Research.....	74
Decedent's Information.....	74
Tissue Banking.....	75
Storage and Access of Research Data.....	75
Research Data Retention Policy.....	76
CONTINUING REVIEW.....	77
Continuing Review Requirements.....	77
Continuing Review - Expedited.....	78
Continuing Review – Full Board.....	79
Progress Reports and Abstract/Summary Forms.....	79

TABLE OF CONTENTS (Cont.)

	PAGE
PROTOCOL AMENDMENTS	82
Protocol Amendments	82
SPONSORS: RESPONSIBILITIES AND OBLIGATIONS	84
Responsibilities and Obligations	84
Sponsor-Investigators	85
Contract Information and Review	86
INVESTIGATIONAL NEW DRUGS AND DEVICES	88
Investigational New Drugs (IND)	88
Storage, Handling and Dispensing of Investigational Drugs, Agents or Biologics in Research	88
Investigational New Drug Exemptions	89
Investigational Devices	90
Investigational Device Exemption (IDE)	90
Exemption from an IDE	91
Determinations of Non-Significant and Significant Risk Device	91
Humanitarian Use Devices	92
Storage, Handling and Dispensing of Investigational Devices in Research	94
Expanded Access	94
Emergency Use of Drugs and Devices	96
COMMUNITY-BASED PARTICIPATORY RESEARCH	101
Community-Based Participatory Research	101
GOOD CLINICAL PRACTICE	102
CONFLICTS OF INTEREST IN RESEARCH POLICY	107
Definitions	108
Disclosure Procedure and Review	110
Resolution and Management of Conflicts of Interest	112
Sanctions	112
REVIEW OF EVENTS AND PROBLEMS	113
Definitions	113
Investigator Reporting Requirements	115
IRB Review of Reported Events	116
Reporting Adverse Events to Federal Agencies	118
COMPLIANCE: RESPONSIBILITIES OF RESEARCHERS	119
Responsibilities of the Research Investigator	119
Responsibilities of the Study Coordinator	120
Compliance and Audits	120
Non-Compliance and Corrective Action	122
When Investigators conduct research without IRB approval	124
Verification of Changes from Sources Other Than The Investigator	125
Suspension and Termination of Protocols	125

TABLE OF CONTENTS (Cont.)

	PAGE
Appeals of IRB Decisions	127
Bringing Forth Concerns	128
Undue Influence of IRB Members	128
REPORTING OF IRB FINDINGS	129
Correspondence with Investigators	129
Reporting of IRB Findings to the Institution	129
Reporting of IRB Findings to Federal Agencies	129

APPENDICES

Appendix 1

Organizational Charts

Appendix 2

Federal Wide Assurances

Institutional Assignment of IRB Authority

Unaffiliated Investigator Agreement

Cooperative Agreement with University of Connecticut Health Center

IRB Authorization Agreement with Yale University IRB

Appendix 3

IRB Committee Membership List

Ethics Committee Membership List

Financial Conflict of Interest Research Committee Membership List

Appendix 4

IRB Application Form Instructions

IRB Application Form – Full Board Review

IRB Application Form – Expedited/Exempt Review

Request for Determination of Human Subject Research

Conflict of Interest in Research Financial Disclosure Form

IRB Consent Form Template 1: Interventional Drug or Device Research

IRB Consent Form Template 2: Social and Behavioral Research

IRB Consent Form Template 3: Establishment of a Registry

IRB Consent Form Template 4: Case Report/Series or Prospective Record Review

Translation Certificate Form

Appendix 5

Authorization and Consent to Access, Use or Disclose Protected Health Information

Waiver of Individual Authorization for Disclosure of Protected Health Information

Approval Request for Waiver of Individual Authorization for Disclosure of Protected Health Information

Data Use Agreement

Limited Data Set

Data Collection for Reviews Preparatory to Research

Research on Decedents Information

Template Form for Authorization to Release Medical Record Information for Research Purposes

Appendix 6

Protocol Progress Report Request for Reapproval/Closure Form

Protocol Progress Report Abstract/Summary Form

Protocol Amendment

Protocol Deviation Report Form

Tracking Form for Adverse Events and Unanticipated Problems

Full Adverse Events and Unanticipated Problems

IRB Audit Form
IRB Member and Consultant Conflict of Interest and Financial Disclosure Form
IRB Member Review Criteria Form
IRB Member Review Checklist for Vulnerable Populations

Appendix 7

Sample Full Board IRB Approval Letter
Sample Expedited IRB Approval Letter
Sample IRB Renewal Letter
Sample IRB Expiration Letter

Appendix 8

Belmont Report

Appendix 9

Significant Differences in FDA and HHS Regulations

Appendix 10

Code of Federal Regulations Title 45 Part 46

Appendix 11

Code of Federal Regulations Title 21 Part 312 (Investigational New Drugs)
Code of Federal Regulations Title 21 Part 812 (Investigational New Devices)

Appendix 12

Significant Risk and Non-Significant Risk Devices

Appendix 13

Applicable Hospital Policy: Investigational Drugs
Applicable Hospital Policy: Consents Policy
Applicable Hospital Policy: Investigator Conflicts of Interest in Funded Research

GENERAL FUNCTIONS AND JURISDICTION OF THE IRB

The Institutional Review Board (IRB) at Trinity Health Of New England has been formally designated by the Institution to review and monitor research involving human subjects. All research projects involving human subjects, regardless of the source of funding, require review and approval by the IRB prior to their implementation.

Trinity Health Of New England is an integrated healthcare delivery system and includes Saint Francis Hospital and Medical Center (SFHMC), Mount Sinai Rehabilitation Hospital (MSRH), Johnson Memorial Hospital (JMH), Mercy Medical Center (MMC), Saint Mary's Hospital (SMH) and all their components, (see Appendix 1 for Organizational Structure of Trinity Health Of New England, the Human Research Protections Program, and the IRB).

Saint Francis Hospital and Medical Center (SFHMC) holds a Cooperative Agreement with the University of Connecticut Health Center (UCHC) regarding reliance upon each other's IRB for review of human subject research projects (Appendix 2). UCHC's IRB will be responsible for the review and approval of protocols where subject enrollment will be done exclusively at UCHC. This will include protocols where the investigators are employees of Saint Francis Hospital and Medical Center. Likewise, the Trinity Health Of New England's IRB will be responsible for the review and approval of protocols where subject enrollment will be done exclusively at SFHMC. This will include projects where the investigators are UCHC employees collaborating with an investigator employed by Trinity Health Of New England. UCHC Medical Students, Residents, and Fellows cannot serve as the principal investigator. For IRB review of protocols that accrue subjects at both SFHMC and UCHC, investigators may request that either UCHC or SFHMC serve as the IRB of record. The request will be based on factors such as where the preponderance of subject enrollment is to occur, the institution employing the principal investigator, and the institution where the majority of clinical research interaction with subjects will occur. The IRB Chairs of each institution will decide which institution's IRB will act as the IRB of record. Each IRB will inform the investigator and the other IRB in writing of its role as either the IRB of record, or its delegation of that role to the other institution. The decision may be that such protocols must be reviewed by one or both IRBs. Both institutions may accept each

others application but reserve the right to require investigators to submit a complete local application packet(s).

The Cooperative Agreement between SFHMC and UCHC includes the review of Connecticut Institute for Clinical and Translational Science (CICATS) protocols. The CICATS program is designed to encourage biomedical and health-related discoveries expedite the translation of those discoveries into products, treatments, and interventions to improve people's lives; and disseminate these discoveries into the community of physicians and healthcare providers throughout Connecticut and beyond. The agreement designates the UCHC CICATS IRB responsible for the review and approval of studies done as part of CICATS regardless of where subject enrollment or study procedures are done. Trinity Health Of New England may elect to have at least one employee serve on the CICATS IRB. Investigators from Trinity Health Of New England will be required to submit the UCHC application for all applicable CICATS protocols.

Under this Cooperative Agreement, both institutions reserve the right to insist on their own IRB review of any protocol that involves their patients, facilities or investigators (including students) for non-CICATS and CICATS protocols. If both institutions are providing IRB oversights for the study, investigators must abide by policies of both institutions. The IRB of record will provide to the other IRB copies of all correspondence related to study activity including initial and continuing approval letters, modifications to the study, reports of serious or continuing non compliance, unanticipated problems, and suspensions or termination of approval. Neither institution shall have the right to overrule a decision made by the other institution to disapprove a study.

Each institution will notify the other of any change in their Federalwide Assurance. The Principal Investigator's home institution will be responsible for required reporting the federal agencies and institutional officials in compliance with the terms of the home institution's FWA.

Trinity Health Of New England IRB does not consider the decisions of other IRBs when reviewing protocols, and does not have a reciprocal agreement with any other Institution's IRB with the exception of UCHC mentioned above. When research is being conducted at multiple sites, the research must be reviewed by the Trinity Health Of New England IRB. When research

reviewed by this IRB will be conducted in outside sites such as schools, churches, or community centers, this IRB will require proof of approval from the IRB at those sites. If an outside site does not have an IRB, this IRB will utilize the OHRP definitions of Engagement of Institutions in Research to determine whether the outside site must hold a Federal Wide Assurance (FWA) for the conduct of research to be permitted. The IRB is based at SFHMC, an Institution owned by the Catholic Church. Consequently, all policies and procedures abide by Catholic Church directives, and investigators and this IRB are required to comply with these directives.

The IRB at Trinity Health Of New England is the Institutional Board responsible for the review of human research protocols from SFHMC, MSRH, JMH, MMC, SMH and their components. Trinity Health Of New England has filed a Federalwide Assurances (FWA) of Protection of Human Subjects with the Department of Health and Human Services (DHHS), Office for Human Research Protections (OHRP) (see Appendix 2). The Federalwide Assurance Number for Trinity Health Of New England is FWA00020300. Trinity Health Of New England IRB has been assigned a unique number by OHRP (IORG0000212) and is registered with Trinity Health Of New England FWA.

In accordance with federal regulations, the IRB has the authority to approve, require modifications in (to secure approval), disapprove, terminate, or suspend research at these sites. No Institutional official or other Institutional committee may override the decisions of the IRB to disapprove a study. However, the Institution may prevent the performance of a study by the IRB. No Institutional official or other Institutional committee may approve research that has not been approved by the IRB, including research that was disapproved. The purpose of the IRB is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in research. The Office of the IRB is located in the Department of Research Administration, 260 Ashley Street, 3rd Floor.

The IRB at Trinity Health Of New England reviews protocols from qualified Investigators who are employed by SFHMC, MSRH, JMH, MMC, SMH and their components and carry out research endeavors at these Trinity Health Of New England sites. The IRB also accepts protocols from members of the Medical/Dental staff who carry out research at Trinity Health Of New England sites and have filed a Federal-wide Assurance or an Unaffiliated

Investigator Agreement. The IRB does not review protocols from members of the Medical/Dental staff for research carried out in private offices, since these are outside the jurisdiction of Trinity Health Of New England. The IRB at Trinity Health Of New England does not review protocols from individuals who are not members of the Hospital Staff or of the Medical/Dental Staff. In cases where students, or trainees, or Investigators from other institutions are applicants, a member of the Medical/Dental Staff shall be a collaborator and sign the application and will be fully responsible to assure compliance with all applicable regulations and guidelines.

The IRB does permit research volunteers to review and extract data from medical records without consent provided the research assistant works with a Trinity Health Of New England investigator. Examples include, but are not limited to, retrospective record reviews with a request of waiver of individual authorization (waiver of consent).

In order to take part in research activities, Research Assistants may be hired by Trinity Health Of New England as Consultants. The Human Resources Department will be responsible for completion of background checks and appropriate hospital orientation, including the Health Insurance Portability and Accountability Act (HIPAA) and Compliance Training (may be completed by in the Director of Volunteer Services). The IRB Program Coordinator must receive email confirmation of completion from the Human Resources Department prior to releasing approval. Research Assistants are to work under the direct supervision of the Principal Investigator of the Study.

Independent or Central IRBs are not used for studies conducted at SFHMC, MSRH, JMH, MMC, SMH, or their components with the exception of 1) A research participant becomes incarcerated and 2) Institution participation in Cooperative Group Oncology studies.

The Trinity Health Of New England IRB does not review studies enrolling prisoners. If a subject becomes incarcerated during the course of a research project, the continued participation or withdrawal of the participant will be reviewed by a Central IRB which includes a prisoner representative.

Trinity Health Of New England holds an IRB Authorization Agreement with Yale University IRB. The agreement is specific to all oncology research protocols for which SFHMC physician,

who is also a Yale researcher serves as the Principal Investigator and for which all research interventions involving human subjects and/or their identified data take place at SFHMC. It also covers all oncology research protocols for which SFHMC physician serves as the Principal Investigator that engage Yale staff as members of the research team (e.g. nurse) and for which all interventions involving human subjects and/or their identified data take place at SFHMC.

The PI is responsible for submission of all personnel amendments involving addition of Trinity Health Of New England research staff to the Trinity Health Of New England IRB prior to submission to Yale IRB. The Trinity Health Of New England IRB will review personnel amendments to ensure institutional compliance with training and conflict of interest policies. In the event a conflict of interest exists, the Trinity Health Of New England IRB will notify Yale IRB of any required management plan.

A copy of the approved above-referenced protocols and all approval letters (initial and continuing review and modifications) will be provided to the Trinity Health Of New England IRB by the PI.

International Research

The Trinity Health Of New England IRB does not sponsor or conduct review of international research.

Case Reports

Case Reports are to be reviewed by the IRB except when the case is being reported by the physician managing the patient. In this instance, the physician should consent the patient (obtain permission to report) but does not need to apply to the IRB.

IRB Chair, Institutional Official, IRB Members, and IRB Program Coordinator

The Chairman of the IRB is appointed by the Chief Executive Officer of Trinity Health Of New England. There is no designated term of service. Selection criteria for the IRB Chair requires that he/she be a member of the staff of any one of the Trinity Health Of New England hospitals with the academic and professional stature necessary to encourage respect from the IRB, Administration and the research community. Currently, the Chair is Dr. Latha Dulipsingh.

The Vice Chair of the IRB is appointed by the Chairman. The Vice Chair will assume the role of Chair in the event of illness, absence, or inability of the Chair to perform this function. There is no designated term of service. Currently the Vice Chair is Dr. James Vredenburg. The IRB Program Coordinator is selected by the Chairman of the IRB. Currently, the IRB Program Coordinator is Ms. Evelyn Cordero. Additionally, the IRB Chair's performance, knowledge, and skills will be assessed by the IRB Members, and will be provided with feedback once per year. The IRB Chair evaluates the IRB Program Coordinator.

The Institutional Official is appointed by the Chief Executive Officer of Trinity Health Of New England. There is no designated term of service. Currently, the Institutional Official is David Bittner Chief Financial Officer and the Senior Vice President of Finance. The responsibilities of the Institutional Official include overseeing the IRB Chair and evaluating them, to ensure compliance with Institutional and IRB policies, and to ensure the Institution does not interfere with the decisions of the IRB. When the IRB evaluates the need for resources they speak directly to the Institutional Official. The plan to evaluate what is needed for the IRB include, but are not limited to: space, personnel, IRB educational program, Legal Counsel, Conflict of Interest, Quality improvement plan, and Community Outreach. These resources are evaluated twice a year and are done by the IRB Program Coordinator and the IRB Chair. The IRB is evaluated to determine whether or not the work flow is going smoothly and if needed, the IRB changes their process to see how well a new process may work. The Institutional Official may not approve research that has been disapproved by the IRB. The Institutional Official is evaluated by the Chief Executive Officer of Trinity Health Of New England and provided with feedback yearly as a function of their employment at Trinity Health Of New England.

The IRB is composed of twelve to fourteen members and one alternate, as deemed necessary (Appendix 3). The members of the IRB represent a wide range of disciplines and have medical, nursing and social knowledge. At least two members are not affiliated with Trinity Health Of New England and do not have scientific expertise. Members are selected by active members of the IRB. Members are chosen by their area of professional expertise, experience and/or affiliation, depending on the needs of the board. Members are formally appointed by the Chairman of the IRB and their nomination is filed with OHRP. It is essential for IRB members

to attend a majority of meetings. IRB members are required to attend 7 of 12 meetings per year. If a member is unable to attend a majority of meetings, an alternate member with similar background may be appointed by the IRB Chair to serve as a replacement when necessary. If an alternate member is designated, the IRB Roster will be revised to identify the member for whom the alternate can substitute. There is no designated term of service, and members of the IRB are not compensated for their services. IRB members' performance, knowledge, and skills will be assessed by the Chair and the Program Coordinator, and IRB members will be provided with feedback once per year. Contribution to IRB meeting discussion, attendance, thoroughness of review, and volume of work reviewed will also be assessed, contributing to the overall evaluation of individual IRB members. If it is determined that an IRB member is unable to perform the function, they will be asked to resign. Newly appointed members are provided with IRB policies and meet with the Chairman and Program Coordinator of the IRB to review IRB policies, their member duties, and review information from OHRP and the FDA.

Trinity Health Of New England is a non-profit, physician-hospital partnership and prohibits individuals who are responsible for business development from serving as a member on the IRB or any involvement in the day to day operations of the review process.

Applicable Regulations, Hospital Policies and Definitions

The IRB at Trinity Health Of New England abides by the principles of the Belmont Report (Appendix 8), and ensures that human subject's research taking place at this Institution is in compliance with all applicable Federal and State laws and Hospital Policies.

Federal Regulations:

- Title 45 CFR 46 (Appendix 10)
- Title 21 CFR 50 and 56
- Health Insurance Portability and Accountability Act (HIPAA)

Connecticut General Statutes

Connecticut law does not specifically address issues pertaining to human subject research, with the exception the statutes set forth in Chapter 368X on AIDS Testing and Medical Information (please see Obtaining Consent for HIV Testing in Human Research Participants,

page 40). However, it is the policy of the IRB that statutes applicable to clinical care (i.e., confidentiality of records, consent for care), also be applied in clinical research. The general statutes of the State of Connecticut can be found at <http://www.cga.ct.gov/current/pub/titles.htm>.

Hospital Policies

All Hospital Policies apply to Research conducted under the auspices of this Institution. The Hospital Policy Manual is available on the SFHMC intranet website, under “Policies and Procedures”. Research-specific Hospital Policies include Investigational Drugs, Consent for Human Research and Experimentation, Investigator Conflicts of Interest in Funded Research and Conflicts of Interest Policy in Saint Francis Personnel (Appendix 13).

Definitions

For the purposes of this policy, the terms used are defined as follows:

“Research” as defined by the Department of Health and Human Services (DHHS) regulations, means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. A systematic investigation is an activity that involves a prospective research plan which incorporates data collection, both quantitative and qualitative, and data analysis to answer a research question. Generalizable knowledge is information from which one may infer a general conclusion; knowledge brought into general use or that can be applied to a wider or different range of circumstances.

A **“human subject”** as defined by FDA regulations, is an individual who is or becomes a participant in research, either as a recipient of a test article or as a control. A subject may be either a healthy human or a patient. “Human subject” includes an individual on whose specimen a device is used.

A **“human subject”** as defined by DHHS regulations, is a living individual about whom a Researcher conducting research obtains data through intervention or interaction with the individual, or identifiable private information. Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes. Interaction includes

communication or interpersonal contact between investigator and subject. Private information includes information about behavior that occurs 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 an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. A subject may be either a healthy individual or a patient.

“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 FDA, or need not meet the requirements for prior submission to the FDA, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

“Test article” means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to FDA regulation.

“Human Subjects Research” means any activity that either (1) meets the definition of research and involves human subjects, or (2) meets the definition of a clinical investigation.

Determination of Human Subjects Research

Any activity with access/use of individually identifiable health information for any purpose other than to provide feedback for a practice/process/program within Trinity Health Of New England is considered research. You must submit your project to the Trinity Health Of New England IRB for further review.

Quality Assessment (QA) and Quality Improvement (QI) activities done with the purpose/intent of prospectively implementing a change in a practice/process/program, whose outcomes will be evaluated through research at a later time, will require Trinity Health Of New England IRB oversight.

Internal Trinity Health Of New England activities, which do not include individually identifiable health information, are not considered research when:

- The purpose of the activity is to assess/evaluate the success of an established internal process/procedure/program in meeting objectives and goals.
- The intended results are to improve the practice/process/program within Trinity Health Of New England.
- The evaluation is used as a management tool for monitoring and improving practice/process/program at Trinity Health Of New England.

Employees and agents of Trinity Health Of New England who wish to complete a determination of whether an activity is human subjects research should submit a request, via iRIS, with a description of the activity and an attached protocol. The request should be submitted on the “Request for Determination of Human Subject Research” form (Appendix 4) completed in iRIS.

