



Seton Institutional Review Board

Policies and Procedures Manual

Seton Family of Hospitals
Office of Research Administration
Clinical Education Center at Brackenridge
1400 North IH 35, Suite C3.400
Austin, TX 78701
Phone (512) 324-7991
Fax (512) 324-7792
<http://www.seton.net/research>

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List of Abbreviations and Terms

Abbreviation	Term
AE	Adverse Event
AAHRPP	Association for the Accreditation of Human Research Protection Programs
CFR	Code of Federal Regulations
CIRB	Central Institutional Review Board
CITI	Collaborative Institutional Training Initiative
CRSC	Clinical Research Steering Committee
CV	Curriculum Vitae
DHHS	Department of Human and Health Services
DMC	Data Monitoring Committee
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
EFIC	Exception From Informed Consent
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HDE	Humanitarian Device Exemption
HIPAA	Health Insurance Portability and Accountability Act
HSP	Human Subjects Protections
HUD	Humanitarian Use Device
IDE	Investigational Device Exemption
IND	Investigational New Drug
IO	Institutional Official
IRB	Institutional Review Board
LAR	Legally Authorized Representative
NCI	National Cancer Institute
NHSR	Not Human Subjects Research
NIH	National Institutes of Health
OHRP	Office of Human Research Protections
ORA	Office of Research Administration
PHI	Protected Health Information
PI	Principal Investigator
QA	Quality Assurance
QI	Quality Improvement
SAE	Serious Adverse Event
SIRB	Seton Institutional Review Board
Sr.	Senior
UP	Unanticipated Problem
VA	Veterans Affairs

Section 1: Introduction

1.0 Purpose and Scope of Manual

The IRB documents its written procedures, according to [45 CFR 46.115\(a\)\(6\)](#), [45 CFR 46.103\(b\)\(4\)](#), and [45 CFR 46.103\(b\)\(5\)](#). This manual contains current policies and procedures and will be regularly updated to reflect new standards, regulations, and Seton Family of Hospitals' policy. All research projects involving human participants¹ conducted by physicians, staff (including contractors), residents, students, and volunteers associated with the Seton Family of Hospitals must receive Institutional Review Board (IRB)² approval prior to initiating the research. The IRB reviews human subjects research, including those involving Investigational drugs³ (IND) granted by the FDA and investigational devices. Some studies may also be subject to FDA regulation and oversight; when in doubt contact the Office of Research Administration (ORA). For more information about Federal Policy for the Protection of Human Subjects, refer to [45 CFR Part 46](#) and [21 CFR Part 50 & 56](#). For more information about basic ethical questions in the conduct of research, consult [The Belmont Report](#).

A brief review of these documents is provided here so that investigators may better understand the reasons for ethical review of research with human participants, the primary ethical principles that govern such research, and statutory basis or enactment of these principles. This document also contains information that should be sufficient to allow researchers to submit an acceptable application for the review of a project involving human subjects. Investigators who read this manual will be informed about the National Institute of Health (NIH) rules and Seton Family of Hospitals' requirement of education for all individuals responsible for the design and conduct of research projects with human subjects. Investigators will also be informed about their obligation to obtain an authorization from research participants for the disclosure of protected health information under the Health Insurance Portability and Accountability Act of 1996 (HIPAA), in what circumstances the authorization may be waived, and the process involved in creating de-identified information in compliance with the HIPAA privacy rule.

¹ Seton Family of Hospitals defines "research involving human participants" to include all activities that are "research" and involve "human participants" according to The Common Rule, and to include all activities that are "research" according to FDA regulation. According to The Common Rule, "research" is a systematic investigation, including clinical investigations, research development, testing and evaluation, designed to develop or contribute to generalizable knowledge and "human participants" are living individuals about whom the investigator conducting research obtains a) data through intervention or interaction with the individual or b) identifiable private information (45 CFR 46). According to FDA regulations "research" is any experiment that involves: (1) a drug other than the use of an approved drug in the course of medical practice, (2) a medical device being evaluated for safety or effectiveness, or (3) any article subject to regulation by the Food, Drug, and Cosmetic Act where the results of the research are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit; AND where one or more individuals are either recipients of the article or controls. FDA regulations define a human subject as an individual who is or becomes a subject in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient [21 CFR 50.3(g), 21 CFR 56.102(e)]. A human subject includes an individual on whose specimen a medical device is used [21 CFR 812.3(p)] or a human who participates in an investigation, either as a recipient of the investigational new drug or as a control [21 CFR 312.3].