The IRB will consider an activity to be human subjects research when, according to the above definitions, the activity is either 1) “research” that involves “human subjects”, or 2) a “clinical investigation”. The IRB Chair or IRB Program Coordinator will review each request, make the determination of whether the described activity represents “human subjects research”, and provide a written response to the Investigator within 7 days. If the request meets the determination of human subjects research, the individual must submit a formal application to the IRB.

No individual will be a subject in research conducted at the hospital or by any of its employees acting within the scope of their job responsibilities, unless the patient/individual or, when appropriate, the patient’s surrogate, has first given informed consent or, when appropriate, waiver of consent has been granted by the IRB.

RELATIONSHIP OF THE IRB TO OTHER INSTITUTIONAL COMMITTEES

Research Committees

Presently, there is no Scientific Research Committee, although outside consultants are utilized when needed.

Scholarly or scientific reviews done here at Trinity Health Of New England of proposed research address the following issues: the research uses procedures consistent with sound research design and the research design is sound enough to yield the expected knowledge needed for review. Since the institution follows ICH-GCP (E6) in regards to the available nonclinical and clinical information on investigational product to support the proposed clinical trials done here at Trinity Health Of New England, the scientific reviewer assigned to these protocols takes this into account when reviewing a study. If concerns arise during the initial review of a protocol by the IRB Chair regarding the scientific design or validity of a protocol, the IRB Chair can request that the protocol be reviewed by an outside consultant. If services are used by an outside consultant, they either attend the convened meeting and share their review, or communicate with the Program Coordinator and the IRB chair via email. If concerns regarding the scientific design or validity of a protocol that has been approved by expedited review arise during a convened meeting of the IRB, IRB members can request that the protocol be reviewed by outside consultants. Outside consultants are used when the area of expertise required to review a protocol is not covered by current members of the IRB. This can be decided by the IRB Chairman at the time of initial review, or by the members of the IRB at a convened meeting. The choice of an outside consultant is decided by the IRB Chairman, or as recommended by an IRB member; however, chosen consultants do not vote with IRB members.

When necessary, outside consultants offer advice on experimental design to the Investigators. Training sessions in experimental design are offered by the Department of Research Administration, and announcements are shared with potential Investigators at all sites. This IRB does not entertain studies involving unapproved radioisotopes.

Ethics Committee

When deemed necessary, the IRB may consult with the Ethics Committee (Appendix 3) and obtain an opinion on specific issues related to ethics in clinical studies.

TRAINING IN THE PROTECTION OF HUMAN SUBJECTS

Investigators, Study Coordinators, and Research Staff

All investigators, study coordinators, and research staff are required to complete training in the protection of human subjects prior to receiving IRB approval of a protocol. The purpose of this training is to ensure that investigators conducting research are qualified to conduct the study, to uphold Belmont Report principles, and ensure compliance with the regulations and the requirements of the IRB in the approved protocol. Minimum standards for approved training programs require the inclusion of the principles of the Belmont Report. Currently, the IRB provides and accepts CITI training. Personnel can complete training at www.citiprogram.org. All study staff are required to complete: Human Subject Research Training; Group 1 Biomedical Research Investigator OR Group 2 Social Behavioral Research Investigator, Good Clinical Practice (GCP for all investigator's (US FDA focus)) and Conflicts of Interest (COI). A quiz is taken after each of the modules, and upon completion of the training a course completion record is issued by the Collaborative Institutional Training Initiative (CITI) group.

Off-site investigators collaborating with an investigator from an approved site must create or affiliate their CITI training account with Trinity Health Of New England and complete all courses that the Trinity Health Of New England IRB requires of their staff.

Training of medical students and house staff usually is required, but assessed on a case-by-case basis, depending on the type of research being conducted, and on whether the mentors are involved in the training process. The minimum training requirement for conducting record review studies is the successful completion of the CITI on-line training modules in "Data Specimens and Record Review" and the Trinity Health Of New England required HIPAA training for all employees.

Subsequent to the initial training, the IRB requires all investigators, study coordinators, and research staff to complete a CITI refresher course via www.citiprogram.org. The refresher course is to be completed every 3 years.

Individuals who do not meet the training requirements of the IRB may not be involved in human research activities. The IRB will take appropriate action to withhold or reverse the

approval of research when training requirements are not met. The IRB will not approve protocols until training requirements have been fulfilled. When an investigator, study coordinator, or research assistant is added to a protocol after the initial approval, training requirements must be met before the individual is involved in human research activities.

IRB Members

Following their appointment, IRB members are provided with training materials, IRB Policies and Procedures, and are instructed personally by the IRB Program Coordinator and Chair. IRB members receive ongoing training during scheduled meetings. Completion of training is documented as meeting attendance in the meeting minutes and maintained in the IRB files. All members must complete group 4 IRB members, GCP for all investigator's (US FDA Focus) and Conflicts of Interest (COI) for CITI training (www.citiprogram.org).

When the written Policies and Procedures of the IRB are revised, a copy of the revised information is emailed as a PDF to the IRB members with their agenda materials. The revised portions are highlighted for easy reference. At the next fully convened meeting of the IRB, the IRB Program Coordinator instructs IRB members in the revisions, which is documented in the minutes of the meeting. The IRB Program Coordinator is available to meet with IRB members to answer questions or concerns at their request. When the revisions include procedural changes to the conduct of IRB review of protocols, changes are implemented and then reviewed by the full board within a 3 month period to assess their effectiveness and make revisions, as necessary.

Signatory Officials of the FWA

Institutional officials that act officially and in an authorized capacity on behalf of this institution as signatories of the Federalwide Assurance with the OHRP are provided with training materials, IRB Policies and Procedures, and are instructed personally by the IRB Program Coordinator and Chair. OHRP on-line assurance training is recommended but not mandatory. The IRB Office also recommends CITI training.

SUBMISSION AND REVIEW OF APPLICATIONS

Initial Contact

Following initial contact with the IRB, investigators are provided with:

1. Application Form (Appendix 4)
2. Consent Form Templates (Appendix 4)
3. Waiver of Individual Authorization for Disclosure of Protected Health Information Questionnaire (Appendix 5) (*This is part of the application form and must be completed for all studies when a waiver of consent is requested.*)
4. Unaffiliated Investigator Agreement (Appendix 2) (*Required from members of the Medical/Dental/Nursing staff not employed by a Trinity Health Of New England site with a Federal Wide Assurance*)
5. Conflict of Interest in Research Financial Disclosure Form (Appendix 4)
6. Training materials, if indicated

Submission of Application

Instructions for submission of applications are on the IRB website found at <http://www.trinityhealthofne.org/irb> . Incomplete protocols may be returned to Investigators.

Application Fee

An initial fee of \$2,500 is charged to studies that are commercially supported (pharmaceutical or device manufacturer), but not to investigator-initiated or federally funded studies. A fee of \$1,000 is charged for continuing review (annually) and \$250 for a study closure for commercially supported studies. A fee of \$500 is charged for a major full board amendment, and \$250 for a minor expedited amendment for all commercially supported studies. All fees are nonrefundable.

(a) Initial Review and Submission Checklists

The Chair and the Program Coordinator review the application to determine whether or not it qualifies for Expedited Review in accordance with guidelines in Title 45 CFR 46.110 and Title 21 CFR 56.110, qualifies for Exemption in accordance with guidelines in 45 CFR 46.101(b)

and 21 CFR 56, or requires full board review. The IRB Program Coordinator ensures the completion of the application by checking the following items:

IRB Protocol Checklist

1. ___ Investigator training verified
2. ___ Typewritten application
3. ___ All sections completed according to form
4. ___ Signed by Principal Investigator (**and** Trinity Health Of New England sponsor, if required)
5. ___ 1 CV for each investigator
6. ___ Research Coordinator Identified (may not be one of the investigators)
7. ___ Full protocol (proposal or grant)
8. ___ Investigator's Brochure (for pharmaceutically sponsored studies)
9. ___ Application
10. ___ Consent form
11. ___ Sponsor sample consent form template, if applicable
12. ___ Documentation indicating why the sponsor sample consent form template or protocol (or both) have been altered in the procedure and/or risks sections, if applicable
13. ___ Questionnaires, interviews, assessment materials, etc.
14. ___ Advertisement, if applicable (see checklist)
15. ___ Application fee (if applicable)
16. ___ Research Financial Disclosure Form
17. ___ DSMB or Safety Officer designated (for all interventional protocols)
18. ___ For research involving an IND or IDE: Form 1571 ___ Form 1572 ___
19. ___ For research involving an IND or IDE: Investigator's Agreement
20. ___ P.I. and Co investigators employees of Trinity Health Of New England
21. ___ Unaffiliated Investigator Agreement

Checklist for Advertisements

1. ___ Name and address of investigator
2. ___ State it is research
3. ___ Purpose of Research
4. ___ Summary of eligibility criteria
5. ___ Benefits (e.g. payment, free treatment)
6. ___ Location of research
7. ___ Name/Phone of person to contact for more information

Checklist for Sponsor Agreements/Contracts

1. ___ Sponsor payment, compensation, or reimbursement schedules for Investigators and/or the Institution.
2. ___ Indication of who (e.g., the sponsor or Institution) will provide additional care for research-related injuries, and who will be responsible for the payment of this additional care.
3. ___ The sponsor's obligation to promptly report to the investigator and Institution any significant new adverse effects, risks, or other findings related to the research study that could possibly affect the safety of subjects, affect the willingness of subjects to continue with participation, influence the conduct of the study, and/or alter the IRB's approval to continue the study.
4. ___ Indication of how interim or final study results will be communicated to the subjects when the information could possibly affect their safety, medical care, and willingness to continue with participation. This includes results from other studies using the same intervention for a similar or other indication.
5. ___ Contract provisions for medical care for research-related injuries are consistent with the consent document.

Consent Form Checklist

1. ___ Wording understandable to subject population
2. ___ Does not contain coercive language
3. ___ Statement that study involves research
4. ___ Purpose of research

5. ___ Approximate number of subjects involved in the study
6. ___ Procedures to be followed
7. ___ Procedures which are experimental
8. ___ Expected duration of subject's participation
9. ___ Description of risks, discomforts and side effects
10. ___ Safeguards to be used
11. ___ Benefits to subject or others which may be expected
12. ___ Alternative treatments that might be advantageous
13. ___ Statement describing extent to which confidentiality of records identifying subject will be maintained
14. ___ A statement that the FDA or other regulatory agencies may inspect subject's medical records
15. ___ List other organizations that may inspect and/or copy records for quality assurance and data analysis (NCI, sponsor, IRB)
16. ___ For research involving more than minimal risk:
 - ___ explanation as to whether compensation and medical treatments are available if injury occurs and what they consist of
 - ___ where further information may be obtained
 - ___ statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which subject is otherwise entitled
17. ___ *If applicable:* Any additional costs the subject will incur, what will be paid for as part of study and by whom
18. ___ Compensation for participation, if any
19. ___ Trinity Health Of New England disclaimer "If you sustain injuries from your participation in this research study, you may not be automatically compensated by Trinity Health Of New England "
20. ___ Statement that subject may withdraw from study, or be withdrawn, at any time without penalty, loss of benefits to which he/she is entitled, or jeopardizing present or future care

21. ____ *If applicable:* Anticipated circumstances under which participation may be terminated by investigator without regard to subject's consent
22. ____ *If applicable:* Consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
23. ____ *If applicable:* Statement that significant new findings developed during course of research which may relate to subject's willingness to continue participation will be provided to subject
24. ____ Name/phone number of Investigator, Co-Investigator, or Study Coordinator to contact with questions or concerns about the research or procedures
25. ____ Name/phone number of Principal Investigator or person to contact if subject experiences problems, adverse events or research-related injury during study
26. ____ For questions about rights as a research subject, address and phone number of IRB. Indication that research participants may also call this number in case they wish to talk to someone not on the research team. (Participants should also be notified of steps the IRB will take to discuss concerns regarding the research. This can be handled when the participant calls the IRB directly. If there is a problem with the research staff, a safety related concern, and anything else the participant wishes to discuss, the IRB can discuss this with the participant, in which an audit will be conducted and the findings will be discussed with the Institutional Official and legal and risk management if necessary. This concern will remain confidential to protect the patient's privacy.)
27. ____ Name/phone number that research participants may contact to discuss problems, concerns, questions, obtain information or offer input with an informed individual unaffiliated with the specific research protocol (may be the IRB)
28. ____ *If applicable:* Statement that clinical trial information will be entered into a databank (www.ClinicalTrials.gov)
29. ____ *If applicable:* Statement that treatment/procedure may involve unforeseeable risks to subject, or to embryo or fetus, if subject is or may become pregnant

30. ___ *If applicable*: Avoidance of pregnancy language that is in accordance with Catholic Church directives
31. ___ *If applicable*, disclosure of benefits to investigators involved in the study
32. ___ *If applicable*, assent statement included

HIPAA Authorization Checklist

1. ___ A specific and meaningful description of what protected health information will be used or disclosed;
2. ___ Identification of who may use or disclose the protected health information of the subject, and to whom this information may be disclosed;
3. ___ Purpose of the use or disclosure of protected health information (i.e., for research purposes);
4. ___ A statement that there is no expiration date related of the use or disclosure of the protected health information for this research project or a statement that the use or disclosure of the protected health information will conclude at the end of the study;
5. ___ A statement of the individual's right to revoke the authorization in writing and the exceptions to the right to revoke;
6. ___ A statement that information used may be subject to re-disclosure by the recipient and no longer be protected by this rule

Recruitment of Research Subjects and Advertisements

The four types of recruitment that are permissible at Trinity Health Of New England are:

1. An Investigator's own patients. When a physician has treated or continues to treat a patient who is eligible as a subject in a clinical trial that the physician is conducting, the informed consent process must differentiate between the physician's roles as clinician and investigator. This is best achieved when someone other than the treating physician obtains the participant's informed consent to participate in the trial. This individual should be protected from the pressure of financial incentives. The purpose of this disclosure is to ensure that a potential subject is not coerced or pressured into

participating, especially in cases where a study may involve subjects who are vulnerable to undue influence.

2. A physician referring patients to an Investigator following a discussion with the patient regarding the study and the patients' permission to be contacted by the investigator.
3. Advertising. The IRB reviews direct advertising for research subjects which is defined as advertising that is intended to be seen or heard by prospective participants to solicit their participation in a study. All advertising materials must be approved by the IRB prior to its use and distribution. Advertisements to recruit subjects may be approved by expedited review, and should be limited to:
 - a. The name and address of the clinical investigator
 - b. Statement that it is research
 - c. Purpose of the research
 - d. Summary of eligibility criteria
 - e. A straightforward and truthful description of the benefits to the subject for participating in the study (e.g. payments or free treatment) and the commitment involved
 - f. The location of the research
 - g. Name/phone number of person to contact for further information

These basic guidelines apply to all forms of advertisements, including those utilizing newspapers, radio, television and fliers.

Advertisements cannot make claims, either explicitly or implicitly, that the test article is safe or effective, or known to be equivalent or superior to any other biologic or device. Advertisements cannot contain language that is exculpatory or promise "free medical treatment" when the intent is to only say subjects will not be charged for taking part in the investigation. If language is to contain terms such as "new treatment", "new medication", or "new drug", the advertisement must explain that the test article is investigational. Advertisements may state that subjects will be paid, but should not emphasize the payment or amount to be paid, by such means as larger or bold type.

The IRB reviews the final copy of printed advertisements, whenever possible, to evaluate the relative size of the type and other visual effects. The IRB will review the information contained in the advertisement and the mode of its communication (e.g. radio broadcast, newspaper ad, poster) to determine that the procedure for recruiting is not coercive to subjects. When advertisements are taped broadcasts or videos, the IRB reviews the final audio and/or video tape and requests a copy of the final transcript. If the advertisement will include a live interview or question/answer session, the IRB requests an outline of topics to be discussed prior to the broadcast and a tape or transcript of the session following the broadcast.

4. Clinical trial websites. Although websites use a different medium than traditional print or broadcast advertisements the requirements are the same. When information posted on a clinical trial website goes beyond directory listings, with basic descriptive information, such information is considered part of the informed consent process, and therefore, requires IRB review and approval. Basic descriptive information includes:

- a. Study title
- b. Purpose of the study
- c. Protocol summary
- d. Basic eligibility criteria
- e. Study site location(s), and
- f. How to contact the study site for further information.

Clinical trial websites that provide *only* directory listings with basic descriptive information about clinical trials in general (as listed above) do not need to be reviewed by the IRB.

Information exceeding such basic listing information will require IRB review and approval. The IRB will ensure that information is presented in a balanced and fair manner, will assess the types of incentives offered to prospective subjects, and will ensure that participation is voluntary.

If the clinical trial website asks viewers to answer questions regarding eligibility for a specific clinical trial, and therefore, identifiable private information is collected, the IRB will review plans for protecting the confidentiality of that information and ensure that the website explains how identifiable private information might be used.

Informed consent will be required for the collection of any information about the respondent unless the IRB has determined that the informed consent requirement can be waived, or altered, in two sets of circumstances, as described in 45CFR46.116 c and d:

1. Research activities designed to study certain aspects of state or local public benefit or service programs;
2. If the IRB finds and documents that:
 - a. the research involves no more than minimal risk to the subjects;
 - b. the waiver or alteration will not adversely affect the rights and welfare of the subjects;
 - c. the research could not practicably be carried out without the waiver or alteration; and
 - d. whenever appropriate, the subjects will be provided with additional pertinent information after participation.
(Note that research involving children as subjects requires parental permission and child assent unless waived (45CFR46.408).)
 - e. the research is not subject to FDA regulation.

The IRB will evaluate the selection of subjects and influence of payment(s) to subjects. Participant payment arrangements may be used to recruit and keep participants enrolled in research studies. The arrangements for such payments must be stated in a straightforward and honest manner on the initial application, and in the informed consent form to ensure that the participants understand what they are entitled to. Proposed payments to research participants are reviewed on a case-by-case basis by the IRB as part of the initial submission process. The IRB will take into consideration the payment fee(s), payment schedule, proposed method of payment (e.g. gift card, cash), and distribution to assure that payment(s) are not coercive or present undue influence. Payments should be based on research participants' time and/or reimbursement for reasonable expenses incurred during their participation in a clinical trial, such as parking, travel, and lodging expenses. The nature and amount of compensation or any other benefit should be consistent with the principle of voluntary informed consent. Per FDA guidelines, payment of a small proportion as an incentive for completion of the study is acceptable, providing that such

incentive is not coercive. The entire payment should not be contingent upon completion of the entire study. The IRB determines that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn. Compensation for participation in a trial offered by a sponsor may not include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

Outreach programs directed at patients at Trinity Health Of New England and the community are conducted by the Institution as well as by individual departments in order to educate the public about participating in research studies. These activities may include distribution of informative pamphlets, lectures or informational talks, and other educational programs. The phone number of the IRB is provided on the IRB web site and should be provided on pamphlets and on other handouts, to establish a safe, confidential and reliable channel for current, prospective, or past research participants or their designated representatives that permits them to discuss problems, concerns, and questions; obtain information; or offer input with an informed individual who may be unaffiliated with a specific research protocol or department. To evaluate the effectiveness of outreach programs, the IRB Program Coordinator will discuss the various activities engaged in during the past year with Study Coordinators.

Data Safety and Monitoring for Interventional Protocols

All interventional protocols require safety monitoring to review accumulated outcome data, including Adverse Event reports to determine whether any of the treatment procedures practiced should be altered or stopped. When evaluating new protocols for data safety monitoring, the type of monitoring required depends upon the size of the study, the nature of the investigation, the complexity of the study design, and the level of risk to study participants. Large, multi-center studies are required to have independent Data and Safety Monitoring Boards to gather and assess study information from all the sites involved in the trial. Local, investigator-originated protocols generally do not need data safety monitoring or a Safety Officer when addressing lesser outcome protocols that involve minimal risk. The IRB reserves the right to designate an independent Safety Officer for investigator-originated protocols to ensure the safety

of research participants and compliance with regulations. This IRB also requires all interventional protocols to have a Study Coordinator.