² "Institutional Review Board" (IRB) is an independent committee comprised of scientific, non-scientific, and non-affiliated members established according to the requirements of federal regulations. The IRB is formally designated by an organization to review research involving humans as participants, to approve the initiation of and conduct periodic review of such research. The term includes, but is not limited to Institutional Review Boards, Investigational Review Boards, Central Review Boards, Independent Review Boards, and Cooperative Research Boards. [45 CFR 46.402(g)] [21 CFR 50.3(i)]

³ "Investigational New Drug" (IND) is an investigational drug or biologic application by which the FDA allows testing in human beings of a substance having an effect in the body. [21 CFR 312, subpart B]

The contents of this document, the description of the information that must accompany an application for the review of a project involving human subjects, the Informed Consent⁴, and Research Proposal templates may be found at: <http://seton.net/research>.

1.1 Applicability

The procedures set forth in this manual are applicable to all persons desiring to use humans (including identifiable private information) as subjects in research and related activities, including research for which investigational devices or drugs are used. Seton requires all research investigators:

1. to be directly affiliated with Seton Family of Hospitals or linked to a principal investigator that is directly affiliated with Seton Family of Hospitals;
2. to ensure all investigators and study personnel (both internal and external to the institution) comply with all relevant:
 - a. (i) IRB determinations,
 - b. (ii) federal and state regulatory requirements, and
 - c. (iii) human participant protection standards; and
3. have the appropriate expertise and training to conduct research at a Seton facility.

The Seton IRB (SIRB) has a complete reciprocity agreement with the University of Texas at Austin IRB and the University of Texas Southwestern IRB. This agreement may be referenced by Federal Wide Assurance (FWA) number 00004937. If a site or investigator requests that an external IRB provide IRB review for a specific protocol, the IRB reviews the appropriateness of such request, utilizing the [Request to Rely on an External IRB](#) form. If approved, the site and the external IRB enter into an [IRB Authorization Agreement](#).

1.2 Mission Statement

The IRB and the Office of Research Administration (ORA) are charged with the following mission:

“To determine and certify that all human subjects research projects (regardless of funding) conform to the regulations and policies regarding the health, welfare, safety, rights, and privileges of human subjects set forth by the Department of Health and Human Services (DHHS) in [45 CFR 46](#) and the Federal Drug Administration (FDA) in [21 CFR 50 and 56](#). These goals include ensuring that each research participant is informed of their rights and are able to give informed consent⁵. Researchers must assure through verified training that the welfare of their research participants is of paramount importance. It is noted that Seton follows ethical standards put forth in [45 CFR 46](#), [21 CFR 50 and 56](#) and relevant state and local regulations and procedures.”

The Seton Family of Hospitals formally grants the IRB the following authorities, relative to the protection of human subjects:

⁴ “Consent/Permission” is the agreement of participant or the parent(s) of or guardian to their, their child’s, or ward’s participation in the research/clinical investigation.

⁵ “Informed Consent” means the agreement to participate in research that is made voluntarily by an individual with legal and mental competence and the requisite decision-making capacity, after disclosure of all material information about the research. Informed Consent means the knowing consent of any individual or his/her legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion. Information conveyed in the informed consent/authorization procedure must include all elements listed in Section 5 of this manual.

1. To approve, require modifications to secure approval, or disapprove all research activities overseen and conducted by the organization;
2. To suspend or terminate approval of research that is not being conducted in accordance with requirements or that has been associated with unexpected serious harm to participants;
3. To observe, or have a third party observe, the consent process;
4. To observe, or have a third party observe, the conduct of the research; and
5. To indicate that officials of the organization may not approve a protocol that has not been approved by the Institutional Review Board.

1.3 Administration of Research Ethics – Federal

The Office for Human Research Protections (OHRP) provides leadership on human research subject protections and implements a program of compliance oversight for Department of Health and Human Services (DHHS) regulations for the protection of human subjects – [45 CFR Part 46](#). OHRP works to support and strengthen the nation’s system for protecting those who volunteer to participate in research that is conducted or supported by agencies of DHHS. To carry out its mission, OHRP has formal agreements with more than 10,000 federally funded universities, hospitals, and other medical and behavioral research institutions in the U.S. and abroad wherein they agree to abide by the human subject protection regulations found in the Code of Federal Regulations ([45 CFR Part 46](#)). OHRP evaluates all written substantive allegations or indications of noncompliance with HHS regulations. The specific institution is notified of the allegation and is asked to investigate the basis for the complaint. The institution then provides a written report of their investigation, along with relevant institutional IRB and research records, to OHRP which determines what, if any, regulatory action needs to be taken.