THE REVIEW PROCESS

For **Full Board Review**, applicants are required to submit:

1. Full Board IRB Application completed in iRIS
2. Consent form and HIPAA Authorization (if not included in consent form) or questionnaire requesting waiver of authorization
3. Sponsor sample consent form template, if applicable
4. Documentation indicating why the sponsor sample consent form template or protocol (or both) have been altered in the procedure and/or risks sections, if applicable
5. Questionnaires, interview protocols, assessment materials, experiment session outlines and descriptions of materials that subjects will encounter
6. Advertisements for subject recruitment, if applicable
7. Protocol, e.g., proposal or grant
8. Investigators' Brochure and any previous animal and human experiments associated with the investigational article supplied by the manufacturer
9. 1 copy of curriculum vitae for each investigator listed on the application
10. Documentation of training of off-site investigators
11. Application fee, if applicable
12. Research Financial Disclosure Form
13. DSMB or Safety Officer designated (for all interventional protocols)

For **Expedited Review**, applicants are required to submit:

1. Expedited IRB application completed in iRIS
2. Consent form and HIPAA Authorization (if not included in consent form) or completed questionnaire requesting waiver of authorization
3. Sponsor sample consent form template, if applicable
4. Documentation indicating why the sponsor sample consent form template or protocol (or both) have been altered, in the procedure and/or risks sections if applicable

5. Questionnaire, interview protocol, assessment materials, experiment session outlines and descriptions of materials subjects will encounter
6. 1 copy of curriculum vitae for each investigator listed on the application
7. Documentation of training of off-site investigators
8. Application fee, if applicable
9. Research Financial Disclosure Form

Applications not meeting the requirements of expedited review are resubmitted following the requirements for full board review (see below, Criteria for reviewing and approving research by the expedited procedure).

The IRB uses the following **criteria for reviewing and approving research by the expedited procedure**:

Applicability

- (A) Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 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 on 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.
- (B) The categories in this list apply regardless of the age of subjects, except as noted.
- (C) The expedited review procedure may not be used where identification of the subjects and/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 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.
- (D) The expedited review procedure may not be used for classified research involving human subjects.

(E) IRBs are reminded 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.

(F) Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

Research Categories

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
 - (a) 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.)
 - (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
 - (c) 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
 - (d) 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.
3. Prospective collection of biological specimens for research purposes by noninvasive means.

Examples:

 - (a) hair and nail clippings in a non-disfiguring manner;

- (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
 - (c) permanent teeth if routine patient care indicates a need for extraction;
excreta and external secretions (including sweat);
 - (d) gum base or wax or by applying a dilute citric solution to the tongue;
 - (e) placenta removed at delivery;
 - (f) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
 - (g) 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;
 - (h) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
 - (i) sputum collected after saline mist nebulization.
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:

- (a) 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;
- (b) weighing or testing sensory acuity;
- (c) magnetic resonance imaging;
- (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging,

* Children are defined in the DHHS 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
Revised June 2018
(Replaces July 2017)

doppler blood flow, and echocardiography; uncannulated saliva collected in an unstimulated fashion or stimulated by chewing moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects [45 CFR 46.101(b)(4)]. This listing refers only to research that is not exempt.)
6. Collection of data from voice, video, digital, or image recordings made for research purposes.
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. (NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects [45 CFR 46.101(b)(2) and (b)(3)]. This listing refers only to research that is not exempt.)
8. Continuing review of research previously approved by the convened IRB as follows:
 - (e) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
 - (f) where no subjects have been enrolled and no additional risks have been identified; or
 - (g) where the remaining research activities are limited to data analysis.
9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories 2 through 8 above do not apply, but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified

10. Minor changes in previously approved research

11. Other categories added to this list by DHHS and published in the *Federal Register*

For **Exempt Review**, applicants are required to submit: Exempt IRB application completed via iRIS

The IRB uses the following **criteria for reviewing and granting research the exempt category** (as stated in 45CFR46.101(b) and 21 CFR 56.104):

Such a determination may include:

- (A) The research holds out no more than minimal risk to subjects.
- (B) Selection of subjects is equitable.
- (C) If there is recording of identifiable information, there are adequate provisions to maintain the confidentiality of the data.
- (D) If there are interactions with subjects, there will be a consent process that will disclose such information as: the activity involves research, participation is voluntary, name and contact information for the Researcher, and there are adequate provisions to maintain the privacy interest of subjects.

Research Categories

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods. This category may not be applied to FDA regulated clinical investigations.
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or

reputation. If the research includes children as participants, this category is limited to educational tests and observations of public behavior when the investigator(s) do not participate in the activities being observed. This category may not be applied to FDA regulated clinical investigations.

3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under item 2 of this section, if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter. This category may not be applied to FDA regulated clinical investigations.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. The reviewed materials must already exist at the time the research is proposed and must not be prospectively collected. This category may not be applied to FDA regulated clinical investigations.
5. Research and demonstration projects which are conducted by or subject to the approval of Department of Agency heads, and which are designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs. The program under study must deliver a public benefit (e.g., financial or medical benefits as provided under the Social Security Act) or a service (e.g., social, supportive, or nutrition services as provided under the Older Americans Act). The research or demonstration project must be conducted pursuant to specific federal statutory authority. There must be no statutory requirement that the project be reviewed by an IRB. The project must not involve significant physical invasions or intrusions upon the privacy of participants. This category may not be applied to FDA regulated clinical investigations. Before granting

this exemption, the IRB Program Coordinator or IRB Chair must communicate with OHRP to confirm that OHRP agrees that this exemption category may be applied to the proposed research.

6. Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

None of the exempt categories may be applied to research that involves prisoners as participants.

Research that meets the criteria for exemption may be referred for further review or disqualified from exempt status if the IRB Chair determines at the time of initial review that the research does not uphold Trinity Health Of New England ethical standards and/or there are concerns or issues with the protocol not related to the regulatory requirements. Such protocols will be reviewed by expedited or full board review, as determined by the IRB Chair. If there is a question about the potential for harm of participants in research exempt from federal regulations, that research will not be granted exempt status, and will be reviewed, approved and monitored by the IRB in a manner appropriate to ensure the safety of the participants.

The IRB Program Coordinator, IRB Chair, or the convened IRB may make exemption determinations. Exemption determinations are not to be made by Researchers or others who might have a conflict of interest regarding the studies. If the IRB Program Coordinator or IRB Chair makes an exemption determination, the category or categories of research allowing the exemption will be recorded in the correspondence to the investigator, and in the minutes of the next fully convened IRB meeting. If the IRB makes the exemption determination, the category or categories of exemption will be recorded in the minutes.

Protocols granted exempt status are exempt from further IRB review. However, investigators should consult the IRB whenever questions arise about whether planned changes to an exempt study might make that study nonexempt human subjects research. The IRB Chair or

designated IRB member will evaluate the planned changes and determine if the study continues to meet the criteria for exemption. Examples of planned changes that may make the study nonexempt human subjects research include but are not limited to: 1) more than minimal risk and 2) collection of identifying materials or data.

The Review

The Chairman of the IRB reviews protocols qualifying for expedited and exempt approval. If the Chairman is unavailable to review a protocol qualifying for expedited and exempt approval, a qualified member of the IRB with expertise in the area of the study will be designated by the Chairman of the IRB as a primary reviewer. Studies involving vulnerable populations, such as children, that are eligible for expedited or exempt approval will be reviewed by the Chairman of the IRB. If there is a question whether one of these protocols poses a greater than minimal risk, the study will be reviewed by a consultant with expertise in that area. If there is a question whether additional state or local laws are applicable to the protocol, the IRB Chairman or qualified member of the IRB may ask Legal Services for assistance in interpreting and applying appropriate laws. Exempt protocols and protocols approved by expedited review are presented to the members of the IRB at the following convened meeting. The approval letter to the investigator and minutes of the meeting indicate the category of the regulation under which expedited or exempt approval was granted. Research evaluated by expedited review procedures may be disapproved only following review by the full committee at a convened meeting. Protocols granted exempt status are exempt from further IRB review.

Approval of a New Study

When the IRB reviews research that is not eligible for expedited or exempt approval and involves subjects likely to be vulnerable to coercion or undue influence, the IRB Chair evaluates each protocol and ensures that at least one IRB member knowledgeable about or experienced in working with subjects will be present at the meeting.

Approval of protocols is granted following exempt, expedited, or full board review and is communicated in writing to the investigator. The letter may include conditions of the approval and the responsibilities of the investigator

When approval of a new protocol is granted by full board review pending specific revisions requiring simple concurrence by the investigator, a letter is sent to the investigator within five days of the IRB decision, listing the additional requirements needed for approval. A response from the investigator is required within 60 days. Following this response, the IRB Chair or a designated member may approve the protocol. If no response is received within 60 days, the protocol is inactivated and the investigator is notified of this action.

In instances where the IRB determines that sufficient information has not been provided to adequately judge the safety of a study, the protocol is disapproved. In instances where there is not sufficient expertise among IRB members to make a determination of a protocol, an outside expert opinion may be requested. This can be decided by the IRB Chairman at the time of initial review, or by the members of the IRB at a convened meeting. The choice of an outside consultant is decided by the IRB Chairman, or as recommended by an IRB member. In such cases, voting will be deferred pending the consultant's review. The IRB can request further supporting documentation from the Investigator, and will review that material, along with the consultant's critique, at a subsequent convened meeting. Investigators are informed in writing of the decision. If the IRB votes for disapproval of a study, the investigator can appeal by responding in writing and presenting the reason for their appeal to the full board at a regularly convened meeting. Institutional officials cannot overturn this decision of the IRB.

Approval Term

Research protocols are most often approved for a period of one year. The expiration date is the last date that the protocol is approved. The calculation of the expiration date is one year minus a day from the date of the initial approval. The IRB may also approve a protocol for a period less than one year. For protocols requiring full board review, the duration of the approval period is determined by members of the IRB at a convened meeting. More frequent review may be required in cases considered to have increased risk to the research subjects. If a study is determined to be potentially risky to participants, it is audited at intervals determined by the members of the IRB as a contingency of the approval.

The criteria which the IRB uses to determine which projects require review more often than annually are:

1. randomly selected projects
2. complex projects involving unusual levels or types of risks to subjects
3. projects conducted by investigators who previously have failed to comply with the requirements of the OHRP regulations or the requirements or determinations of the IRB
4. projects where concern about possible material changes occurring without IRB approval have been raised based upon information provided in continuing review reports or from other sources.

THE CONSENT PROCESS

Consent and Consent Forms

Informed consent is a process of information exchange that may include, in addition to reading and signing the informed consent documents, subject recruitment materials, verbal instructions, question/answer sessions and measures of subject understanding. The IRB requests that the principal investigator provide on the initial application a complete list of individuals who will be authorized to obtain consent, assent, or authorization from subjects. Individuals must be listed as an investigator or study coordinator on the research application and must be knowledgeable of the research protocol and able to respond to questions from subjects. The IRB will consider on a case by case basis each individual and determine whether their level of training and experience are appropriate for conducting the consent process for the research study. In some cases the IRB may require that the individual receive additional training in conducting the consent process. The principal investigator is ultimately responsible for ensuring that the informed consent process is conducted appropriately and the consent is obtained from each research subject before that subject participates in the study. The individual conducting the consent process shall give the subject adequate opportunity to review the consent and ask any questions regarding the research procedures.

A written document which includes the elements of an informed consent must be provided to the IRB for review and approval. Recommended consent form templates are provided with the application form (Appendix 4). Consent forms are reviewed and approved by members of the IRB to ensure compliance with 45 CFR 46.116 and 21 CFR 50.25. The IRB places an approval stamp with effective and expiration dates on each page of the original consent form document and stipulates that copies of the approved original document be used in obtaining consent. It is the policy of the IRB that potential subjects are contacted initially by a health care provider involved in their care to assess their willingness to participate in the study. Patients willing to participate are referred to the principal investigator or a study coordinator, and either one will explain the protocol in detail to the subject and obtain a signed consent form. Individuals without full knowledge of the protocol and not listed as participants in the application

form cannot consent subjects entering the study. The principal investigator is ultimately responsible to ensure that the subject is fully cognizant of the risks and benefits of the study.

In some instances, the patient's primary care physician may also be the Principal Investigator or a co-investigator conducting the study. This must be verbally disclosed to the patient during the consent process and included in the consent form. The purpose of this disclosure is to ensure that a potential subject is not coerced or pressured into participating, especially in cases where a study may involve subjects who are vulnerable to undue influence. In addition, the investigators must disclose to the subject any benefits which may be realized for conducting and recruiting subjects into a study. Investigators and study coordinators are encouraged to document in the subject's record the procedure followed to obtain consent. A subject is considered enrolled in a research study once the subject has agreed to participate and signed the Informed Consent document, whether or not interventions have been initiated.

Unless waived by the IRB, informed consent shall be:

1. Documented by the use of a written consent form approved by the IRB.
2. Signed by the participant or the participant's legally authorized representative, when applicable (for the definition of a legally authorized representative, please see information on page 67)
3. Dated by the participant or the participant's legally authorized representative, when applicable
4. A copy given to the individual signing the form

The use of telephone consenting may be appropriate for studies that involve no more than minimal risk to subjects and do not employ the use of an interventional test article or device. Please refer to the section "Waiver of Documentation of Informed Consent" for more information regarding terms and use of telephone consenting procedures.

Written consent documents must be in language understandable to the subject. When the study subject population includes non-English speaking individuals, the consent interviews are to be conducted in the language understood by the subject, using a translator if necessary, and a translated consent form is prepared. For further information regarding non-English speaking/reading populations, please refer to page 45.

When the study subject population includes illiterate persons who understand English, the form may be read to the subject or subject's legally authorized representative (when applicable) and the subject may "make their mark" on the consent. When this method is used, there shall be a witness to the oral presentation. A Short form may be used for blind or illiterate persons. For further information regarding the use of the short form for blind or illiterate persons for English and non-English speaking subjects, please refer to pages 44-45.

It is the policy of the IRB not to allow any form of interventional research in subjects unable to consent themselves unless it meets requirements stipulated under conditions of medical emergencies. Unconscious patients or those unable to consent due to the influence of drugs or intoxicants, mental illness, or other temporary impairment of reasoning capability, may be enrolled in research that is non-interventional and involves no more than minimal risk to the subjects. In such cases, the investigator may obtain permission to enroll the subject from a legally authorized representative. Subsequent to regaining their mental capabilities, enrolled subjects will be consented for the research to continue. For further information regarding cognitively impaired individuals and legally authorized representatives, please refer to pages 68-69.

It is within the authority of the IRB to observe, or have a third party observe, the consent process for purposes of an audit, or when the IRB determines at the time of initial or continuing review that there is concern regarding the consent process of a protocol. The IRB may consider observing the consent process as a method to protect subjects when study inclusion criteria may hinder the capacity of an individual to provide informed consent, as it is a policy of the IRB not to allow any form of interventional research in subjects unable to consent themselves. The IRB may also consider observing the consent process to ensure protection of subjects as a result of a complaint from a previously enrolled subject. The IRB requires that all consent documents list the name(s) and phone numbers of the investigator(s), co-investigator(s), or study coordinator(s) to contact if the subject should experience problems, adverse or unanticipated events or research-related injuries, and to address any questions or concerns that study participants have. The address and phone number of the IRB is also included should subjects have questions or concerns regarding their rights as a research participant.

Instructions for the completion of an acceptable consent form are included in the IRB application form. The Consent Form Checklist on pages 16-18 of this policy includes the required elements of an acceptable consent form.

Consent Form, Individual Authorization Form and Waivers

The Consent Form is the subject's consent to participate in research. The Health Insurance Portability and Accountability Act (HIPAA) Authorization Form is the subject's permission to use and disclose their Protected Health Information (PHI). The IRB may approve a consent procedure that does not include, or which alters, some or all of the elements of informed consent set forth in the "Consent and Consent Forms" section of these policies. Please refer to the section on Consent for criteria for approval of a waiver of consent.

It is required that a HIPAA Authorization be obtained from research subjects, unless a waiver of authorization is requested and granted. The Informed Consent template currently available on the IRB website has a HIPAA Authorization Form incorporated into the "Confidentiality" section. It is acceptable to use this combined Consent/Authorization form, or a separate HIPAA Authorization form may be used in addition to an approved Consent Form.

Specific criteria must be met for approval of a research project which involves accessing or using an individual's PHI without the express authorization of the individual. Refer to the section entitled "HIPAA Compliance" for the criteria for approval of a Waiver of Individual Authorization.

Waiver of Informed Consent

a) **Waiver or Alteration of the Consent Process/ Waiver of Parental Permission**

The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirement to obtain informed consent, provided the IRB finds and documents that:

- The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

- Public benefit or service programs;
 - 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;
- The research could not practicably be carried out without the waiver or alteration.
 - The research involves no more than minimal risk to the participants;
 - The waiver or alteration will not adversely affect the rights and welfare of the participants;
 - Whenever appropriate, the participants will be provided with additional pertinent information after participation.
 - The research is not subject to FDA regulations.

*existing language applies to waiver of parental permission as well

Where DHHS guidance requires specific findings on the part of the IRB the IRB will document such findings in the minutes of the IRB meeting, including protocol-specific information justifying each IRB finding.

b) Waiver of Documentation of Informed Consent

The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all participants if it finds either:

That all of the following are true:

- The only record linking the participant and the research would be the consent document.
- The principal risk would be potential harm resulting from a breach of confidentiality.
- Each participant will be asked whether the participant wants documentation linking the participant with the research, and the participant's wishes will govern.

- The research is not subject to FDA regulations.

That all of the following are true:

- The research presents no more than minimal risk of harm to participants.
- The research involves no procedures for which written consent is normally required outside of the research context.

In cases where the documentation requirement for informed consent is waived, the IRB may require the investigator to provide participants with a written statement regarding the research. The written statement must be submitted to the IRB for review and approval prior to its use in the research. The IRB will consider each case and determine whether to have the investigator provide the subject with the written statement. Where DHHS guidance requires specific findings on the part of the IRB, such as approving a procedure which waives the requirement for obtaining a signed consent form, the IRB will document such findings in the minutes of the IRB meeting, including protocol-specific information justifying each IRB finding.

In cases where the use of a telephone informed consent process will replace documentation of written informed consent, the investigator must submit to the IRB for review and approval a text script which will be read to each subject. The text script must include all the elements of consent and a copy must be provided to the subject following their verbal assent to participate in the study.

c) Exception from Informed Consent in Planned Emergency Research

Planned emergency research allows research on life-threatening conditions for which available treatments are unproven or unsatisfactory, and when it is not possible to obtain informed consent. Both the FDA and OHRP permit a waiver of the general requirements for informed consent for research involving greater than minimal risks to subjects when specific conditions are met (21 CFR 50.24). Currently, this Institution does not participate in planned emergency research.

Obtaining Consent for HIV Testing in Human Research Participants

If research includes HIV testing, Chapter 368x of the Connecticut General Statutes requires adults and parents of children to provide written informed consent for HIV testing using

the hospital HIV consent form. At the time of communicating test results to the patient, the attending physician should inform the patient of the possible need for counseling and medical care. Please refer to the hospital's "Consents Policy", Appendix 13, also available on the intranet.

Obtaining Permission of the Parent(s) / Assent of the Child

For research involving children as subjects, the IRB must determine that adequate provisions are made for soliciting the assent of the children, when the IRB determines the children are capable of providing assent. In determining whether children are capable of assenting, the IRB takes 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 accordance with the requirements for waiver of consent contained in 45 CFR 46.116 of Subpart A. The IRB will document assent determinations and requirements in the meeting minutes and study approval letter.

The IRB will also determine 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 will determine if: 1) the permissions of both parents are required unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent had legal responsibility for the care and custody of the child, or 2) the permission of one parent is sufficient even if the other parent is alive, known, competent, reasonably available, and shared legal responsibility for the care and custody of the child. The IRB may find that the permission of one parent is sufficient for research to be conducted under §46.404 (research not involving greater than minimal risk) or §46.405 (research involving greater than minimal risk but presenting the

prospect of direct benefit to the individual subjects). Where research is covered by §46.406 (research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition) or §46.407 (research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children), 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.

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 accordance with the requirements for waiver of consent contained in 45 CFR 46.116 of Subpart A 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.

When research studies involving children are reviewed and approved by the IRB, determinations as required by the regulations, or protocol-specific findings justifying the IRB's determinations, are documented by citation in the approval letter to the Investigator and in the minutes of the IRB.

SHORT FORM WRITTEN CONSENT DOCUMENT

The use of the short form is allowed under certain circumstances in which a potential research subject may be blind or illiterate.

Use of a Short Form Written Consent Document for English Speaking Subjects

The Institutional Review Board allows oral presentation of informed consent information in conjunction with a short form written consent documents (stating that the elements of informed consent required by Sec. 46.116 have been presented orally) and a written summary of what is presented orally to the subject. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject. Only the short form itself is to be signed/dated by the subject. However, the witness shall sign/date both the short form and a copy of the summary, and the person actually obtaining consent shall sign/date a copy of the summary. A copy of the summary shall be given to the subject, in addition to a copy of the short form.

Use of a Short Form Written Consent Document for Non-English Speaking Subjects

When this procedure is used with subjects who do not speak English, the oral presentation and the short form written documents should be in a language understandable to the subject. The IRB-approved English language informed consent document may serve as the summary. It is strongly recommended that the full English consent be translated into the participant's language. The translator/interpreter should be fluent in both English and the language of the subject. There must be a witness during the entire consenting procedures. Adequate time should be afforded to the subject, to make an informed decision regarding participation in the research.

At the time of consent, the short form document must be signed and dated by the subject and the witness. The summary must be signed/dated by the person obtaining consent (as authorized under protocol) and the witness. The translator/interpreter may serve as the witness. A copy of the summary shall be given to the subject, in addition to a copy of the short form.

If a member of the study staff speaks the subject's language, the staff member can act as the translator/interpreter and person obtaining consent, but should not also act as a witness.

Expedited review of all foreign language versions are acceptable if the protocol, the full English language informed consent document, and the English version of the short form document have already been approved by the convened IRB.

It is the responsibility of the IRB to determine which of the procedures at 46.117(b) is appropriate for documenting informed consent in protocols that it reviews.

NON-ENGLISH SPEAKING/READING POPULATIONS

When some or all of the participants of a research protocol are likely to be non-English speaking/reading populations, the recruitment materials, consent documents, and other study documents (i.e. questionnaires) must be translated into the language understood by the targeted group (45CFR46.116-117 and 21CFR50.20).

When non-English speaking/reading individuals are to be consented, an interpreter must be present to facilitate oral communication in more than one language.

All documents translated from English to another language must receive IRB review and approval before use, to assure that the rights and welfare of research participants are adequately protected and the accuracy of the translation. The IRB does not provide translation or interpretation services. Please contact Center for Health Equity for more information on translation and language services.

The IRB recommends that document be translated in one of two ways:

- (a) Single Back Translation: The translated document is translated back into English. The translator providing the back translation into English must be different from the person who provided the original translation. Each person providing translation service must complete and sign the Translation Certification Form (Appendix 4)
- (b) Double Translation: Two individuals independently translate the same document from English into another language. An arbitrator reviews both translated documents to determine any differences between the two translated documents. Changes to documents will be made, if applicable. Both Translators must complete and sign the Translation Certification Form (Appendix 4)
 - a) The IRB encourages the use of a certified translator. Written documentation of qualification of each translator must be submitted if they are not certified. The IRB may invite a consultant to review the translated materials to determine cultural appropriateness.

MEETINGS OF THE IRB

Meetings and Quorum

The IRB convenes monthly in a Conference Room at 260 Ashley Street, 3rd Floor, at SFHMC, Hartford, Connecticut. Emergency meetings are convened when requested by a physician to treat urgent medical situations requiring the use of experimental drugs or devices. In this situation, the IRB meets within five working days of notification and, in most instances, within 24 to 48 hours. The IRB does not provide expedited review for emergency medical care or expanded access use. Scheduled and emergency meetings require the presence of a quorum (51% or greater of membership), including one unaffiliated non-scientific member. The unaffiliated non-scientific member will represent the general perspective of participants. Quorum is established by the IRB Chair and is documented in the IRB minutes for each monthly meeting. If quorum is lost during a meeting, the IRB cannot take votes until the quorum is restored. If required members (e.g. non-scientific) leave the room and if quorum is lost votes cannot be taken until the quorum is restored, even if half of the members are still present. To the extent allowable by applicable laws and regulations, meetings will be considered closed. At the discretion of the Chair, outside observers or experts will be allowed to attend IRB meetings.

The IRB Chair runs the meetings and is responsible for calling a vote. The IRB Chair votes on every item that is presented at the meeting. However, in the case that the IRB Chair has a conflict with a protocol, they step out and the Vice-Chair will assume responsibility for the vote. This is then noted in the minutes. The Vice-Chair also covers for the Chair if the Chair cannot make a meeting. The IRB Chair arrives at the meeting prior to the members and is available for questions before, during and after the meeting. The Vice-Chair is readily available when their schedule permits. The Vice-Chair signs off on anything the Chair is involved on.

Review Process

All submitted materials are emailed to all members of the IRB with a copy of the meeting agenda at least one week prior to a scheduled meeting. The Chairman of the IRB reviews or assigns a primary reviewer to assess each protocol to ensure appropriate and complete review of

submissions. A summary of findings is presented by the IRB Chair or primary reviewer to the full board at fully convened meetings.

For the review of new protocols, IRB members can access electronic copies of all submitted materials, which includes the protocol application, consent form, investigator's brochure, full protocol (proposal or grant) (if applicable), and questionnaires and advertisements (if applicable). Primary reviewers are assigned and required to complete a review criteria checklist (Appendix 6) which will be submitted to the IRB following the review and kept on file with the initial protocol application in iRIS. For protocols involving the participation of pregnant women, fetuses, neonates, children, or other vulnerable population, the primary reviewer must also complete a vulnerable population review criteria checklist (Appendix 6). Members may also request a checklist prior to a convened meeting to be used as a review reference or if they wish to complete a checklist for a particular research proposal or study under review.

For conducting continuing review, IRB members access all materials in iRIS which includes reapproval request forms, abstract/summary forms, and current consent forms (when applicable). Amendments made to the protocol that were approved by the IRB in the past year are summarized on the abstract/summary form, and the full protocol file is available to the IRB members at the time of the convened meeting. A primary reviewer conducting continuing review receives all submitted materials, as stated above, including the review criteria checklist. For protocols involving the participation of pregnant women, fetuses, neonates, children, or other vulnerable population, the primary reviewer must also complete a vulnerable population review criteria checklist (Appendix 6). Completed checklists will be kept on file with the application submitted for continuing review.

For protocol amendments, IRB members can access the amendment form and supporting documentation of the changes and consent forms (when applicable) via iRIS. Primary reviewers of modifications to previously approved research receive a copy of all submitted materials, which includes the revised protocol and investigator's brochure, amendment form with supporting documentation of the changes, and consent form (when applicable). The IRB will consider the review criteria checklist during amendment review and consider the vulnerable population

review criteria checklist for protocols involving the participation of pregnant women, fetuses, neonates, children, or other vulnerable population (Appendix 6).

IRB members also receive a training article, copies of correspondence, copies of audits conducted in the past month, and follow-up information on old business (if applicable).

At scheduled and emergency meetings, members of the IRB review applications and consent forms. All protocols are reviewed by the Chairman of the IRB or a qualified member designated by the Chairman of the IRB. Investigators are encouraged to be present and answer questions at the convened IRB meeting. Investigators are not present during protocol discussion and voting. Approval or disapproval requires majority vote.

Criteria used for the approval of research include:

1. Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably 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 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. Informed consent will be sought from each prospective subject, unless a waiver is appropriate or the research falls under emergency research provisions or life threatening situations.
3. Selection of subjects is equitable. In making this assessment the IRB should take into account 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, mentally disabled persons, or economically or educationally disadvantaged persons.
4. 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 §46.116, unless a waiver is appropriate or the research falls under emergency research provisions or life threatening situations.
 5. Informed consent will be appropriately documented in accordance with, and to the extent required by §46.117.
 6. Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. For all interventional studies, the IRB requires designation of a study coordinator, and a Data Safety Monitoring Board or Safety Officer.
 7. Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
 8. When some or all of the subjects, such as children, 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

IRB Member Conflicts of Interest

The Conflict of Interest in Research Policy applies to IRB members, as well as any reviewer of a research protocol, and any outside consultants. It is contingent upon IRB members to disclose any conflict of interest, as defined in the Conflict of Interest in Research Policy. When an IRB member is an investigator on a research study being considered, that member may not participate in the initial or continuing reviews of any study, in review of unanticipated problems involving risks to participants or others, or in the review of non-compliance with regulations or laws of the requirements of the IRB (either in full board meetings or in the expedited review process) associated with a study, except to provide information requested by the IRB. All members will disclose conflicts of interest that are not apparent on a disclosure form (Appendix 6). At the start of each convened meeting, the IRB Program Coordinator or IRB

Chair will verbally ask members if the disclosure status has changed since the previous convened meeting. Members with a disclosure status change will fill out a new disclosure form noting disclosure changes. Members are not present during IRB deliberations, voting, and are not counted towards quorum on protocols in which they have a conflict of interest. Outside consultants will be notified in the written correspondence requesting their opinion that any potential conflict of interest as defined in the Conflict of Interest in Research Policy must be divulged prior to their acceptance of the invitation. A copy of the policy will be sent with the correspondence. If a significant conflict of interest is identified, an alternate consultant will be obtained.

If the Chair has a conflict of interest, the Vice Chair will assume the responsibilities of signing off on submissions. If both the Chair and the Vice Chair have a conflict of interest, the Program Coordinator will assign a primary reviewer to assume responsibilities of signing off on submissions.

Minutes of IRB Meetings

The minutes of the IRB meetings are recorded by the IRB Program Coordinator and are reviewed and signed by the Chairman of the IRB. Minutes of the meetings are sent electronically in PDF format to all members of the IRB for review and voting at the following meeting. The minutes are filed in the office of the IRB, and will provide the following information:

1. Date and time the meeting was called to order
2. Members present and absent
3. Identification of members present via telephone, and a statement justifying the members' ability to vote (a statement such as the member has received and reviewed the agenda)
4. Identification of non-scientific members
5. When an alternate member replaces a primary member.
6. Guest Observers, if applicable
7. When members arrive after the meeting was called to order, or when members leave the meeting, prior to its completion, if applicable
8. Review of minutes of previous meeting

9. The training topic
10. Information regarding audits that were performed, if applicable
11. For non-compliance, a definitive statement describing the determination regarding whether reports were serious or continuing non-compliance
12. Listing of protocols and amendments approved by expedited review since the previous meeting, the minutes will provide the appropriate subparts of the Code of Federal Regulations under which the protocol was approved
13. Protocol-specific findings justifying determinations for:
 - a. waiver or alteration of the consent process
 - b. research involving participants with diminished capacity
14. Information regarding closures of protocols, if applicable
15. For termination of protocols by the IRB, the minutes will provide the details of the discussion, voting, and conflicts of interest.
16. New protocols, amendments and progress reports requiring full IRB review. In the review of research involving children, the additional protections of 45 CFR 46 Subpart D and 21 CFR 50 and 56 Subpart D will be followed. In the review of research involving pregnant women, human fetuses, and neonates, the additional protections of 45 CFR 46 Subpart B will be followed. The determinations of the IRB required by these regulations along with protocol specific information the IRB used to justify the determinations will be documented the minutes and the approval letter.
17. For protocols, renewals and amendments requiring full review, the minutes will provide
 - a) Summary of the discussions and controversial issues
 - b) Documentation of reasons for disapproval and tabling of protocols
 - c.) Documentation of consideration of appropriate subparts of the Code of Federal Regulations
 - d) Documentation of approval of protocols, consent forms, and advertising material
 - e) Documentation of required revisions
 - f) Voting, including number of votes in favor, against, and abstentions (including name(s) of abstaining members)

- g) Conflicts of interest, including the name(s) of the member(s) – (Members with conflicts of interest do not count towards quorum and must excuse themselves during discussion and voting. The term “total” in the minutes reflects quorum, therefore the “total” does not include the recused vote. The “total” includes in favor, against, and abstained votes.)
 - h) For initial and continuing review, the approval period.
18. Follow-up actions or votes on protocols that IRB members have expressed serious concerns about.
 19. Documentation of the basis for requiring changes to protocols.
 20. For protocols involving the use of a test device or article, the minutes will provide the rationale for significant risk/non-significant risk device determinations.
 21. For protocols submitted with a DHHS approved sample consent document, the meeting minutes will provide the justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the document.

To ensure that the above information is consistently documented, the meeting minutes will be peer-reviewed quarterly and assessed for completeness. The reviewer will be provided with a list of required elements and the meeting minutes for the appropriate quarter. The reviewer will provide recommendations to the IRB Program Coordinator and/or the IRB Chair regarding elements that are missing or lacking information. Where applicable, the IRB Program Coordinator will ensure that recommendations and deficiencies are addressed in the proceeding month’s meeting minutes.

To the extent allowable by applicable laws and regulations, all IRB files and documentation will be considered privileged information, and every effort will be made to maintain confidentiality and non-disclosure of this information.

Documentation and Retention of IRB Records

All correspondence and documents received by the IRB office are date stamped upon receipt. All original copies of consent forms, other forms requiring IRB approval, and letters with the approval signature of the IRB Chair are sent to the Investigator. Copies are retained in

the IRB's protocol file. Original, signed copies of IRB required forms, such as the Amendment Form and the Protocol Reapproval/Closure Form, are retained by the IRB and copies are sent to the Investigator. The effective date and the expiration date, if applicable, are clearly noted on all documents.

All IRB records are retained for at least 3 years after the completion of the research conducted at a Trinity Health Of New England site. IRB records for protocols that have been 1) withdrawn prior to the release of approved materials or 2) cancelled without subject enrollment are retained for at least 3 years after withdrawal/cancellation. These records are maintained and stored in locked file cabinets in the IRB office, currently in the Education and Research Building, 3rd floor, on the campus of Saint Francis Hospital and Medical Center (260 Ashley Street).

Protocols that are approved through the expedited or full board review mechanism are assigned and given an IRB number and a file is opened. Each study contains information relating to:

1. Initial application and all associated documents and materials that may include the protocol, informed consent form, investigator brochure(s), questionnaires, advertisements, grant information, sponsor/investigator contracts/agreements, IND or IDE information, and pertinent correspondence. Copies of approval letters from the IRB, collaborating site IRBs, and Nursing Committee are kept with the initial application.
2. Protocol and consent form revisions, amendments, continuing review and progress reports, and continuing investigator-sponsor-IRB correspondence. Folder may also contain information regarding sponsor specific or multi-center meetings.
3. Safety reports and adverse event reports.

IRB records for initial and continuing review of research by the expedited procedure include:

- The justification for using the expedited procedure.
- Actions taken by the reviewer.
- Any findings required by laws, regulations, codes, and guidance to be documented.

The IRB files information in order of receipt in the IRB Office from newest to oldest to allow a reconstruction of a complete history of all IRB actions related to the review and approval of the protocol, the IRB records include copies of:

- Scientific evaluations, when provided by an entity other than the IRB.
- Unanticipated problems involving risks to participants or others.
- Documentation of non-compliance.
- Significant new findings.

Protocols meeting criteria for exempt review and approval are kept together in a locked file cabinet and are filed by year in chronological order of approval. The following information is filed with each exempt protocol: initial application and supporting documentation, any investigator-IRB correspondence, and determination letter with review category.

Copies of meeting agendas and minutes are kept in a binder in the IRB Office by year and are uploaded to iRIS. There is a separate binder to track yearly new protocol review and approval. The information recorded in this binder includes the name of the protocol, assigned protocol number, principal investigator, date of submission, date of review, and date of original approval.

All IRB records are accessible for inspection and copying by authorized representatives of federal agencies or departments at reasonable time and in a reasonable manner.

Retention of Investigator Records

The HHS protection of human subjects regulations require institutions to retain records of IRB activities and certain other records frequently held by investigators for at least 3 years after completion of the research (45 CFR 46.115(b)). In addition, other regulations may apply and require retention of these records for a longer period of time. Documentation of the informed consent of the subjects must be retained for at least 3 years after completion of the research, unless the IRB waived the requirement for informed consent or the requirement for documentation of informed consent. Such records may be preserved in hardcopy, electronic or other medical form and must be accessible for inspection and copying by authorized representative of HHS at reasonable times and in a reasonable manner. If investigators who have been designated to retain records on behalf of the institution leave Saint Francis Hospital and Medical Center, the investigators and the IRB should identify the successor responsible for maintaining those institutional records, either at the original institution or wherever the records

are relocated, for the period of time required under HHS regulation. Other regulations or policies may apply to the retention of records, including study data.

REVIEW OF RESEARCH INVOLVING VULNERABLE POPULATIONS

When some or all of the participants of a research protocol are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards must be included in the study to protect the rights and welfare of these participants. In the review of research involving children, the additional protections of 45 CFR 46 Subpart D and 21 CFR 50 and 56 Subpart D will be followed. In the review of research involving pregnant women, human fetuses, and neonates, the additional protections of 45 CFR 46 Subpart B will be followed. The determinations of the IRB required by these regulations along with protocol specific information the IRB used to justify the determinations will be documented in the minutes and the approval letter. When evaluating protocols to determine whether there is a need for additional protections for participants, some of the factors that the IRB considers include the equitable selection of subjects, the inclusion/exclusion criteria, and the fair distribution of risks and benefits. If necessary, the IRB will consult with the Institution's Ethics Committee for further guidance.

Additional Protections for Research Involving Pregnant Women, Fetuses or Neonates

The IRB will abide by provisions stipulated under **45 CFR 46.201 to 46.207 (Subpart B)** and the guidelines and directives of the Catholic Church in research involving pregnant women, fetuses or neonates. For the purposes of this policy, the definition of pregnancy encompasses the period of time from the implantation until delivery. Research protocols involving pregnant women, fetuses or neonates as subjects will be reviewed by the IRB using the "IRB Member Review Checklist for Vulnerable Subjects" (Appendix 6).

45CFR46.201 - To what do these regulations apply?

(a) Except as provided in paragraph (b) of this section, this subpart applies to all research involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates conducted at Saint Francis Hospital and Medical Center, whether or not it is supported by the Department of Health and Human Services (DHHS).

(b) The exemptions at Sec. 46.101(b)(1) through (6) are applicable to this subpart.

(c) The provisions of Sec. 46.101(c) through (i) are applicable to this subpart. Reference to State or local laws in this subpart and in Sec. 46.101(f) is intended to include the laws of federally recognized American Indian and Alaska Native Tribal Governments.

(d) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

45CFR46.202 - Definitions

The definitions in Sec. 46.102 shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) Dead fetus means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.

(b) Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means.

(c) Fetus means the product of conception from implantation until delivery.

(d) Neonate means a newborn.

(e) Nonviable neonate means a neonate after delivery that, although living, is not viable.

(f) Pregnancy encompasses the period of time from conception 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.

(g) Secretary means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(h) Viable, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the Federal Register guidelines to assist in determining whether a neonate is viable for purposes of this subpart. If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements of subparts A and D of this part.

45CFR46.203 - Duties of IRBs in connection with research involving pregnant women, fetuses, and neonates

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart and the other subparts of this part.

45CFR46.204 - Research Involving Pregnant Women or Fetuses

Pregnant women may be involved in research if all of the following conditions are met:

- (a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
- (b) The risk to the 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;
- (c) Any risk is the least possible for achieving the objectives of the research;
- (d) 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 subpart A of this part;
- (e) 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 subpart A of this part, 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.
- (f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

- (g) For children as defined in Sec. 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;
- (h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
- (i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
- (j) Individuals engaged in the research will have no part in determining the viability of a neonate
- (k) All activities will be in accordance with Catholic Church directives.

45CFR46.205 - Research Involving Neonates

(a) Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

- (1) Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
- (2) Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
- (3) Individuals engaged in the research will have no part in determining the viability of a neonate.
- (4) The requirements of paragraph (b) or (c) of this section (see below) have been met as applicable.
- (5) The research is in accordance with Catholic Church directives.

(b) Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research unless the following additional conditions have been met:

- (1) The IRB determines that:
 - (i) 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 that objective, or
 - (ii) 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

(2) 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 subpart A (45CFR46.101 to 46.124) of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

(c) Nonviable neonates. After delivery nonviable neonate may not be involved in research covered by this subpart unless all of 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; and

(5) The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of Sec. 46.116(c) and (d) do not apply. However, 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. 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.

(d) 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 (45CFR46.101 to 46.124) and D (45CFR46.401 to 46.409) of this part.

45CFR46.206 - Research Involving, After Delivery, The Placenta, The Dead Fetus or Fetal Material

(a) 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, and in accordance with Catholic Church directives.

(b) If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of this part are applicable.

45CFR46.207 - 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

Research that the IRB does not believe meets the requirements of Sec. 46.204 or Sec. 46.205 will be considered only if:

(a) The IRB 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 pregnant women, fetuses or neonates; and

(b) The Secretary of DHHS, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the Federal Register, has determined either:

(1) That the research in fact satisfies the conditions of Sec. 46.204, as applicable; or

(2) The following:

(i) 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;

(ii) The research will be conducted in accord with sound ethical principles;

(iii) Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part.

(c) The research is in accordance with Catholic Church directives.