OHRP provides guidance to IRB members and staff as well as to scientists and research administrators on the complex ethical and regulatory issues relating to human subject protections in medical and behavioral research. The office conducts national educational workshops in partnership with other federal agencies and organizations. OHRP also provides on-site technical assistance to institutions conducting DHHS-sponsored⁶ research.

OHRP provides quality improvement consultation and research ethics training to domestic and foreign institutions involved in international biomedical and behavioral research to help ensure that recognized ethical protections are afforded to persons participating in research conducted in countries outside the United States. OHRP prepares policies and guidance documents as well as interpretations thereof on human subject protections and disseminates this information to the research community. In addition, every institution engaged in human subjects’ research conducted or supported by DHHS must obtain an assurance⁷ of compliance approved by OHRP. At the Seton Family of Hospitals, the criterion for determining whether the institution is engaged in human subjects’ research is through the following decision chart:

1. Determine whether the activity is human subjects research. Stop if not.
2. Determine whether the individual conducting the research is an employee or agent of the organization. Stop if not.
3. Determine whether the organization is engaged in the research using OHRP’s guidance on

⁶ “Sponsor” is an entity who takes responsibility for and initiates research, but who may not conduct the investigation. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct research it has initiated is considered to be a sponsor, and the employees are considered to be investigators. [21 CFR §50.3(k)] [21 CFR §56.102(j)] [21 CFR §312.3]

⁷ “Assurance” is an agreement between an Organization and a federal agency that stipulates that the Organization will comply with regulatory requirements. [45 CFR §46.103]

engagement, "[Engagement of Institutions in Research](#)."

Within DHHS, the Food and Drug Administration (FDA) has oversight over FDA-regulated research (drugs, biologics, medical devices, and foods). [21 CFR Part 50 and 56](#) describe FDA oversight policies. The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. Please contact the ORA with questions about DHHS, OHRP, and FDA policies, jurisdiction, and oversight.

1.4 Applicable State of Texas Laws

[Section 261.101 of the Texas Family Code](#) provides that a person having cause to believe that a child's physical or mental health or welfare has been adversely affected by abuse or neglect by any person shall immediately make a report. The second clause of the statute addresses the reporting obligation of professionals (i.e., those licensed or employed by the state). The third clause waives any confidentiality privilege of an attorney, member of the clergy, medical practitioner, social worker, mental health professional or an employee of a clinic or health care facility that provided reproductive services who becomes aware of abuse or neglect of a child.

[Section 48.051 of the Texas Human Resources Code](#) states that:

- (a) Except as prescribed by Subsection (b), a person having cause to believe that an elderly or disabled person is in the state of abuse, neglect, or exploitation, including a disabled person receiving services as described by Section 48.252, shall report the information required by Subsection (d) immediately to the department.
- (b) If a person has cause to believe that an elderly or disabled person, other than a disabled person receiving services as described by Section 48.252, has been abused, neglected, or exploited in a facility operated, licensed, certified, or registered by a state agency, the person shall report the information to the state agency that operates, licenses, certifies, or registers the facility for investigation by that agency.
- (c) The duty imposed by Subsections (a) and (b) applies without exception to a person whose knowledge concerning possible abuse, neglect, or exploitation is obtained during the scope of the person's employment or whose professional communications are generally confidential, including an attorney, clergy member, medical practitioner, social worker, and mental health professional.
- (d) The report may be made orally or in writing. It shall include:
 - (1) the name, age, and address of the elderly or disabled person;
 - (2) the name and address of any person responsible for the elderly or disabled person's care;
 - (3) the nature and extent of the elderly or disabled person's condition;
 - (4) the basis of the reporter's knowledge; and
 - (5) any other relevant information.
- (e) If a person who makes a report under this section chooses to give self-identifying information, the caseworker who investigates the report shall contact the person if necessary to obtain any additional information required to assist the person who is the subject of the report.

Under federal law a 'Legally Authorized Representative' means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to that subject's participation in the procedures involved in the research [[45 CFR 46.402\(c\)](#) and [21 CFR 50.3\(l\)](#)]. The individuals authorized under Texas law to consent on behalf of a prospective participant to participation in

the procedures involved in the research are the parent or legal guardian⁸ if the patient is a child, a legal guardian if the individual has been adjudicated incapacitated⁹ to manage the individual's personal affairs, an agent of the individual authorized under a durable power of attorney for health care, an attorney ad litem appointed for an individual, a guardian ad litem appointed for the individual, or an attorney retained by the individual [[Section 241.151 Texas Health and Safety Code](#)].