Additional Protections for Children Involved as Subjects in Research

The IRB will abide by provisions stipulated under **45CFR46.401 to 46.409 (Subpart D)** for clinical investigations involving children. Research protocols involving children as subjects will be reviewed by the IRB using the “IRB Member Review Checklist for Vulnerable Subjects” (Appendix 6).

45CFR46.401 - To what do these regulations apply?

(a) This subpart applies to all research involving children as subjects conducted at Saint Francis Hospital and Medical Center, whether or not it is supported by the Department of Health and Human Services.

(1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (e) of §46.101 of Subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions at §46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at §46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at §46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

(c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of §46.101 of Subpart A are applicable to this subpart.

45CFR46.402 - Definitions

The definitions in §46.102 of Subpart A shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) "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. In the state of Connecticut, a child is a person under the age of 18. Under Connecticut law, any minor who has reached his or her sixteenth (16) birthday and is residing within the state may qualify, after a Probate Court petition, as a legally emancipated minor. The court order of emancipation gives the minor the legal status of an adult. A minor may also be considered emancipated under common law in the following circumstances:

1. The minor has been validly married at any time.
2. The minor is on active duty with the Armed Forces of the United States.
3. The minor lives willingly separate and apart from his or her parents or guardian.
4. The minor manages his or her own financial affairs, regardless of the source of any lawful income.

Please see attached Institutional "Consents Policy" (Appendix 13). Any minor who has given birth to a child may give consent for the child.

(b) "Assent" means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

(c) "Permission" means the agreement of parent(s) or guardian to the participation of their child or ward in research.

(d) "Parent" means a child's biological or adoptive parent.

(e) "Guardian" means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care. In the state of Connecticut, a court appointed guardian or court appointed conservator may act as a patient representative for a child.

45CFR46.403 - IRB duties

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

45CFR46.404 - Research not involving greater than minimal risk

DHHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.

45CFR46.405 - Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

DHHS will conduct or fund research in which the IRB finds that 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, only if the IRB finds that:

- (a) the risk is justified by the anticipated benefit to the subjects;
- (b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
- (c) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

45CFR46.406 - Research Involving Greater Than Minimal Risk and No Prospect of Direct Benefit to Individual Subjects, but Likely to Yield Generalizable Knowledge About the Subjects' Disorder or Condition

The IRB will find and document that:

- (a) The risk represents a minor increase over minimal risk;
- (b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations;
- (c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
- (d) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

45CFR46.407 - Research Not Otherwise Approvable Which Presents an Opportunity to Understand, Prevent or Alleviate a Serious Problem Affecting the Health or Welfare of Children

If the IRB does not believe a study meets the requirements of 46.404, 45.405, or 46.406, such studies will be considered only if:

- (a) the IRB 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; and
- (b) the Secretary of DHHS or the Commissioner of Food and Drugs, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

(1) that the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or (2) the following:

- (i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
- (ii) the research will be conducted in accordance with sound ethical principles;
- (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.

45CFR46.408 - Requirements For Permission By Parents or Guardians and For Assent By Children

- (a) In addition to the determinations required under other applicable sections of this subpart, 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 §46.116 of Subpart A.

- (b) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by §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.
- (c) In addition to the provisions for waiver contained in §46.116 of 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 of this part and paragraph (b) of this section, 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.
- (d) Permission by parents or guardians shall be documented in accordance with and to the extent required by §46.117 of Subpart A.
- (e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

45CFR46.409 - Wards

- (a) 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:

(1) related to their status as wards; or

(2) conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the research is approved under paragraph (a) of this section, 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 investigator(s), or the guardian organization.

Prisoners

The Trinity Health Of New England IRB does not review studies enrolling prisoners. However, an enrolled subject may become a prisoner during the course of a study. In this circumstance, the investigator must notify the IRB immediately, and all research interactions and interventions with the now-incarcerated subject will cease, unless it is in the best interest of the subject to remain in the research study, as determined by the IRB Chairperson. Following this determination, the IRB will notify the OHRP and ensure compliance with all OHRP requirements as specified in 45 CFR 46, Subpart C. The continued participation, or withdrawal, of the incarcerated subject then will be reviewed by a central IRB, which includes a prisoner representative. Research that involves prisoners is not exempt from federal guidelines.

Cognitively Impaired Subjects in Research

It is the policy of the IRB not to allow any form of interventional research in subjects unable to consent themselves unless it meets requirements stipulated under conditions of medical emergencies. Patients whose decision-making capacity may be in question, and whose current and prospective ability to understand and consent to research is uncertain, may not be enrolled as research subjects in this Institution.

Unconscious patients or those unable to consent due to the influence of drugs or intoxicants, mental illness, or other temporary impairment of reasoning capability, may be enrolled in research that is non-interventional and involves no more than minimal risk to the subjects, as determined by the IRB Chair (for protocols eligible for expedited review) or by the full IRB (for protocols reviewed by the full board) at the time of initial review and approval of a protocol. Research protocols will be reviewed by the IRB using the IRB member review criteria and review of vulnerable subject checklists (Appendix 6).

In such cases, the investigator may obtain permission to enroll the subject from a legally authorized representative. A legally authorized representative is an individual or other body authorized under applicable law who can consent on behalf of an individual and may be any of the following, in order of preference:

- a legal guardian or court appointed conservator of person; or if none,
- an individual in possession of a patient appointed health care power of attorney; or,
- the patient's next of kin.

Subsequent to regaining their mental capabilities, enrolled subjects will be consented for the research to continue.

The IRB must determine that adequate provisions are made for soliciting the assent of the cognitively impaired subject, when the IRB determines the subject is capable of providing assent. In determining whether the subject is capable of assenting, the IRB takes into account the age, psychological, and physiological state of the individual involved. This judgment may be made for all subjects to be involved in research under a particular protocol, or for each subject, as the IRB deems appropriate. 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 accordance with the requirements for waiver of consent. The IRB will document assent determinations and requirements in the meeting minutes and study approval letter.

PRIVACY AND CONFIDENTIALITY IN RESEARCH

HIPAA Compliance

Privacy is the right of persons not to share information about themselves. Confidentiality is the obligation to keep private information that has been collected from being shared with others. It is the obligation of this Institution and all Investigators, Study Coordinators and employees involved in medical research to respect the rights of human research subjects by protecting their privacy and confidentiality before, during and after their participation in research. Trinity Health Of New England conforms to the Health Insurance Portability and Accountability Act (HIPAA), and all federal, state and local laws regarding patient privacy and confidentiality.

The IRB serves as the Privacy Board and ensures compliance with HIPAA regulations as they apply to Research. Consequently, the IRB ensures the privacy of the Protected Health Information (PHI) that is created, accessed or shared in the course of Research activity. PHI is individually identifiable information transmitted or maintained in any form (electronic means, on paper, or through oral communication) that relates to the past, present or future physical or mental health or conditions that can reasonably be used to identify an individual. The use and disclosure of PHI requires review and approval by the IR B (Privacy Board). "Use" of PHI is the sharing of PHI within the institution (i.e., from nurse to doctor). "Disclosure" of PHI is the sharing of PHI outside of the institution (i.e., from principal investigator to study sponsor).

The "Notice of Privacy Practices" is a written document, provided to all patients and research subjects entering Trinity Health Of New England sites, describing the Institutional policy on how medical information is used and disclosed and how patients can access their records. Research subjects will be provided with the Notice when admitted to the hospital or directly by the Investigator. A copy of the signature page, acknowledging receipt of the Notice, will be kept in the subject's research file.

Research subjects will provide "authorization" for the use and disclosure of PHI, unless the investigator requests a waiver of authorization to the IRB.

Categories of Health Information

The HIPAA regulations categorize information in the following way:

1. Identifiable information (PHI, to which HIPAA applies)
2. De-identified information (to which HIPAA does not apply)
3. Limited Data Set (a middle option, to which limited parts of HIPAA apply)

(1) **Identifiable Information and HIPAA Authorization**

Investigators may incorporate a HIPAA authorization into the "Confidentiality" section of the Consent Form (Appendix 4), or use a separate HIPAA Authorization (Appendix 5) in addition to a Consent Form that does not incorporate HIPAA authorization language.

Waiver of Individual Authorization

For research projects that involve accessing or using PHI without the express authorization of the individual, Investigators are required to meet specific requirements and to submit a Request for Waiver of Individual Authorization for Disclosure of Protected Health Information Questionnaire (Appendix 5) with the IRB application. Requests are reviewed by the IRB Chair, and approved waivers are submitted to the Principal Investigator, the Director of Medical Records, and the Privacy Officer. Criteria for approval of a Waiver of Individual Authorization are:

1. Disclosure involves no more than minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
 - a) an adequate plan to protect patient identifiers from improper use and disclosure
 - b) an adequate plan to destroy patient identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law
 - c) adequate written assurances that protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, and restricts most disclosures of information to the minimum intended purpose
2. Research could not be conducted without the waiver

3. Research could not be conducted without access to and use of protected health information

(2) De-Identified Information

For record review studies, it may be required that the PHI being requested be de-identified prior to its release. The 18 criteria for de-identification of PHI are:

1. Names
2. All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes (initial 3 digits of zip code may be retained)
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death
4. Telephone numbers
5. Fax numbers
6. Electronic mail addresses
7. Social Security numbers
8. Medical record numbers
9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers and serial numbers, including license plate numbers
13. Device identifiers and serial numbers
14. Web Universal Resource Locators (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger and voice prints
17. Full face photographic images and any comparable images
18. Any other unique identifying number, characteristic, or code

De-identified information is not considered PHI, and is therefore exempt from HIPAA regulations. De-identified and limited data set information are used primarily for research involving the review of records.

(3) Limited Data Sets

A limited data set allows for the retention of specific types of dates, geographic information, and other unique codes or characteristics that are not expressly excluded. The investigator must submit a "Data Use Agreement" (Appendix 5) to the IRB to be permitted access and use of this level of information. A limited data set is PHI that **excludes** the following 16 direct identifiers of the individual, or of relatives, employers, or household members of the individual:

1. Names
2. Postal address information, other than town or city, state, and zip code
3. Telephone numbers
4. Fax numbers
5. Electronic mail addresses
6. Social Security numbers
7. Medical record numbers
8. Health plan beneficiary numbers
9. Account numbers
10. Certificate/license numbers
11. Vehicle identifiers and serial numbers, including license plate numbers
12. Device identifiers and serial numbers
13. Web Universal Resource Locators (URLs)
14. Internet Protocol (IP) address numbers
15. Biometric identifiers, including finger and voice prints
16. Full face photographic images and any comparable images

A limited data set allows for the **retention** of:

- Dates (e.g., date of birth, admission and discharge dates)
- Some geographic information (city, state and zip code but not street address)

- Other unique codes or characteristics that are not expressly excluded (see above)

Preparatory to Research

For activities involved in preparing for research, the IRB will obtain from the researcher a signed Data Collection for Reviews Preparatory to Research Agreement (Appendix 5) indicating that 1) the use or disclosure is sought solely to review PHI as necessary to prepare a research protocol or for similar purposes preparatory to research, 2) that no PHI will be removed from the Institution in the course of the review, and 3) that the PHI for which use or access is sought is necessary for the research purposes.

Decedent's Information

To obtain medical information from deceased patients, investigators are required to sign an agreement for Research on Decedent's Information (Appendix 5) prior to obtaining decedent information. The agreement will indicate that the use or disclosure sought is solely for research on the PHI of decedents; that at the request of the institution, documentation of the death of such individuals will be provided; and that the PHI for which use or disclosure is sought is necessary for research purposes.

Tissue Banking

When tissue samples from research subjects are provided to entities outside SFHMC for future research, the IRB requires that:

1. Secondary IRB review will be conducted prior to the release of tissue samples to other investigators for future research
2. The specific groups or agencies that may have access to the tissue samples for future research be disclosed
3. The participant specifically consents to the future use of tissue samples and is offered the opportunity to decline to this use. Whenever possible, the enrolled subject is offered a mechanism to withdraw consent for future use of the tissue sample.
4. Tissue banking is not conducted for financial gain or commercial purposes.

It is recommended, but not required, that studies with a tissue banking component where tissues are being released to entities outside of Trinity Health Of New England sites, that the agency or cooperative responsible for receiving and maintaining the tissue have a Certificate of Confidentiality. The purpose of this measure is to ensure the highest level of confidentiality in the handling of individually identifiable health information of research subjects at this institution.

Storage and Access of Research Data

All new protocols must have a plan for the secure storage of research data, including procedures to protect against or minimize potential risks and to assure privacy and confidentiality. Research data are the property of Trinity Health Of New England and may not be removed from hospital premises unless permission has specifically been granted by the Institution. If a study is sponsored by a pharmaceutical company or a cooperative research group, the investigator and this Institution have been contracted to provide research data to that entity. Therefore, the data is owned by the contracting company or agency, as stipulated in the research agreement.

The IRB reviews all new applications for proposed methods of recruitment, justification for the access, use and disclosure of PHI, potential risks to subjects, the plan to protect patient identifiers from improper use and disclosure, plan to destroy identifiers at the earliest opportunity, justification for retaining the identifiers, and the plan to protect or destroy audio or videotapes or research data at the conclusion of the research project.

Research Data Retention

The IRB follows the FDA's policy of data retention regarding the withdrawal of subjects from a clinical investigation, whether the subject elects to discontinue further interventions or the clinical investigator terminates the subject's participation in further interventions.

When a subject withdraws from a study, the data collected on the subject to the point of withdrawal remains part of the study database and may not be removed. The IRB does not allow consent documents to give the subject the option of having data removed.

An investigator may ask a subject who is withdrawing whether the subject wishes to provide continue follow-up and further data collection subsequent to their withdrawal from the

interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through noninvasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.

If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described above, the investigator must obtain the subject's consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). IRB approval of consent documents would be required (21 CFR 50.25, 56.109(b), 312.60, 312.66, 812.100).

If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, an investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

CONTINUING REVIEW

Continuing Review Requirements

There is no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. The expiration date is the last date that the protocol is approved. The calculation of the expiration date is the period of the approval minus a day from the date of the initial approval. If the investigator fails to provide continuing review information to the IRB, or the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research must stop, unless the IRB finds that it is in the best interest of individual subjects to continue participating in the research interventions or interactions. Enrollment of new subjects cannot occur after the expiration of IRB approval. When continuing review of a research protocol does not occur prior to the end of the approval period specified by the IRB, the approval expires automatically. Such expiration of IRB approval will not be reported to the OHRP.

For protocols granted a one year approval:

When the IRB grants approval for one year at the time, the IRB performs continuing review and reapproves (with or without conditions) the research within 30 days *before* the IRB approval period expires, the IRB may maintain the anniversary of the expiration date of the initial IRB approval as the expiration date of each subsequent one-year approval period. The same guidelines apply when the IRB reviews and approves research under expedited review procedures in accordance with 21 CFR 56.110.

1. If the IRB reviews and approves a protocol without any conditions at a convened meeting, continuing review will occur within 1 year of the date of the meeting;
2. When the IRB reviews a protocol at a convened meeting and approves the protocol contingent on specific minor conditions, the effective date of the initial approval is the date on which the IRB chair or his/her designee can verify fulfillment of those conditions. In such circumstances, the expiration date of the initial approval period is the date by which the *first* continuing review must occur (21 CFR 56.115 (a)).;

3. If the IRB reviews a study at a convened meeting and has serious concerns or lacks significant information that requires IRB review of the study at subsequent convened meetings, continuing review will occur within 1 year of the date of the convened meeting at which the final review occurred and approval was granted.

The same conditions apply for protocols approved for a period of less than one year, however the abbreviated approval period applies to all stated timeframes.

The IRB will use the review criteria checklist for all continuing reviews

45CFR46.111

(Appendix 6).

The IRB will follow expedited review applicability criteria and use the appropriate research categories when conducting continuing review of previously approved research. Please refer to the section entitled “The Review Process”, pages 25-35, for a complete list of the applicability criteria and research categories. The **expedited review** procedure will be used for the continuing review of previously approved research for:

1. Research previously approved by expedited review when no significant changes have occurred in the protocol
2. Research previously approved at a convened IRB meeting when:
 - a) the research is permanently closed to the enrollment of new subjects and all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects or
 - b) no subjects have been enrolled at this site and no additional risks have been identified at any site where the protocol is conducted or
 - c) the remaining activities are limited to data analysis
 - d) research is not conducted under an investigational new drug application or investigational device exemption where the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

All submitted materials are preliminarily reviewed by the IRB Program Coordinator to ensure completeness. The IRB Chair or member conducting continuing review will receive all

submitted materials including a copy of the original abstract, a copy of the most recently approved protocol, and a list of any protocol modifications previously approved by the IRB, which is provided by the IRB office and is sent with the agenda. For expedited review, investigators are required to provide the following: Protocol Progress Report/Reapproval Request Form, Abstract/Summary form (Appendix 6), a current consent form/HIPAA Authorization, if applicable, and all materials requiring reapproval, as applicable, such as questionnaires and surveys.

Full board review will be used for continuing review of other studies. All submitted materials are preliminarily reviewed by the IRB Program Coordinator to ensure completeness. All submitted materials are reviewed by IRB members when conducting continuing review, including a copy of the original abstract, and a list of any protocol modifications previously approved by the IRB, which is provided by the IRB office and is sent with the agenda. A copy of the most recently approved protocol is brought to convened meetings for review. Investigators are required to submit:

1. Protocol Progress Report/Request for Reapproval/Closure Form and any attachments included as part of the report
2. current consent form / HIPAA Authorization
3. an Abstract/Summary form which includes a recent literature search (conducted within 30 days of submitting Progress Report) and its impact on the study

Progress Reports and Abstract/Summary Forms

Investigators are required to provide a progress report and, if reapproval is desired, a formal reapproval request (see Appendix 6). The progress report is due in six weeks prior to the expiration date. Requests for renewal for sponsored pharmaceutical/device research protocols must be submitted eight weeks prior to the anniversary date with completed Financial Disclosure Forms. Investigators are required to provide a progress report whether patients were entered in the study or not. Investigators should also provide an abstract/summary form (Appendix 6). In order to provide the IRB with sufficient information to determine whether the research protocol

continues to fulfill the criteria for approval, the following information must be included on the Reapproval Request and Abstract/Summary forms:

- An abstract or summary of the protocol from the original application.
- A progress report summarizing activities and events of the past period of approval which includes:
 1. Have the inclusion/exclusion criteria changed during the last year?
 2. Have there been any subject complaints during the last year?
 3. Has the risk/benefit assessment changed over the past year?
 4. Summary of adverse events that occurred at this site during the last year.
 5. Summary of adverse events that occurred at multi-center sites during the last year.
 6. Summary of any unanticipated problems involving risk to participants or others during the last year at this site.
 7. Summary of benefits to subjects participating in this protocol.
 8. Summary of interim findings/discoveries affecting the trial since the last IRB review. Please include a copy of interim analysis report, if available.
 9. Summary of amendments and modifications since the last IRB review, and relevant reports, including results obtained from multi-center sites.
 10. A statement from the Data Safety and Monitoring Board or Officer, if available.
 11. Summary of activity of this protocol for the last year at this site.

Research Financial Disclosure Forms (see Appendix 4) will be updated at the time of renewal of protocols for all Investigators, or if there is a new reportable Significant Financial Interest obtained by an Investigator. New reportable financial disclosures will require Investigators to fully disclose the financial interest and Investigators indicating a disclosure of more than \$5000 will be referred to the Financial Conflict of Interest in Research (FCOIR) Committee for review (see Appendix 13). Funded research protocols with a management plan will be reviewed annually by the (FCOIR) Committee to determine if the management plan needs to be revised. All questions on all forms must be answered in full. Incomplete forms will be returned to investigators. Investigators are also required to notify the IRB and provide a final report at the time a protocol is closed.

Failure to provide progress reports results in expiration of the protocol. Investigators will be notified by the IRB in writing that all research activities must stop, including (but not limited to) new enrollment, screening, study visits, medical record review, data analysis, presentations and publications. The letter will also indicate that the Investigators have 30 days to submit the material or the study would be closed. In order to continue the research after the closure, Investigators will have to submit an initial application and go through the review process.

The IRB Program Coordinator will meet with Investigators following closures of protocols to ensure that research activities stopped when IRB approval expired. In instances of a closure of a protocol when an investigator leaves the Institution and does not officially close a protocol/arrange for transition to another appropriate trained investigator within the Institution, a follow up audit will be conducted when feasible. If the IRB (or chair) finds that there is an overriding safety concern or ethical issues making it in the best interest of the participant to continue in the study, the IRB may permit research activities to continue for the brief time required to complete the continuing review process. Failure to provide progress reports may also result in loss of the privilege to use IRB services in the future.