Under federal law, "children" are persons who have not attained the legal age for consent to treatments or procedures involved in research or clinical investigations, under the applicable law of the jurisdiction in which the research or clinical investigation will occur. In Texas, individuals under the age of 18 are children unless emancipated by filing a petition and meeting the statutory requirements, or they have been adjudicated to be an adult for the purpose of criminal prosecution.

If research takes place outside the state of Texas, the IRB will consult with legal counsel; legal counsel provides guidance and interpretation to the IRB.

1.5 Ethical and Religious Directives for Catholic Health Care Services

The purpose of the [Ethical and Religious Directives](#) is twofold: first, to reaffirm the ethical standards of behavior in health care that flow from the Church's teaching about the dignity of the human person; second, to provide authoritative guidance on certain moral issues that face Catholic health care today.

All research within the Seton Family of Hospitals must follow the ethical standards set forth in the Ethical and Religious Directives. If there are any questions regarding the Directives, please contact the ORA.

1.6 Administration of Research Ethics – Seton Family of Hospitals

The Senior Vice President of Medical Affairs, the Institutional Official (IO), is responsible for the administration and oversight of research ethics at the Seton Family of Hospitals. This includes the Office of Research Administration (ORA), which oversees the functioning of the Institutional Review Board (IRB) and provides the IRB administrative support. Supervisors periodically evaluate administrative support staff regarding their knowledge and interpretation of relevant policies and procedures to human subjects' research protection.

For any questions about the rules or procedures for ethical review or the applicability of the information in this manual, contact the ORA at:

Office of Research Administration
Clinical Education Center at Brackenridge
1400 North IH-35, Suite C3.400
Austin, Texas 78701
Phone: 512-324-7991
Fax: 512-324-7792
Website: www.seton.net/research

⁸ Pursuant to Section 601 of the Texas Probate Code, a "guardian" means a person who is appointed guardian of the person and/or the estate of an incapacitated person under a court order issued pursuant to Section 693 of the Texas Probate Code.

⁹ Incapacitated persons include "minors", that is, persons under the age of 18 years and who have never been married or who have not had the disablements of a minor removed for general purposes; and adult individuals, who, because of a physical or mental condition, is substantially unable to provide food, clothing, or shelter for themselves, or to care for their own physical health, or to manage their own financial affairs.

1.7 Designation of the Institutional Review Board

The Seton Family of Hospitals has one IRB responsible for conducting initial and continuing reviews¹⁰ and providing oversight for all research activities involving the use of human subjects performed within the institution or at any location under the purview of the Seton Family of Hospitals. The IRB will conduct initial and continuing reviews, as well as any other applicable review, of research activities according to Sections 6 and 7 of this manual. All review procedures will meet or exceed the requirements set forth in [45 CFR 46](#) and [21 CFR 50 and 56](#).

1.8 The Institutional Review Board

The IRB is composed of regular voting members and alternate voting members. The IRB may use, as necessary, non-voting members and consultant reviewers' considerations and discussions. The Common Rule, FDA regulations, and the Seton Family of Hospitals' FWA require that the IRB have at least 5 regular voting members with sufficient qualifications¹¹ to review the range of research activities commonly conducted by the institution. At least one member on the IRB must have primarily scientific concerns, one must have primarily nonscientific concerns, and one must be unaffiliated with the Seton Family of Hospitals, [[45 CFR 46.107](#); [21 CFR 50](#) and [56.107](#)]. The Seton IRB maintains a roster of more than the minimum required number of members to ensure adequate and efficient review.

The IRB membership reflects expertise in both scientific and non-scientific fields. Qualifications of non-scientific members include members with experience in the community and non-scientific fields either through their employment or service activities but do not have educational preparation as a scientist or in a scientific field. Examples of acceptable backgrounds for non-scientific members include theology, law/jurisprudence, business, education, ethics, counseling, and arts-based preparation. Community members of the IRB will be knowledgeable about the local community and willing to discuss issues and research from that perspective. They are chosen from the greater Austin area. Neither they, nor their immediate families, may have an affiliation with the Seton Family of Hospitals. Candidates for these positions include, but are not limited to: clergy, lawyers, teachers, state employees, and businesspersons. Qualifications of scientific members include backgrounds in a science-based field (e.g., biology, epidemiology, pharmacology, psychology, nursing, or medicine). The scientific members will be selected to represent diverse disciplines and experience with the vulnerable populations that may be included in research protocols at Seton institutions (i.e., children, pregnant women, neonates, fetuses, mentally incapacitated persons, prisoners, Seton staff).

At times, the IRB may not have the necessary expertise to judge the scientific soundness of a research protocol and may be unable to make a fair and accurate determination of the protocol's risks-benefits ratio. For these protocols, the IRB may call upon ad hoc consultations for assistance in review for scientific merit (See Section 2.7).

¹⁰ "Continuing Review" is the periodic review of a research study by an IRB to evaluate whether the study continues to meet organizational and regulatory requirements. Federal regulations stipulate that continuing review should be conducted at intervals appropriate to the level of risk involved in the study, and not less than once per year. [45 CFR §46.109(e)] [21 CFR §56.109(f)].

¹¹ Qualifications of SIRB Members: The composition of the SIRB will be reviewed at a minimum on an annual basis by the Sr. Director of the Office of Research Administration, SIRB Chair, and Institutional Official to ensure that the Board has adequate representation of diverse disciplines. SIRB members are selected with varying backgrounds of expertise, experience, and diversity to promote complete and adequate review of research activities commonly conducted at the Seton Family of Hospitals.

Annually, the IO provides feedback to IRB members in a letter acknowledging service. Upon appointment and again at time of annual reappointment, each IRB member is queried to determine roster information such as affiliation status, relationship of the member to the organization, indications of experience, and other relevant information. The appointment period for each IRB member runs from January through December of each calendar year.

It is highly encouraged that each regular voting member of the IRB has an appointed alternate member from his or her department or another similar discipline. IRB members are asked to identify their potential alternates although their respective departments or a department director may nominate individuals. However, final appointment remains at the discretion of the IO. Alternate IRB membership requirements are the same as regular voting membership and alternates are evaluated by the same process and criterion. The IRB roster lists the alternate with the primary IRB member they represent; and the alternate member may serve in his or her place. Alternate members may be called upon to serve when regular members are absent from a meeting, but can be available even in the presence of their regular member to contribute to discussions. Alternate members will have voting rights and be counted in quorum only when they replace their respective regular member. When an alternate indicates that they will attend an IRB meeting – including when they substitute for their designated primary member –, they are sent, for advance review, the same IRB materials that the primary members received. These materials are available in electronic formats.

Additional staff (i.e., from legal services, HIPAA compliance, etc.) at the Seton Family of Hospitals may serve as ex-officio, non-voting members of the IRB should the IO, Sr. Director of the ORA, or IRB Chair decide that such persons would be of assistance to the IRB in conducting its duties. Ex-officio, non-voting members are expected to adhere to the same conflict of interest standards and documentation requirements as are regular IRB member and alternates. However, ex officio members may not vote on any IRB action or determination and do not count towards quorum, but can participate in discussions and deliberations. The IO, IRB Chair, or Sr. Director of the ORA, may appoint a non-voting member who will serve on the Board only as long as requested.

Generally, the IRB will have a Chair and a minimum of one Vice Chair. The Chair and Vice Chair will typically be filled by staff of the Seton Family of Hospitals, knowledgeable in human subject research, including the federal and state regulations, Seton Family of Hospitals policies, and ethics relevant to such research. The IO annually appoints the Chair and Vice Chair; however, subject to the discretion of the IO this appointment may extend beyond one year. Whenever the Chair is not available, the Vice Chair will assume the responsibilities of the Chair during the period of his or her absence.

As membership changes are made, the IRB Coordinator(s) will report IRB membership to the Office of Human Research Protections (OHRP).

1.9 Evaluation of the SIRB

The Sr. Director of the ORA, the IRB Chair, and IRB support staff annually review the SIRB; including IRB members, IRB leadership, IRB member feedback, and any input from outside the IRB (see Section 2.8) and provide recommendation(s) to the IO regarding the recruitment, retention, or dismissal of members. This review includes examination of attendance, specialty, expertise, education, affiliation, and diversity. Thus, the membership and composition of the IRB is annually and periodically reviewed and adjusted to meet regulatory and organizational requirements. This review also includes an evaluation of the performance of individual IRB members. Additionally, the IO annually evaluates the performance of the IRB Chair.