PROTOCOL AMENDMENTS

Investigators are required to request, in writing, IRB approval of protocol changes prior to their implementation by submitting a Protocol Amendment Form (Appendix 6), and when indicated, an amended consent form. Investigators are required to submit electronically in iRIS:

1. Protocol Amendment Form
2. Consent Form, if amended (one copy with changes highlighted)
3. amended document (one copy with changes highlighted) or new proposed document
4. supporting documentation (such as revised protocol and investigator's brochure – one copy with changes flagged or highlighted)

Protocol Amendments are reviewed in the same manner as initial reviews, and the determination of eligibility for expedited and full board review apply. The IRB will consider the review criteria checklist for protocol amendments (Appendix 6). A revision may not be disapproved by expedited review. The IRB Chair or primary reviewer may recommend that the revision be reviewed by the full board. Minor changes are reviewed and approved by expedited review by the Chairman of the IRB or a designated primary reviewer, and the applicable regulation justifying the approval is documented in writing on the Amendment form and in the minutes of the IRB meeting. Examples of minor changes that are eligible for expedited approval include, but are not limited to:

1. Administrative or informational changes
2. Additions or deletions of investigators or study coordinators
3. Corrections of grammatical or typographical errors
4. Changes leading to clarification of a protocol
5. Minimum changes in numbers of enrolled participants
6. Changes recommended by members of the Institutional Review Board at an adjourned meeting during which the Chair or the IRB has been designated to approve the changes by the expedited mechanism
7. Changes secondary to drug dispensation, software upgrades

8. Changes in the consent form to incorporate Health Insurance Portability and Accountability Act (HIPAA) language
9. Revisions that include changes to the protocol that may impact research participants, but that do not affect the risks to participants
10. Advertisements for recruiting study subjects

When advertisements are taped broadcasts or videos, the IRB reviews the final audio and/or video tape and requests a copy of the final transcript. If the advertisement will include a live interview or question/answer session, the IRB requests an outline of topics to be discussed prior to the broadcast and a tape or transcript of the session following the broadcast.

Significant changes in a protocol that involve increased risk to participants undergo full IRB review and voting at a convened meeting. Enrollment may continue and the currently approved protocol must be followed until notification by the IRB that the changes have been approved. Any changes that incorporate unanticipated added risks due to adverse events, including but not limited to informed consent documents, will be reviewed by the full board. Investigators must not use informed consent forms that do not include all known risks and side effects. Therefore, new enrollment must be suspended pending full IRB review of additional risk and approval of revised consent documents. In cases where enrollment has been suspended pending IRB review and the timing of entry of a subject into a protocol is an issue, an emergency meeting of the IRB will be called.

IRB approval is required prior to implementation of any change. However, investigators are permitted to take measures in order to eliminate apparent immediate hazards to the subjects without prior IRB approval. The investigator must report the incident to the IRB within 5 working days (see section entitled “Investigator Reporting Requirements”, pages 115-116).

SPONSORS: RESPONSIBILITIES AND OBLIGATIONS

Responsibilities and Obligations

The Institution does not allow any research involving human research participants to take place without the approval of the IRB, and as such, it is the policy of the Institution to apply all federal, state, and local laws during the review of *all* research protocols, whether or not they are funded by federal monies. All Investigators who apply for research approval assume the Investigator's Responsibility for ensuring that all safety provisions and other measures of protection will be enacted. These protections would be in place, regardless of a written agreement with the sponsor. The IRB approval is the assurance that procedures will be used to protect research participants.

Sponsor means a person or other entity that initiates a clinical investigation, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

Sponsor-investigator means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., it does not include a corporation or agency. The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

Sponsors are responsible for selecting qualified investigators who have appropriate training and experience to investigate the scientific question, provide them with the information they need to conduct an investigation properly, ensure proper monitoring of the investigation(s), ensure that the investigation(s) is conducted in accordance with the general investigational plan and protocols, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the test article. If a protocol is being conducted under an IND or IDE, the sponsor shall maintain an effective IND or IDE with respect to the investigations filed with the FDA.

Sponsor-Investigators

Sponsor-investigators are responsible for meeting all applicable sponsor and investigator responsibilities under FDA regulations 21 CFR 312.50-312.70, 812.1-812.19, and 21 CFR Parts 50 and 56, and all applicable DHHS regulations. A sponsor-investigator is responsible for ensuring that the test article is manufactured in compliance with the FDA's good manufacturing practices (GMPs) (21 CFR Parts 210, 211, 600, 610, and 820).

To ensure that a sponsor-investigator understands their responsibilities, the IRB Chair or IRB Program Coordinator will meet with the P.I. to discuss the applicable regulations. Investigator-initiated studies involving the use of an investigational drug or device will be audited by the IRB as necessary to monitor for compliance and safety. The Legal Services department, or authorized individual, is responsible for the review and approval of contracts between the sponsor-investigator and manufacturer of a device or drug.

For studies that involve the use of an investigational drug or device, two forms must be completed and submitted to the FDA before a study may begin: Form FDA 1571 and Form FDA 1572. For studies that involve investigational devices, an "Investigator's Agreement for Investigations with Significant Risk Devices" also must be signed and submitted by each investigator. A copy of each of these forms, when applicable, must be submitted with the IRB application.

FDA reporting requirements for sponsor-investigators includes Annual Reports, Adverse Experience Reports, and other safety report requirements. For studies involving investigational drugs, annual reports to the FDA are due each year within 60 days of the anniversary date that an IND went into effect. Adverse event reporting involves three steps: reviewing, reporting, and follow-up of adverse drug or device effects. For IND safety reporting requirements, see 21 CFR 312.32 (Appendix 11). For adverse device effect reporting requirements, see 21 CFR 812 subparts C (Responsibilities of Sponsors) and E (Responsibilities of Investigators) (Appendix 11). All studies require reapproval by the IRB annually, or at shorter intervals as determined by the IRB.

Contract Information and Review

A written contract or budgetary agreement should be in place prior to submitting to the IRB, specifying the nature of the research services to be provided and the basis for payment for those services. Contracts or agreements outlining financial arrangements between the sponsor and the investigator or Institution must be submitted to the Department of Legal Services and to the Office of Grants and Contracts to review and approve contracts and agreements prior to the sponsored protocol submission to the IRB. The consent document should also be provided at the time of contract submission or as soon as possible to ensure consistency regarding payment for subject injury and medical care provisions. The IRB will receive and review the approved contract or agreement at time of protocol submission to ensure that arrangements are clear in the consent document, contract or other agreement. Changes to financial arrangements between the sponsor and the investigator or Institution must be reported to the Department of Legal Services or to the Office of Grants and Contracts and the IRB prior to their implementation.

The Department of Legal Services and Office of Grants and Contracts will ensure that payment to clinical investigators or this Institution by research sponsors will be reasonable and based on work performed by the investigator and the investigator's staff, not on any other considerations. Any financial compensation received from trial sponsors must be commensurate with the efforts of the physician performing the research. Financial compensation should be at fair market value and the rate of compensation per patient should not vary according to the volume of subjects enrolled by the physician. When enrollment is particularly challenging, reasonable additional payments may be made to compensate the investigator or Institution for time and effort spent on extra recruiting efforts to enroll appropriate research participants. It is unethical for physicians to accept payment solely for referring patients to research studies. Therefore, payments to investigators and research staff in exchange for referrals of potential subjects (i.e. "finder fees") and payments designed to accelerate recruitment that are tied to the rate or timing of enrollment (i.e. "bonus payments") are prohibited. Payments or compensation of any sort should not be tied to the outcome of the trial. The nature and source of funding and financial incentives offered to investigators must be disclosed to potential participants as part of the informed consent process.

In addition, contracts and agreements will be reviewed for the following:

1. Sponsor payment, compensation, or reimbursement schedules for Investigators and/or the Institution.
2. Indication of who (e.g., the sponsor or Institution) will provide additional care for research-related injuries, and who will be responsible for the payment of this additional care.
3. The sponsor's obligation to promptly report to the investigator and Institution any significant new adverse effects, risks, or other findings related to the research study that could possibly affect the safety of subjects, affect the willingness of subjects to continue with participation, influence the conduct of the study, and/or alter the IRB's approval to continue the study.
4. Indication of how interim or final study results will be communicated to the subjects when the information could possibly affect their safety, medical care, and willingness to continue with participation. This includes results from other studies using the same intervention for a similar or other indication.
5. Contract provisions for medical care for research-related injuries are consistent with the consent document.

INVESTIGATIONAL NEW DRUGS AND DEVICES

Investigational New Drugs (IND)

Investigations undertaken to develop safety and effectiveness data for investigational new drugs will be conducted according to the requirements of the investigational new drug application (IND) regulations of FDA (21 CFR Part 312). An IND is required when the investigational new drug is not approved for use by the FDA or the drug is being tested for a new indication. If a research study will utilize an investigational new drug, the sponsor must provide the Principal Investigator with proof of an IND approval, and must be included in the initial application to the IRB. The sponsor confirms that the IND or IDE number is valid. The investigator must provide verification of the IND or IDE to the IRB in terms of one of the following: commercial or sponsored protocol with the IND number, communication from the commercial sponsor, communication from the FDA. The investigator brochure is not to be used to determine validity of an IND. The IRB does not accept an investigational drug protocol without a valid IND. Therefore, recruiting, obtaining consent, and screening participants for a specific study that is subject to the IND cannot begin until the IRB receives the IND and approval by the IRB is granted. The IND goes into effect 30 days after the FDA receives the IND, unless the sponsor receives earlier notice from the FDA. If a research study does not require the use of an IND, the sponsor must provide the Principal Investigator with proof that the protocol met one of the FDA exemptions from the requirements to have an IND. This information must be included in the initial application to the IRB.

Storage, Handling and Dispensing of Investigational Drugs, Agents or Biologics in Research

The Department of Pharmacy is responsible for the storage, handling and dispensing of investigational drugs (see Policy for Investigational Drugs, Appendix 13). When a protocol involving an investigational drug, agent or biologic has been approved by the IRB, the IRB Program Coordinator notifies the Research Pharmacist by sending a copy of the approval letter. It is the Investigators responsibility to provide the Pharmacy Department with a copy of the

protocol and all subsequent protocol amendments, new protocol versions and new Investigator Brochures.

Investigational New Drug Exemptions

1. The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of 21 CFR 312 if all the following apply:
 - (i) 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;
 - (ii) 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;
 - (iii) 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;
 - (iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and
 - (v) The investigation is conducted in compliance with the requirements of § 312.7.
2. (i) A clinical investigation involving an in vitro diagnostic biological product listed in paragraph (b)(2)(ii) of this section 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 312.160.
 - (ii) In accordance with paragraph (b)(2)(i) of this section, 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. 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 312.160.

4. FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b)(1) of this section.
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. A clinical investigation involving an exception from informed consent under 21 CFR 50.24 of this chapter is not exempt from the requirements of this part.

Investigational Devices

Investigational Device Exemption (IDE)

Any device found to pose a significant risk of harm by the sponsor, by any reviewing IRB, or by the FDA must have an Investigational Device Exemption. Investigations undertaken to develop safety and effectiveness data for medical devices will be conducted according to the requirements of the IDE regulations of the FDA (21 CFR Part 812.2(b)), and the following should be included:

- The device fulfills the requirements for an abbreviated IDE.
- The device is not a banned device.
- The sponsor labels the device in accordance with 21 CFR 812.5.
- The sponsor 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.
- The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, consent under 21 CFR 50 and documents it, unless documentation is waived.
- The sponsor complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations;
- The sponsor maintains the 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);

- The sponsor ensures that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and
- The sponsor complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.

All new applications that have an IDE will be reviewed by the full board. If a research study will utilize an investigational device, the sponsor must provide the Principal Investigators with proof of an IDE application, which must be included in the initial application to the IRB. If a research study will utilize a device without an IDE, the sponsor must provide the Principal Investigators with proof that the device fulfilled the requirements for an abbreviated IDE or met one of the exemption categories this information must be included with the initial application to the IRB.

Exemption from an IDE

A device may also be exempt from the IDE requirements, and studies of devices that are IDE-exempt may be eligible for expedited review. To qualify for an exemption from an IDE, investigations must meet the criteria as stated in 21 CFR 812.2, paragraph c (Appendix 11).

Determinations of Significant or Non-Significant Risk Device

When a sponsor or investigator claims that an investigational device is a non-significant risk (NSR), the IRB will ask the sponsor or investigator to provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, whether other IRBs have reviewed the proposed study and what determination was made, the FDA assessment of the risk of the device, if such an assessment has been made, as well as any other information requested by the IRB. In the case of review by an expedited procedure, the IRB Chair will make the determination of whether a device is significant risk (SR) or NSR. Otherwise, the convened IRB will make the determination.

The IRB considers a device to be SR if it (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. Otherwise the IRB considers the device to be NSR.

If the IRB decides the study is NSR, the study is reviewed and, if approved, the sponsor and investigator will be asked to comply with “abbreviated IDE requirements”, informed consent, and IRB regulations. If the IRB disagrees with the sponsor’s assessment, the IRB will notify the sponsor of its decision in writing. The sponsor must notify the FDA that a SR determination has been made. The IRB will review the study after FDA approval of the IDE application.

In the case of review by an expedited procedure, the reviewer will document the SR/NSR determination in the protocol file. In the case of review by a convened IRB, the SR/NSR determination will be documented in the minutes. In both cases the SR/NSR determination will be noted in the letter to the investigator. A complete list of significant and non-significant risk devices is included in Appendix 12).

Humanitarian Use Devices

An Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. The HUD provision of the regulation provides an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations.

To obtain approval for an HUD, a humanitarian device exemption (HDE) application is submitted to FDA. An HDE is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or

significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market.

An approved HDE authorizes marketing of the HUD. However, an HUD may only be used in facilities that have established a local institutional review board (IRB) to supervise clinical testing of devices and after an IRB has approved the use of the device to treat or diagnose the specific disease. The labeling for an HUD must state that the device is an humanitarian use device and that, although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been demonstrated. An approved HDE application is valid for as long as the use of the device continues to meet the conditions of the HDE application.

Use of an HUD is the only situation where federal regulations require the IRB to approve and monitor an activity that is not research. The IRB follows full board review procedures when reviewing requests to use an HUD. Submission requirements are the same as for full board review; however, the following conditions also apply:

1. A letter or document from the device sponsor must be submitted that documents the following 10 items:
 - a. the generic and trade name of the device
 - b. the FDA HDE number (a six digit number preceded by the letter H)
 - c. the date of HUD designation
 - d. indications for use of the device
 - e. a description of the device
 - f. contraindications, warnings, and precautions for use of the device
 - g. adverse effects of the device on health
 - h. alternative practices and procedures
 - i. marketing history
 - j. summary of studies using the device

2. The IRB has the discretion to determine the conditions of HUD use and whether to approve each individual use of the device. The IRB may approve the use of the device in general, or in a specific number of patients or only under specific conditions.
3. The IRB will conduct both initial and continuing review of an HUD. Continuing review will be annually, unless otherwise specified by the IRB at the time of initial review.
4. A letter stating that the HUD is not being used as part of a research project or clinical investigation designed to collect data to support an FDA premarket approval application must be submitted with the initial application. If the HUD is being used in a research project or clinical investigation, the IRB complies with all FDA regulations related to IRB review of research.
5. Regulations do not require informed consent to use an HUD outside the research setting. This IRB may require that informed consent be obtained in situations that it deems appropriate. This determination will be made by the full board at the time of review.

Storage, Handling and Dispensing of Investigational Devices in Research

The Principal Investigator is responsible for the storage, handling and dispensing of investigational devices in research. IRB applications involving investigational devices must list the method for storage and inventory control to prevent the unauthorized use of the device. The monitoring plan for control of investigational devices is handled on a case-by-case basis by the IRB. Following approval of a study involving investigational devices, the IRB Program Coordinator will monitor the storage of devices for compliance and safety at intervals determined by the IRB at the time of initial review.

Expanded Access

Whenever possible, use of an approved drug, biologic, or medical device as part of a clinical trial is preferable; however, under certain circumstances physicians can use unapproved drugs, biologics, and medical devices outside of clinical trials, including emergency use of drugs, biologics, and devices. Expanded access mechanism allows access to an investigational device or drug for patients who do not meet the requirements for inclusion in a clinical trial but for whom the treating physician believes the device or drug may provide a benefit in treating and/or

diagnosing their serious (albeit not life-threatening) disease or condition. This is not the same as “off-label use” of an approved drug, device, or biologics. The IRB follows full board review procedures when reviewing requests for expanded access use.

General criteria:

- The patient and a licensed physician are both willing to participate;
- The patient’s physician determines that there is no comparable or satisfactory therapy available to diagnose, monitor, or treat the patient’s disease or condition;
- That the probable risk to the person from the investigational product is not greater than the probable risk from the disease or condition;
- FDA determines that there is sufficient evidence of the safety and effectiveness of the investigational product to support its use in the particular circumstance;
- FDA determines that providing the investigational product will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval;
- The sponsor (generally the company developing the investigational product for commercial use) or the clinical investigator (or the patient’s physician in the case of a single patient expanded access request) submits a clinical protocol (a document that describes the treatment plan for the patient) that is consistent with FDA’s statute and applicable regulations for INDs or investigational device exemption applications (IDEs), describing the use of the investigational product; and
- The patient is unable to obtain the investigational drug under another IND or to participate in a clinical trial.
- Emergency use of a device 21 CFR 56.104(c) – 21 CFR 50.23 – 21 CFR 812.35(a)(2) – 21 CFR 812.150(a)(4)
- Compassionate use of a device (21 CFR 812.35(a))

Emergency Use of Drugs and Devices

“Emergency use” means the use of an unapproved drug, biologic, or device in a life-threatening situation, or the compassionate use of an unapproved device that does not have an IDE, and in which there is not sufficient time to convene a full board IRB meeting with quorum for approval. Whenever possible the researchers must notify the IRB prior to the proposed emergency use. When emergency medical care is initiated the patient may not be considered a research participant under 45 CFR 46. The IRB does not currently review protocols involving the pre-planned use of a test article in an emergency situation. In cases of medical emergencies, physicians will follow federal regulations for Emergency Use of Drugs and Devices (21 CFR 56.102(d) and 21 CFR 56.104(c)).

Human subject research activities subject to 45 CFR 46 may not be started, even in an emergency, without prior IRB review and approval; therefore, emergency use of a test article cannot be claimed as research, and data generated during the use of the test article cannot be reported as being obtained through a prospectively conceived research activity.

In cases of medical emergencies, physicians will follow federal regulations for Emergency Use of Drugs and Devices (21 CFR 56.102(d) and 21 CFR 56.104(c)). The emergency use provision in 21 CFR 56.104(c) is an exemption from prior review and approval by the IRB. The exemption, which may not be used unless all of the conditions described in 21 CFR 56.102(d) exist, allows for one emergency use of a test article without prospective IRB review.

Each of the following conditions must exist to justify emergency use of a drug or biologic:

- In order to use a test article in a life-threatening situation without prior IRB review:
 - The participant is confronted with a disease or condition that is either life-threatening or severely debilitating;
 - No generally acceptable alternative treatment is available.
 - There is not sufficient time to obtain IRB approval;

- The treating physician will document in the medical record that the above findings are met;
- The treating physician will report the emergency use to the IRB within five working days that the above conditions are met;
- Any subsequent use of the test article is subject to IRB review;
- The FDA has issued an IND;
- The use is not subject to DHHS regulations;
- Consent will be obtained in accordance with FDA regulations, or the circumstances meet the exception to the requirement for consent in FDA regulations. *Or all of the following are true:*

Informed consent is not required because all of the following are true:

- Immediate use of the test article is, in the investigator's opinion, required to preserve the life of the participant;
- Time is not sufficient to obtain the independent determination a physician who is not otherwise participating in the clinical investigation; and
- Before the use of the test article the investigator will certify in writing all of the following:
 - The participant is confronted by a life-threatening situation necessitating the use of the test article, and immediate use of the test article is necessary;
 - Informed consent cannot be obtained from the participant because of an inability to communicate with, or obtain legally effective consent from, the participant;
 - Time is not sufficient to obtain consent from the participant's legal representative;
 - There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the participant; and
 - The treating physician will report the emergency use to the IRB within five working days that the above conditions are met.

Unlike in the case of unapproved drugs and biologics, FDA does not consider the emergency use of an unapproved device to be clinical investigation and FDA does not require compliance with 21 CFR §50 and 21 CFR §56.