The IO formally appoints IRB members, including regular IRB members and alternate members. The IO considers the following factors in the selection process: experience, expertise, racial, cultural, and gender diversity, and community involvement, in addition to feedback from the Sr. Director of the ORA and the IRB Chair. This ensures the IRB will be able to ascertain the acceptability of proposed research in terms of institutional commitments, regulations, applicable laws, and standards of professional conduct and practice [[45 CFR 46.107](#) and [21 CFR 50 and 56](#)].

Section 2: The Institutional Review Board

2.0 General IRB Policies

The governing regulations for the Seton Institutional Review Board (SIRB) are [45 CFR Part 46](#), [21 CFR Parts 50, 312](#), and [12](#) and [Health Insurance Portability and Accountability Act \(HIPAA\)](#). Seton Family of Hospitals' Federal Wide Assurance (FWA) 00004937 with Office for Human Research Protections (OHRP) specifies that the institution will follow [45 CFR 46](#) and [21 CFR 50 and 56](#) for all federally funded research.

2.0.1 Functions and Responsibilities

Safeguarding the rights and welfare of subjects at risk in any research activity, whether financially supported or not, and irrespective of the source of any supporting funds, is primarily the responsibility of the institution. In order to provide for the adequate discharge of the institutional responsibility, no research activity involving human subjects may be undertaken by any staff, faculty, clinician, employee, resident, or student at the Seton Family of Hospitals unless an Institutional Review Board (IRB) has reviewed and approved the research prior to commencing the research activity.

1. The review will determine whether the subjects will be placed at risk and, if risk is involved, that:
 - a. Risks to participants are minimized by using procedures which are consistent with sound research design and do not unnecessarily expose participants to risk.
 - b. Risks to participants are minimized whenever appropriate, by using procedures already being performed on the participants for diagnostic or treatment purposes.
 - c. Risks to participants are reasonable, in relation to anticipated benefits, if any, to participants, and the importance of the knowledge that may reasonably be expected to result.
 - d. Selection of participants is equitable.
 - e. Informed consent will be sought from each prospective participant or the participant's legally authorized representative (LAR), in accordance with, and to the extent required by the regulations; unless a waiver or alteration of informed consent requirements are apply.
 - f. Informed consent will be appropriately documented, in accordance with, and to the extent required by the regulations, unless a waiver or alteration of informed consent requirements are apply.
 - g. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of the participants.
 - h. When appropriate, there are adequate provisions to protect the privacy of participants.
 - i. When appropriate, there are adequate provisions to maintain the confidentiality of data.
 - j. When some or all of the participants 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 have been included in the study to protect the rights and welfare of these participants.
 - k. The conduct of the activity will be reviewed at intervals determined by the IRB, but not less than annually.
2. The determination of when an individual is at risk is a matter of the application of common sense and sound professional judgment as it relates to the circumstances of the research activity in question.
 - a. The IRB will carefully weigh the relative risks and benefits of the research procedures to

be applied to the subject.

- i. Research activities designed to yield fruitful results for the benefit of individual subjects or society in general may incur risks to the subjects provided such risks are outweighed by the benefit derived from the activity.
 - ii. The degree of risk involved in any study activity should never exceed the humanitarian importance of the problems to be solved by the activity. Likewise, compensation to volunteers should never be such as to constitute an undue inducement to the subject.
 - iii. There is a wide range of medical, social, and behavioral research projects and activities in which no immediate physical risk to the subject is involved (e.g. those utilizing personality inventories, interviews, questionnaires, or the use of observation, photographs, taped records, or stored data); however, some of these procedures may involve varying degrees of discomfort, harassment, or invasion of privacy.
- b. There may also be projects that involve tissues, body fluids, and other materials obtained from human subjects. The use of these materials, obviously involves no element of physical risk to the subject; however, their use for research, training, and service purposes may present psychological, sociological, or legal risks to the subjects. In these instances, application of the policy requires IRB review to determine that the circumstances under which the materials are to be procured and, if the subject is deemed to be at risk, that adequate and appropriate consent will be obtained for the use of these materials for research purposes.
 - c. Some studies depend upon stored data or information that was often obtained for quite different purposes. Here, the IRB will determine whether the use of these materials is within the scope of the original consent, or whether consent should be waived or obtained.

The qualifications of the PI should be considered when reviewing protocols. The investigator's professional development should be taken into account and related to the degree of protocol complexity and risk to human subjects. The IRB may require less experienced research investigators to be sponsored by seasoned researchers. In the case of student PIs, the review includes an assessment of the faculty sponsor/advisor's qualifications to serve as a mentor/sponsor to the student. Proposals that require skills beyond those held by the PI should be modified to meet the investigator's skills, have additional qualified personnel added, or be disapproved.