Emergency use of medical devices – the researcher and IRB must determine:

Emergency use of an unapproved device:

- There is a life-threatening disease or serious condition requiring immediate use;
 - No generally acceptable alternative for treating, diagnosing, or monitoring the patient is available;
 - There is no time to follow existing procedures to obtain an IDE;
 - There is no IDE, or the treating physician wants to use the device in a way not approved under an existing IDE;
 - The treating physician is not part of the IDE study;
 - The probable risk to the patient is not greater than the probable risk from the disease;
 - The treating physician has substantial reason to believe that benefits will exist;
 - All institutional clearances as required by institutional policy are obtained;
 - There is concurrence from the IRB chairperson;
 - There is authorization from the sponsor if an IDE exists;
 - A physician uninvolved with the emergency use of the device will certify in the medical record that the above findings are met.
- If there is no time to find an uninvolved physician, the physician makes and documents the above determinations in the medical record, and has the evaluation reviewed by an uninvolved physician, and the treating physician's and uninvolved physician's concurrence are reported to the IRB within 5 working days after the use.
 - Informed consent was sought from the patient or patient's legally authorized representative (does not have to follow informed consent requirements at 21 CFR 50.25)
 - If no informed consent can be obtained, the treating physician, and a physician who is not participating in the clinical investigation must certify:

- A life-threatening situation necessitating use of the device exists
- There is no alternative therapy
 - After the use:
- If an IDE exists, the researcher must notify the sponsor; the sponsor must report to the FDA
- If an IDE does not exist, notify the FDA of the emergency use and provide FDA a written summary of the emergency use, patient protection measures, and any scientific results
 - After the use, the treating physician must report to the IRB within five days

Compassionate use of a device:

- Compassionate use is not a clinical investigation
- Prior FDA concurrence is required before compassionate use occurs
- The treating physician certifies:
 - There is a life-threatening disease or serious condition requiring immediate use
 - There are no alternatives
 - If there is an existing study, but the patient does not meet inclusion criteria for the existing study
 - The probable risk to the patient is not greater than the probable risk from the disease
- The treating physician requests authorization from the sponsor; the sponsor may agree or disagree; if the sponsor disagrees, the treating physician is not allowed to use the device; if the sponsor agrees with the use, the sponsor submits an IDE supplement requesting approval for a protocol deviation
- The treating physician should create a schedule for patient monitoring, address specific needs of the patient, and detect possible problems
- All institutional clearances must be obtained as required by institutional policy are obtained
- There is concurrence from the IRB chairperson
- The treating physician will obtain consent from the patient

- The treating physician will report any problems to the IRB and the sponsor
- The treating physician will write a summary of the use and provide to the sponsor
- The IRB must review IRB chair's documented concurrence; confirm FDA concurrence, review the consent document, receive reports after the use, receive reports of problems

For any emergency use - If a similar need is likely, the researcher must submit an IRB application within 30 days and obtain an IND or IDE.

COMMUNITY-BASED PARTICIPATORY RESEARCH

Community-based participatory research (CBPR) is research that is conducted as a partnership between researchers and members of a community. The term “community” generally refers to a geographic community, a community of individuals with a common problem or issue, or a community of individuals with a common interest or goal.

Trinity Health Of New England supports concerns of research participants and their communities, and the involvement of community members in community-based research. Researchers may consult with community members for input and may involve community members in the research process, including the design and implementation of research and the dissemination of results, when appropriate. However, it is recommended that researchers refer to published guidelines for conducting CBPR prior to approaching the community and designing the research plan.

Community members may be considered vulnerable to coercion or undue influence. Vulnerable populations may include children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons. Additional safeguards must be included in the study to protect the rights and welfare of these participants. For more information, refer to the IRB policy entitled “Review of Research Involving Vulnerable Populations”.

GOOD CLINICAL PRACTICE GUIDANCE FOR RESEARCHERS ON CLINICAL TRIALS

Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practice (GCP) and the applicable regulatory requirements.

When following ICH-GCP (E6), the items below should be reviewed:

- Manufacturing, handling, and storage in accordance with applicable good manufacturing practice.
- Where allowed or required, the investigator may assign some or all duties for investigational articles accountability at the trial sites to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator.
- The investigator, pharmacist, or other designated individual will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each participant, and the return to the sponsor or alternative disposition of unused products. These records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational products and trial participants.
- Investigators should maintain records that document adequately that the participants are provided the doses specified by the protocol and reconcile all investigational products received from the sponsor.
- When adults are unable to consent, the IRB determines:

- A non-therapeutic clinical trial (i.e. a trial in which there is no anticipated direct clinical benefit to the participant) should be conducted in participants who personally give consent and who sign and date the written consent document.
- Non-therapeutic clinical trials may be conducted in participants with consent of a legally acceptable representative provided the following conditions are fulfilled:
 - The objectives of the clinical trial cannot be met by means of a trial in participants who can give consent personally.
 - The negative impact on the participant's wellbeing is minimized and low.
 - The opinion of the IRB is expressly sought on the inclusion of such participants, and the written opinion covers this aspect.
 - Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Participants in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.
- The researcher provides evidence of his or her qualifications through up-to-date curriculum vitae or other relevant documentation requested by the sponsor, the IRB, or the regulatory authority.
- The reviewer is provided and reviews the investigator's current curriculum vitae or other documentation evidencing qualifications.
- The researcher is familiar with the appropriate use of the investigational product, as described in the protocol, in the current investigator brochure, in the product information, and in other information sources provided by the sponsor.
- During and following a participant's participation in a clinical trial, the researcher ensures that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the clinical trial.
- The researcher ensures the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.
- The researcher must maintain a list of appropriately qualified persons to whom they have delegated significant clinical trial-related duties.

- The researcher reports all serious adverse events (SAEs) to the sponsor except for those SAEs that the protocol or other document (e.g., investigator's brochure) identifies as not needing immediate reporting. The researcher follows regulatory requirements related to the reporting of unexpected serious adverse drug reactions to the regulatory authority and the IRB.
- The researcher provides written reports to the sponsor, the IRB, and, where applicable, the organization on any changes significantly affecting the conduct of the clinical trial or increasing the risk to participants.
- If the researcher terminates or suspends a clinical trial without prior agreement of the sponsor, the researcher informs the organization, sponsor, and the IRB.
- If the IRB terminates or suspends approval of the clinical trial, the researcher promptly notifies the sponsor.
- Upon completion of the clinical trial, the researcher informs the organization; the IRB with a summary of the trial's outcome; and the regulatory authority with any reports required.
- During and following a participant's participation in a clinical trial, the researcher ensures that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the clinical trial.
- The researcher follows the clinical trial's randomization procedures, if any, and ensures that the code is broken only in accordance with the protocol. If the clinical trial is blinded, the researcher promptly documents and explains to the Sponsor any premature unblinding.
- A qualified physician (or dentist, when appropriate), who is a researcher or a co-researcher for the clinical trial, is responsible for all clinical trial-related medical (or dental) decisions. Researchers inform participants when medical care is needed for other illnesses of which the researchers become aware.
- The researcher informs the participant's primary physician about the participant's participation in the clinical trial if the participant has a primary physician and if the participant agrees to the primary physician being informed.

- Although a participant is not obliged to give his or her reasons for withdrawing prematurely from a clinical trial, the researcher makes a reasonable effort to ascertain the reason, while fully respecting the participant's rights.
- The researchers and research staff provide all the disclosures and follow the requirements pertaining to consent

When following ICH-GCP (E6), the IRB determines that the following disclosures are included:

- The alternative procedures or treatment that might be available to the participant, and their important potential benefits and risks.
- That the monitor, the auditor, the IRB, and the regulatory authority will be granted direct access to the participant's original medical records for verification of clinical trial procedures or data, without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations and that, by signing a written consent form, the participant or the participant's legally acceptable representative is authorizing such access.
- The approval of the IRB.
- Documentation of the consent process include:
 - Prior to a participant's participation in the trial, the written consent document should be signed and personally dated by the participant or by the participant's legally acceptable representative.
 - Prior to a participant's participation in the trial, the written consent document should be signed and personally dated by the person who conducted the informed consent discussion.
 - If a participant is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion.
 - After the written consent document and any other written information to be provided to participants, is read and explained to the participant or the participant's legally acceptable representative, and after the participant or the

participant's legally acceptable representative has orally consented to the participant's participation in the trial and, if capable of doing so, has signed and personally dated the consent document, the witness should sign and personally date the consent document.

- By signing the consent document, the witness attests that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the participant or the participant's legally acceptable representative, and that consent was freely given by the participant or the participant's legally acceptable representative.
- Prior to participation in the trial, the participant or the participant's legally acceptable representative should receive a copy of the signed and dated written consent document and any other written information provided to the participants.

CONFLICTS OF INTEREST IN RESEARCH POLICY

Trinity Health Of New England promotes objectivity in research and has established standards to ensure there is no reasonable expectation that the design, conduct, or reporting of research to be performed will be biased by any conflicting financial interest of an Investigator. Financial interests in human subject's research are distinct from other interests in institutional life, because their existence may entail special risks. Specifically, opportunities to profit from research may affect – or appear to affect – the judgment or decisions of an investigator. At Trinity Health Of New England, all significant financial conflicts of interest in human subjects research are regarded as potentially problematic, and therefore, require close scrutiny. It is the purpose of this policy to set forth the principle for identifying the potential for conflicts and the procedures for reviewing and addressing those potential conflicts that occur. This is done to ensure that the research may be performed in a manner consistent with preserving the safety and welfare of human subjects that participate in such research, as well as ensure the overall integrity of the research. The specific purpose of the policy is:

- To identify actual or potential conflicts of interest in research, and to eliminate, reduce or manage such conflicts;
- To maintain the integrity of research endeavors;
- To ensure compliance with federal and state laws and regulations and institutional policies regarding conflict of interest as it relates to research.

This policy applies to all individuals affiliated with the hospital in some manner who, on behalf of Trinity Health Of New England, are responsible for, or are in the position to influence, the design, conduct, or reporting of the research or other scholarly activity. This includes:

- Full or part-time employees at Trinity Health Of New England
- Members of the Medical/Dental and Nursing Staff at Trinity Health Of New England and components
- Trainees, and medical, nursing, pharmacy and dietary students

Definitions

- **Trinity Health Of New England** means Saint Francis Hospital and Medical Center, Mount Sinai Rehabilitation Hospital, Johnson Memorial Hospital, Mercy Medical Center, Saint Mary's Hospital and their components where a research study is conducted, whether it is initiated by an investigator or by an outside entity.

- **Investigator** means the principal investigator and any other person who is responsible for the design, conduct, or reporting of a research project. For purposes of this policy, "Investigator" includes the Investigator's family members: spouse, children, and any other person living in the same household.

- **Research** means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge relating broadly to public health, including behavioral and social sciences research. The term encompasses basic and applied research and product development.

- **Significant Financial Interest Related to Research** is defined as a financial interest in the sponsor, product or service being tested, or competitor of the sponsor. This covers anything of monetary value, including, but not limited to, salary or other payments for services (e.g., consulting fees or honoraria); equity interest (e.g., stocks, stock options or other ownership interest); and intellectual property rights (e.g., patents, copyrights and royalties from such rights). For the purposes of this policy, Disclosable Financial Arrangements are:

1. Compensation made to the investigator in which the value of compensation could be affected by study outcome, or compensation of more than \$0 in the past year related to the research from entities other than the sponsor when aggregated for the immediate family.
2. A proprietary interest in the tested product, including but not limited to: a patent, trademark, copyright or licensing agreement.
3. Any equity interest in the sponsor of a covered study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices or other measure of fair market value.

4. Any equity interest in a publicly held company that exceeds \$0 in value, or whose value represented 0% or more interest in any one single entity.
5. Significant payments of other sorts, which are payments that have a cumulative monetary value of more than \$0 made by the sponsor of a covered study to the investigator or the investigator's institution to support activities of the investigator exclusive of the costs of conducting the clinical study or other clinical studies (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for 1 year following completion of the study.
6. Board or executive relationship related to the research, regardless of compensation.

The term does not include:

- Salary, royalties, or other remuneration from - Trinity Health Of New England affiliates;
- Income from seminars, lectures, or teaching engagements sponsored by public or non-profit entities;
- Income from service on advisory committees or review panels for public or non-profit entities;
- An equity interest that when aggregated for the Investigator and the Investigator's family members, meets both of the following tests: Does not have value as determined through reference to public prices or other reasonable measures of fair market value, and does not represent ownership interest in any single entity;
- Salary, royalties or other payments that when aggregated for the Investigator and the Investigator's family members over the next twelve months, are not reasonably expected to exceed \$0.
- **Significant Non-Financial Interest Related to Research** is defined as an interest in the sponsor, product or service being tested, or competitor of the sponsor which excludes financial interest. For the purposes of this policy, Disclosable Non-Financial Arrangements are:

1. Having a Board or executive relationship related to the research, regardless of compensation.
2. Have been involved, or plan to become involved in the design, conduct, or reporting of the research.
3. Having direct supervision of or by the researcher, participation on a research project with the researcher, or other issues that might influence decision-making

Saint Francis Hospital and Medical Center on behalf of Trinity Health Of New England will:

1) Maintain an appropriate written, enforced policy on conflict of interest that complies with state and federal guidelines and regulations, and inform each Investigator of that policy, the Investigator's reporting responsibilities, and of these regulations. If Trinity Health Of New England sites carry out research through subcontractors, or collaborators, Trinity Health Of New England must take reasonable steps to ensure that Investigators working for such entities comply with this policy, either by requiring those Investigators to comply with Trinity Health Of New England's policy or by requiring the entities to provide assurances to Trinity Health Of New England that will enable Trinity Health Of New England to comply with this policy.

2) Require that all financial disclosures be made at the time of application to the IRB of a research project, and on an annual basis thereafter, or as new reportable Significant Financial Interests are obtained.

3) Provide guidelines consistent with this policy for the designated official(s) to identify conflicting interests and take such actions as necessary to ensure that such conflicting interest will be managed, reduced, or eliminated.

Maintain records of all financial disclosures and all actions taken by Trinity Health Of New England with respect to each conflicting interest for three years.

Disclosure Procedures and Review

Research Financial Disclosure Forms will be completed and on file prior to the approval of a research project by the IRB. Forms must be completed by Principal Investigators and all Co-Investigators for each funded research project, annually, or at the time of renewal of a protocol,

or if there is a new reportable Significant Financial Interest by the Investigator. Forms must be completed and on file prior to the renewal of a research project. All forms will be submitted to the IRB for review.

All Financial Disclosure Forms are reviewed initially by the office of the IRB. All forms indicating a Significant Financial Interest will require full disclosure of relevant information by the Investigator and filed with the IRB office. All forms indicating a financial interest will be referred to the Financial Conflict of Interest in Research (FCOIR) Committee for review. The FCOIR Committee will establish whether a significant financial conflict exists and review the interest to determine whether or not the conflict may adversely affect the rights or welfare of research subjects or could directly and significantly affect the design, conduct, or reporting of the proposed research (Appendix 13). The FCOIR Committee is responsible for determining when such an interest must be managed, reduced or eliminated. If the FCOIR Committee determines that a conflict exists, it will communicate this determination and the means it has identified for eliminating or managing the conflict, in writing, to the relevant Investigator and to the office of the IRB. Conflict of interest management plans and requests to reduce or eliminate an interest will be referred back to the IRB for review by the fully convened IRB. The determination will be utilized during the research review process by the IRB. The IRB will communicate the conditions for approval of the research protocol to the Investigator. The IRB may refer back the determination to the FCOIR Committee if changes are deemed necessary.

In accordance with Institutional Policies, investigators with a financial interest greater than \$50,000 cannot participate in the research.

At renewal if new financial interests are disclosed, they will be managed following the same procedures outlined for new protocol submissions.

Renewal of research protocols with an active management plan will be reviewed by the fully convened IRB at the time of renewal. Updated forms and a written statement of any changes in the financial interest must be completed at the time of renewal of a protocol and submitted to the office of the IRB. If the financial interest has changed, the office of the IRB will refer to the FCOIR Committee to evaluate whether or not the management plan needs to be modified. The determination of the FCOIR Committee will be communicated to the Investigator

and office of the IRB. The IRB has the final say with the plan. If the FCOIR Committee does not agree, then the plan gets amended and reevaluated by both the IRB and the FCOIR Committee.

Resolution and Management of Conflicts of Interest

A conflict of interest exists when the FCOIR Committee reasonably determines that a Significant Financial Interest could directly and significantly affect the design, conduct, or reporting of the proposed research. If a conflict of interest has been identified as a result of the procedures as outlined above, the FCOIR Committee will be responsible for taking the appropriate actions(s):

- 1) Determine if there are compelling circumstances which are sufficient to allow the research to proceed in the face of the conflict.
- 2) For projects that are allowed, review of the nature of the conflict at a fully convened IRB meeting, with recommendations made to manage the conflict.
- 3) Determine the appropriate strategies to properly oversee and manage potential conflict(s), taking into consideration the possible remedies as outlined below.
- 4) Inform the investigator of the actions and decisions of the IRB, including restrictions.

Restrictions that might be imposed to manage conflicts of interest include, but are not limited to:

- 1) Public disclosure of significant financial interests;
- 2) Monitoring of the research by independent reviewers;
- 3) Modification of the research plan;
- 4) Disqualification from participation in all or a portion of the research;
- 5) Divestiture of significant financial interests, or;
- 6) Severance of relationships that create actual or potential conflicts.

Sanctions

If the failure of an Investigator to comply with the conflict of interest in research policy of Trinity Health Of New England has biased the design, conduct, or reporting of the research, Trinity Health Of New England will consider the situation, and as necessary, take appropriate action. Sanctions will include, but are not limited to:

- 1) Letter of reprimand
- 2) Notification to funding agencies and/or professional journals or societies
- 3) Termination of research project
- 4) Suspension
- 5) Termination

Any financial benefit to the Investigator must be disclosed in the consent form and during the consent process. The fees and payments that the Investigators and Institution receive are negotiated by the sponsor, the Investigator and the Institution. Sponsors of research are responsible for ensuring that there is an absence of financial interest of investigators who conduct their studies, or to disclose those interests.

REVIEW OF EVENTS AND PROBLEMS

This procedure describes the process followed by the IRB to ensure prompt reporting of unanticipated problems, adverse events or protocol deviations involving risks to participants or others to the IRB, institutional officials and regulatory agencies.

Definitions

The following definitions are used in this policy:

Protocol deviation is an incident involving non-compliance with the approved protocol, but typically does not have a significant effect on subjects' rights, safety or welfare, or the integrity of the study.

Related event is an event that in the opinion of the investigator is more likely than not to be caused by or affects the research procedures.

Unanticipated problem involving risks to subjects or others is an event that includes any incident, experience, or outcome that meets **all** of the following criteria:

1. unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. related or possibly related to participation 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.

Adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Unexpected adverse event is an adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either:

1. the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
2. the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Serious adverse event is any event that results in death; is life-threatening and places the subject at immediate risk of death from the event as it occurred; results in inpatient hospitalization or prolongation of existing hospitalization; results in a persistent or significant disability or incapacity; results in a congenital anomaly or birth defect; or 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.

Expected adverse event is an adverse event that does not meet the criteria for an "unexpected event."

Investigator Reporting Requirements

Investigators are required to report to the IRB the following using the **Full Unanticipated Problem and Adverse Event Report Form** (Appendix 6) when discovered during the course of research and no later than 5 working days after their occurrence:

1. Unexpected AND related adverse events (on-site or off-site)
2. The death of a research subject on site
3. Unanticipated problem that is a serious adverse event (on-site or off-site)
4. Any complaint of a participant that indicates an unanticipated risk or which cannot be resolved by the research staff
5. Any other event or other problems which in the opinion of the principal investigator was (1) previously unforeseen and (2) presents risks to research subjects or others
6. Any event that requires prompt reporting according to the protocol or the sponsor

Investigators are required to report to the IRB significant protocol deviations using the **Protocol Deviation Report Form** (Appendix 6) when discovered during the course of research and no later than 5 working days after their occurrence. Examples of significant reportable events include, but are not limited to:

1. Protocol deviations which harmed a subject or that may affect the safety of other research participants by placing them at increased risk of harm
2. Protocol deviations that have the potential to recur
3. Any change to the protocol taken by an investigator or member of the research staff without prior IRB review to eliminate apparent immediate hazard to a research participant
4. Any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected change to the risks or potential benefits of the research

Events that do not meet the above reporting requirements, but which sponsors request Investigators to report to the IRB, should be logged on a **Tracking Form for Unanticipated Problems and Adverse Events** (Appendix 6) and submitted to the IRB as soon as possible. Multiple events can be reported on a single form, with the IND or manufacturer's safety report attached. If the investigator answers "yes" to the following three questions on the form, a **Full Unanticipated Problem and Adverse Event Report Form** must be filled out and submitted for that event: 1. Was the event unexpected? 2. Was the event related to study drug/device or procedure? 3. An event that placed the subject or others at greater risk of harm than was previously known or recognized?