Compliance with this policy or the procedures set forth herein will in no way render inapplicable pertinent laws of the State of Texas, any local law which may bear upon the proposed activity or the Rules and Regulations of the Seton Family of Hospitals.

2.0.2 Confidentiality of the Review Process

During the review of a research activity, materials provided to the IRB and the ORA shall be considered privileged information and the IRB and ORA shall assure the confidentiality of the information and data contained therein. This applies to all staff of the ORA as well as any consultants or observers of the IRB.

2.0.3 External IRB Use

Seton Institutional Review Board (SIRB) may rely on an external IRB, meaning the IRB of another institution or organization, or an independent (central/commercial) IRB, for review and approval of human

research if such reliance benefits the Seton Family of Hospitals, its investigators, and/or its research participants. Examples of when such reliance may be considered include:

1. The research is a major multi-center clinical trial and the Seton PI is not the overall PI of the trial,
2. The research is a multi-center research consortium project,
3. The research is a multi-center clinical trial with a central IRB,
4. The research is a Phase III or IV clinical trial utilizing a central IRB,
5. The research is an industry-initiated protocol,
6. The research is an industry-funded clinical trial, Seton is engaged in the human research solely because it is receiving federal funds (employees or agents of the institution do not interact or intervene with subjects, gather or possess private identifiable information about subjects, nor obtain consent of the subjects), or
7. The PI is a student utilizing Seton Family of Hospitals data for the research project.

The following are examples of research that are ineligible for use of an external IRB:

1. Phase I Clinical Trials
2. Clinical Trials involving the following vulnerable populations: prisoners, HIV patients, fetuses, pregnant women, the mentally incapacitated, or other unidentified vulnerable population that is deemed too high risk for use of an external IRB
3. Exception from Informed Consent (EFIC) Trials
4. Humanitarian Use Device (HUD) Trials
5. Investigational Device Exemption (IDE) Trials of which the PI is the primary holder of the IDE

SIRB will apply the following criteria in selecting an external IRB that qualifies to conduct the review of the Seton Family of Hospitals protocols:

1. The external IRB is currently registered with OHRP/FDA.
2. The external IRB is in good standing with OHRP/FDA (no recent warning letters, no open investigations).
3. For commercial IRBs: the commercial IRB is AAHRPP-accredited
4. For non-commercial IRBs: the IRB is AAHRPP-accredited or determined as part of the administrative review to meet Seton Family of Hospital standards
5. The external IRB is located within the U.S.

In accordance with OHRP Guidance, when SIRB relies on an external IRB for review and approval of human research, the relationship is documented with a signed, executed IRB Authorization Agreement. Note that on [June 20, 2011](#), OHRP announced: "*The revised FWA form replaces a prior requirement that all IRBs (both internal and external IRBs) relied upon by the institution be specifically designated with a requirement that only internal IRBs be specifically designated or that, if an institution does not have an internal IRB, only one external IRB be specifically designated. All IRBs must be registered with OHRP before they can be designated on an OHRP-approved FWA.*" Therefore, the external IRB does not need to be specifically designated on the relying institution's (Seton Family of Hospital's) FWA.

Responsibilities of the PI:

1. Maintain a regulatory binder with all IRB and study related documentation.
2. Execute the research plan as described in protocol, including obtaining informed consent from all subjects as deemed appropriate by the IRB.

3. Conduct this research in accordance with the policies and procedures of Seton Family of Hospitals and the IRB which has reviewed this research.
4. Comply with applicable federal, international, state, and local laws, regulations, and policies that may provide additional protection for human subjects participating in research conducted under this application.
5. Report immediately to the IRB any unanticipated problems involving risks to subjects or others in research covered under this protocol.
6. When responsible for enrolling subjects, obtain, document, and maintain records of informed consent for each subject or each subject's legally authorized representative, as required under HHS regulations, 45 CFR 46, and as stipulated by the IRB.
7. Report to sponsors and agencies as required.
8. Maintain records of research, including consent documents, for a minimum of three (3) years beyond the termination of the study or, if longer, as specified by the funding agency/sponsor of the project.

Failure to comply with any of the above regulations may result in closure of the study by this institution.

2.0.4 Research Determinations

Investigators seeking guidance regarding whether an activity is human subjects research should consult the ORA. Investigators seeking determination about whether an activity is human subjects' research should refer to the quality improvement links on the ORA website. This information can help with the initial determination of whether the proposed activity is considered human subjects research or quality improvement; and whether IRB review and approval is required.