IRB Review of Reported Events

The Chair of the IRB or a designated member reviews all reports. If the IRB Chair determines that the event did not represent an unanticipated problem involving risks to participants or others, the chair signs and dates the report and the report is filed.

If the IRB Chair or designated member determines that an event might represent an unanticipated problem involving risks to participants or others, and related to the investigation, the chair signs and dates the report. The IRB Program Coordinator places the item on the agenda

for discussion and provides all IRB members with a copy of the report, all supporting documentation to review, and a copy of the current consent document. The IRB Chair will review the information, or a primary reviewer is assigned who is given a copy of the currently approved protocol and investigator's brochure. The IRB Chair determines whether to ask the Principal Investigator to present the report.

The IRB votes to determine whether the event is an unanticipated and related problem involving risks to participants or others and the determination of the IRB is recorded in the minutes. If the IRB determines that an event is an unanticipated problem involving risks to participants or others, the IRB Program Coordinator will follow the procedures outlined in “Reporting of IRB Findings to Federal Agencies.”

If IRB determines that an event is an unanticipated and related problem involving risks to participants or others, it will consider the following actions:

1. No action
2. Modification of the research protocol
3. Modification of the information disclosed during the consent process
4. Additional information provided to past participants
5. Notification of current participants (required when such information may relate to participants' willingness to continue to take part in the research)
6. Requirement that current participants re-consent to participation
7. Modification of the continuing review schedule
8. Monitoring of the research
9. Monitoring of the consent
10. Suspension or termination of the research
11. Referral to other organizational entities (e.g., legal counsel, risk management, or institutional official)

If no action is required, a copy of the fully executed reporting form is sent to the Principal Investigator, and the original document is filed in the protocol file labeled “Safety Reports and Unanticipated Adverse Events”. If the IRB takes any actions or imposes any requirements, the

IRB Program Coordinator documents those actions and requirements in the minutes and in a letter to the Investigator.

Reporting Unanticipated and Adverse Events to Federal Agencies

The Chairman or the Program Coordinator of the IRB will report to the OHRP, and if applicable, to the FDA, and inform the signatory of the FWA, within 48 hours of any unanticipated problems involving risk to human subjects or others that occur at this site. Please refer to the section entitled “Reporting of IRB Findings to Federal Agencies”, pages 128-129.

COMPLIANCE: RESPONSIBILITIES OF RESEARCHERS

Responsibilities of the Research Investigator

1. Research investigators acknowledge and accept their responsibility for protecting the rights and welfare of human research subjects and for complying with all applicable provisions of this Institution's IRB. The Principal Investigator is responsible for the compliance of all co-investigators, student investigators, and research associates with the IRB decisions, conditions, and requirements.
2. Research investigators are responsible for conducting studies in accordance with the protocol.
3. Research investigators are required to complete periodic training in the protection of human subjects, as required by Federal regulations and IRB policy.
4. Research investigators are responsible for obtaining consent and for providing a copy of the IRB-approved and signed informed consent document to each subject at the time of consent.
5. Research investigators are responsible for ensuring that only authorized research staff will conduct the consent process.
6. Research investigators will promptly report changes in previously approved human subject population or research activities to the IRB. Changes will not be initiated without IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subjects.
7. Research investigators are responsible for reporting progress of approved research to the IRB, as often as and in the manner prescribed by the IRB, on the basis of risks to subjects, but not less than once per year.
8. Research investigators are responsible for notifying the IRB of any change in financial relationships of any investigators that may result in a conflict of interest that was previously undisclosed.
9. Research investigators will promptly report to the IRB any injuries or other unanticipated problems involving risks to subjects or others no later than 5 working days after their occurrence.
10. Research investigators are responsible for notifying the IRB and providing a final report when a study is closed.

11. Research investigators are responsible for notifying the IRB of any gaps in investigator involvement in a study.
12. Research investigators are responsible for ensuring, whenever necessary, that the trial is properly registered with clinicaltrials.gov.
13. Research studies have the resources necessary to protect human subject participants.
14. Researchers are qualified to conduct the research.
15. Adequate time is allotted for the researchers to conduct and complete the research. There are also an adequate number of qualified staff and adequate facilities.
16. Researchers have access to populations that will allow recruitment of the necessary participants.
17. The researchers are provided with the availability of medical or psychosocial resources that participants may need as a consequence of the research.
18. Researchers will follow Good Clinical Practice guidelines (refer to pages 102-106).
19. Researchers must disclose significant financial interests including those of the Researcher, and the Researcher's spouse and dependent children (refer to Investigator Conflicts of Interest in Funded Research Policy).

Responsibilities of the Study Coordinator

To ensure safety of research participants and compliance with regulations, the IRB requires all interventional protocols to have a Study Coordinator. The Study Coordinators serve as impartial safety monitors. The duties of Study Coordinators are delegated by the Principal Investigator and may include the consenting of research subjects, ensuring accuracy of the data recorded, acting as liaison between the study sponsor and the Institution, acting as liaison between the Principal Investigator and the IRB and other Institutional officials and committees, and general oversight of conduct of protocols.

Compliance and Audits

As part of providing adequate oversight of studies, the IRB randomly selects protocols and conducts periodic audits to ensure compliance with the protocol, applicable Federal, State and local regulations, and IRB policies and guidelines. Audits also are conducted when and if

the IRB is concerned about the safety of a study or the process for obtaining consent. Audits are conducted by a qualified member of the IRB and/or the IRB Program Coordinator. Results of audits are summarized in a letter to the Principal Investigator, and a report is presented to IRB members at the next convened meeting (Record of Audit - Appendix 6). Investigators are required to address deficiencies, as requested by the IRB. It is at the discretion of IRB members to estimate the safety of participants in a given study and determine when other sources are necessary for verification of compliance by investigators. Examples of protocols that the IRB will monitor by the audit process for safety and compliance include:

1. Phase I studies on a case by case basis
2. Phase II studies
2. Studies carried out by investigators with a record of non-compliance
3. Protocols that carry significant physical or social risks to the participants
4. Studies in which there is concern about possible material changes occurring without IRB approval
5. Studies that have been revised based upon information provided from Institutional employees, subjects enrolled or any other reliable source
6. Studies in which enrolled subjects express concerns to the IRB
7. Investigator-initiated studies that involve the use of an investigational drug or device
8. Studies eligible for full board continuing review with enrolled subjects.
9. Studies eligible for expedited continuing review, where the protocol remains active with enrolled subjects.

The IRB will notify Investigators, in writing, of the actions required to correct any deficiencies encountered during a routine or prompted audit, or as the result of a complaint, and a response must be received within 5 working days.

All interventional protocols require a Study Coordinator. To ensure ongoing compliance, the IRB Program Coordinator is in continued contact with Study Coordinators to review the safety of research projects, changes to protocols and monitor research activities.

Non-Compliance and Corrective Action

For the purposes of this policy, the terms used are defined as follows:

Non-compliance is the failure of investigators to comply with Federal regulations, the Policies and Procedures of the IRB, or the determinations or requirements of the IRB. Examples of non-compliance include, but are not limited to: expired CITI training, lack of submitting a study renewal, reporting adverse events or protocol deviations outside the specified timeframe and incorrectly and failure to notify the IRB of any change in financial relationships of any investigators that may result in a conflict of interest that was previously undisclosed.

Serious non-compliance is an action or omission taken by an Investigator that any other reasonable Investigator would have foreseen as compromising the rights and welfare of a research participant. Examples of serious non-compliance include, but are not limited to: deliberate failure to follow the protocol as approved by the IRB, failure to report serious or on-going unanticipated problems involving risks to subjects or others, or failure to correct noted deficiencies as required by the IRB.

Continuing non-compliance is a repeated pattern that indicates the inability or unwillingness of an Investigator to comply with Federal regulations, the Policies and Procedures of the IRB, or the determinations or requirements of the IRB.

It is the responsibility of all investigators and study coordinators engaged in research to report incidents or allegations of non-compliance to the IRB. When the IRB receives written or verbal allegations of non-compliance, complaints from research subjects, or finds instances of non-compliance, the IRB Chair and Program Coordinator will conduct an audit of the research within 48 hours to establish whether non-compliance has occurred. The Chair of the IRB and the IRB Program Coordinator will review the available information to determine whether there is serious or continuing non-compliance, and whether immediate suspension of participant enrollment is necessary to protect the rights and welfare of the participants.

If suspension is not necessary, and there is a determination that the issue was of a non-serious or non-continuing nature, the IRB Chair, IRB Program Coordinator and the Principal Investigator (P.I.) agree to a plan of action, and a written report is sent to the P.I. and filed with the protocol. In all instances of determinations of serious or continuing non-compliance, the

study is suspended, following the IRB policy titled “Suspension and Termination of Protocols”. If the IRB Chair or Program Coordinator are not able to investigate a situation immediately or adequately for any reason, the issue is forwarded to the Senior Vice President of Finance and Chief Financial Officer for action.

If the problem is of a non-serious and non-continuing nature and, in essence, a miscommunication or misunderstanding, a plan for corrective action and its timeframe is agreed upon between the IRB Chair and the P.I. The study is allowed to continue, and a follow-up audit conducted within 30 days to ensure continued compliance.

If the IRB Chair and Program Coordinator determine that an incident indicates serious or continuing non-compliance, following the IRB policy titled “Reporting of the IRB Findings to Federal Agencies”. A written report is sent by the IRB Program Coordinator within 48 hours of the phone call. Following the audit, the IRB Chair will determine the recommended actions. The P.I. is notified in writing of the IRB requirements within 48 hours by the IRB Program Coordinator. Written audit results, which include a summary of the allegation, IRB audit findings, action taken by the Chair or Vice-Chair, and the required response of the investigator, are reviewed by the full IRB at its next convened meeting. Enrollment is suspended until the audit process is complete and the subsequent IRB requirements have been met, as determined by the IRB Chair and IRB Program Coordinator, or by the convened IRB. Such suspensions are reported following the IRB policy titled “Reporting of the IRB Findings to Federal Agencies”.

The process for management of serious or continuing non-compliance by the convened IRB must include notifying current participants when such information might relate to the participants’ willingness to continue to take part in the research. There are several optional actions that may take place, which include, but are not limited to; modification to the protocol, modification of the information disclosed during the consent process, providing additional information to past participants, requiring current participants to re-consent to participate, monitoring the research and the consent process and a referral to other organizational entities.

When Investigators conduct any form of research (exempt, expedited or full board) without IRB approval

Federal regulations and guidelines do not allow for review and post hoc approval of studies that have been conducted involving human participants or identifiable data that can be connected to any living individual.

Investigators are responsible for providing the IRB with sufficient information and related materials about the research (e.g., grant applications, research protocols, sample consent documents) so that the IRB can fulfill its regulatory obligations, including making the required determinations under 45 CFR 46.111. Investigators should follow institutional policies and procedures for IRB review that are required by HHS regulations at 45 CFR 46.103. Investigators must promptly to the IRB proposed changes in a research activity and ensure that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval, except where necessary to eliminate apparent immediate hazards to the human subjects

In these cases the IRB and the Institutional Official will take into consideration the nature, severity and the risk it poses on human subjects and decide on the appropriate corrective action plan that may include but not limited to the following:

1. For data that has already been collected, if the data is intended for publication, the investigator must disclose to the publication editor or at the National Meetings that the data was collected prior to approval from the IRB
2. If they are currently collecting data without prior IRB approval, then they need to submit a protocol and application to the IRB within 7 days and cannot use any of the data collected prior to the approval
3. Re-educate the investigator and their team on Good Clinical Practice (GCP) and Belmont principles
4. They will be audited by the Trinity Health Of New England privacy and compliance officer to ensure that they have patient authorization to collect and store their data.

5. Once the IRB has intervened with a corrective action plan and the investigator is found to have undertaken another study without IRB approval, then the investigator and their team will be placed on probation and will not be allowed to conduct research for a specified time and will be reported to the Office of Human Research Protections (OHRP)

6. The department chair will be notified of the above actions

Verification of Changes From Sources Other Than the Investigator

The IRB will vote on protocols that require verification from sources other than the investigators, and will use auditing as the vehicle to verify that no changes have occurred. The following are examples of protocols that the IRB will monitor by the audit process:

1. Phase I studies on a case by case basis
2. Phase II studies
3. Studies carried out by investigators with a record of non-compliance
4. Protocols that carry significant physical or social risks to the participants
5. Studies in which there is concern about possible material changes occurring without IRB approval
6. Studies that have been revised based upon information provided from Institutional employees, subjects enrolled or any other reliable source
7. Studies in which enrolled subjects express concerns to the IRB

For continuing review of research under expedited procedures, the IRB Chair or member assigned to review determines:

1. Whether the protocol needs verification from sources other than the researchers that no material changes had occurred since previous IRB review.

Suspension and Termination of Protocols

Suspension of IRB approval is defined as a temporary halt in IRB approval of some or all research activities and extends beyond suspension of enrollment. The IRB is authorized to suspend enrollment or terminate the approval of research that is not being conducted in accordance with the IRB's requirements, or that has been associated with unexpected serious harm to subjects (45 CFR 46.113 and 21 CFR 56.113). Suspensions and terminations represent

an action by the IRB to temporarily or permanently withdraw approval for some or all research procedures. The IRB Chair, or in their absence, the Vice-Chair, has the authority to immediately suspend research when such action needs to be taken to eliminate risk of serious harm to subjects before the matter can be reviewed at the next convened meeting of the IRB, at which time the IRB must determine whether to continue, withdraw or modify the suspension. If a research protocol is suspended by someone other than the IRB (i.e., the sponsor), the IRB must be notified immediately by the PI, and the suspension will be reviewed by the convened IRB.

Protocols approved by the IRB can be suspended or terminated:

- At the discretion of the IRB in cases of continued lack of compliance or significant unanticipated adverse events;
- At the recommendation of the DSMB or Safety Officer;
- At the time of full-board review of suspensions, audits, or reapproval requests, if the IRB members determine there is cause.

When a study approval is suspended or terminated by the IRB, the following actions must be taken by the investigator:

- Current participants are notified that the study has been suspended or terminated. When termination or suspension is Investigator-initiated, participants are to be notified by the Investigator. When termination or suspension is IRB-initiated as a result of non-compliance or at the recommendation of the DSMB or Safety Officer, participants will be notified by the IRB.
- Procedures for withdrawal of enrolled participants consider the rights and welfare of participants.
- When follow-up of participants for safety reasons is permitted/required by the IRB, the participants should be so informed.
- When follow-up of participants for safety reasons is permitted/required by the IRB, any adverse events/outcomes should be reported to the IRB and the sponsor.

When study approval is suspended or terminated, the IRB or the person ordering the suspension or termination:

- Considers actions to protect the rights and welfare of currently enrolled participants.
- Considers whether procedures for withdrawal of enrolled participants take into account their rights and welfare (e.g., making arrangements for medical care outside of a research study, transfer to another researcher, and continuation in the research under independent monitoring).
- Considers informing current participants of the termination or suspension.
- Has any adverse events or outcomes reported to the IRB.

For a full description of the process the IRB uses to suspend or terminate previously approved research, please refer to the section entitled “Non-Compliance and Corrective Action”, pages 122-123. Correspondence with investigators regarding suspensions or terminations will include a statement of the reasons for the IRB’s actions, and will be reported promptly to the investigator, appropriate institutional officials and regulatory authorities. Please refer to the section entitled “Reporting of IRB Findings”, page 123-124, for a description of how suspensions and terminations are communicated to the Investigator, Institutional officials, and Federal agencies. This policy applies to all research conducted at this Institution, regardless of the source of funding. Investigators with active protocols who leave the institution are required to either officially close the studies or arrange for transition to another appropriate trained investigator within the institution.

Appeals of IRB Decisions

Investigators may appeal to the IRB, in writing, documenting the reasons for the appeal. These will be addressed to the Chair of the IRB and discussed at a convened meeting. Based on the Investigator’s response, the IRB may approve or disapprove the protocol, or require additional information or changes, in which case voting will be deferred pending receipt of the Investigator’s response. The IRB can vote to allow the IRB Chair to approve the protocol when the IRB requirements have been satisfactorily met, or require full board review at the next convened meeting. The outcomes will be communicated to the investigator in writing by the Chair of the IRB. No Institutional official or other Institutional committee may override the

decisions of the IRB to disapprove a study. However, the Institution may prevent the performance of a study approved by the IRB.

Bringing Forth Concerns

Investigators may bring forth any concerns or suggestions they have regarding the functions of the Institutional Review Board or the protection of human research subjects to the IRB itself, or the Institutional Official appointed by the CEO. Investigators are invited to IRB meetings to present their new protocols, and they may also address concerns and issues directly with IRB members at that time.

Undue Influence of IRB Members

Members of the IRB and the IRB Chair are in the position where they may be subject to undue influence from investigators to provide a favorable decision. If such an incident were to occur, the IRB member should immediately report the incident to the Chair of the IRB or if it involves the Chair this matter should be taken to the signatory of the applicable FWA to discuss the appropriate course of action. Such coercion will not be tolerated and may result in the investigator's loss of IRB privileges. If a member of the IRB is subject to undue influence by the IRB Chair, they should report the incident to the Institutional Official.

REPORTING OF IRB FINDINGS

Correspondence with Investigators

Following full or expedited review of a protocol by the IRB, the Chairman corresponds with the Investigator regarding the decision of the IRB (approval, disapproval and deferral). Letters are sent to Investigators within five working days of a decision. A sample letter of approval is provided in Appendix 7. If the IRB votes to disapprove a research activity, it shall include in its written notification a statement of the reasons for the decision and give the investigator an opportunity to respond in writing and in person at a convened meeting of the IRB. All Investigators are informed of OHRP policies as outlined in the FWA filed with OHRP by providing them with a copy of the FWA document with the application form and periodic mailings. Compliance with IRB, OHRP and FDA regulations and guidelines is expected from Principal and collaborating investigators. In the approval letter, investigators are instructed to inform the office of the IRB, in writing, of all changes in protocols prior to their implementation, and terminations, should they occur prior to the renewal due date.

Reporting of IRB Findings to the Institution

Agendas for IRB meetings are provided to the signatories of the Federal Wide Assurances one week prior to the meeting date. As written notification of IRB decisions to these officers, Minutes from each IRB meeting are emailed to the signatories of the Federal Wide Assurances within 48-72 business hours of the meeting.

These officers will be notified in writing within 5 working days by the Chair of the IRB following documentation of significant lack of compliance by an investigator. Officers will be notified of all incidents reportable to the OHRP and the FDA.

Reporting of IRB Findings to Federal Agencies

The Chairman of the IRB will report to the OHRP changes in IRB membership and the IRB Program Coordinator will report changes in FWA signatory officials.

In the case of any i) unanticipated problems involving risks to subjects or others; ii) serious or continuing non-compliance with this policy or the requirements or determinations of the IRB; or iii) a suspension or termination of previously approved research, the OHRP and, if applicable, the FDA, is notified within 48 hours by telephone by the IRB Chair or the IRB Program Coordinator to inform them of the incident. A written report is sent within 48 hours of the phone call.

The information to be included in incident reports is as follows:

1. Name of the Trinity Health Of New England component (SFHMC, MSRH, JMH, MMC, or SMH and their components)
2. Title of the research project and/or grant proposal in which the problem occurred;
3. Name of the principal investigator on the protocol;
4. Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement);

In addition:

A. For unanticipated problems involving risks to subjects or others:

1. A detailed description of the problem; and
2. Actions the institution is taking or plans to take to address the problem.

B. For serious or continuing noncompliance:

1. A detailed description of the noncompliance; and
2. Actions the institution is taking or plans to take to address the noncompliance.

C. For suspensions and terminations:

1. A detailed description of the reason for the suspension or termination; and
2. The actions the institution is taking or plans to take to address the suspension or termination.

The IRB Chair approves the report. The IRB Program Coordinator sends a copy of the report to the P.I. and study coordinator, the signatory of the FWA, the P.I.'s Department Chair, and members of the IRB, the sponsor or their contract research organization (CRO) (if research is sponsored), other sites as appropriate, OHRP, and the FDA (if research is FDA regulated). The IRB Program Coordinator need not send a copy of the report to Federal agencies if the event has

been reported through other mechanisms, such as reporting by the investigator, sponsor or another organization. The IRB Program Coordinator will ensure that the reporting requirements of this policy are completed within 5 business days of when the convened IRB has completed an evaluation of the event.