If research involves the use of a food, biologic, nutritional, or food supplement that might fit the FDA definition of a 'drug,' ORA staff will review this definition in the Federal Food, Drug, and Cosmetic Act [Section 321\(g\)\(1\)](#) to determine whether the research involves use of a drug. If the research involves a drug, ORA staff will consult the FDA regulations [21 CFR 312.2\(b\)](#) to determine whether the drug is exempt from the requirement for an IND. If an IND is required, the IRB will not review the research and ORA staff will return the protocol to the investigator with a written explanation.

If research involves the use of a device that might fit the FDA definition of a 'device,' ORA staff will review this definition in the Federal Food, Drug, and Cosmetic Act Section 201(h) to determine whether the research involves the use of a device. If the research involves the use of a device, ORA staff will consult the FDA regulations [21 CFR 812.2\(c\)](#) to determine whether the device is exempt from the requirement for an IDE. If an IDE is not required, the protocol may be reviewed by the IRB. If an IDE is required, ORA staff will evaluate whether the sponsor or investigator has claimed that the device is not significant risk, not banned, and the research meets the requirements of [21 CFR 812.2\(b\)](#). If not, the IRB will not review the research and the ORA staff will return the protocol to the investigator with a written explanation. Otherwise, the IRB will review the protocol and consider whether the device is not significant risk, using the [Investigational Device Exemption Checklist](#).

If an investigator or sponsor claims a device is not significant risk, then the IRB will review the research involving the investigational device at a convened meeting. The IRB will determine whether the device is not significant risk by reviewing the criteria in [21 CFR 812.3\(m\)](#). If the IRB determines that the device is not significant risk, it will document that determination in the [Primary Reviewer Checklist](#) and it will be documented in the minutes along with the IRB's rationale for the decision. Otherwise, the IRB will disapprove the research, and notify the investigator, and, sponsor, if applicable.

2.0.5 Undue Influence of IRB members or ORA Staff

The IRB acts autonomously and considers research protocols with the ultimate mission of protection of the human subjects. While approval of research from other departments, department heads, or committees within the Seton Family of Hospitals may be required per institutional policy, the IRB's decision to approve, conditionally approve, table, or disapprove a submission is made independently and is not influenced by rank, prestige, potential funding, or other benefit that may accrue to the institution.

In cases in which an IRB member or an ORA staff person experiences either direct or indirect undue influence or coercion to make a ruling for a specific research study or investigator, the following process should be used:

1. The IRB member or ORA staff person is asked to document the issues related to the case in writing to both the Sr. Director of the ORA and the IO, in order to open a formal report.
2. The IO will formally review the information and may convene a meeting and/or otherwise obtain additional information, as necessary.
3. The Sr. Director of the ORA will subsequently inform the IRB of the findings.

The IO has the authority to take corrective action in consultation with the IRB.

2.0.6 Suspension & Termination

Suspension means a temporary withdrawal of approval of some or all research, or a permanent withdrawal of approval of some research activities. A suspended protocol requires continuing review. Termination means a permanent withdrawal of approval of all research activities. A terminated protocol does not require continuing review. The IRB has the authority to suspend or terminate approval of a research protocol that has been determined to not be conducted according to the Seton Family of Hospitals' human subjects' research policies and procedures, or in cases in which there has been unexpected, increased serious harm to participants.

While the IRB Chair and Sr. Director of the ORA have the right to suspend a study that poses an immediate increased or undue risk to participants, generally, suspensions will be determined by a vote of the full IRB. Suspensions or terminations ordered by the Chair of the IRB or Sr. Director of the ORA must be placed on the agenda of the next IRB meeting for consideration, continuation, or reversal of the suspension. Should a study be suspended or terminated so that interventions or interactions with current participants will stop or change, the IRB will communicate to the PI in its letter that the PI must inform current participants that the study has been suspended or terminated along with the reasons for such suspension or termination. The PI-Subject letter must be submitted to the full IRB for formal approval prior to use. Before suspending or terminating research, the person or committee ordering suspension or termination will consider whether the action might adversely affect the rights or welfare of current participants. In such cases, the IRB will require explicit stipulations for participant withdrawal. The IRB will consider whether follow-up of participants for safety reasons is necessary and if so, the IRB will require that the PI notify participants of this and require the PI to continue to report unanticipated problems. Such information must be formally submitted to the IRB for their review and approval.

The written report of the IRB's suspension or termination of approval will be written by the ORA for review and approval by the full IRB, unless the suspension or termination is enacted by the Chair or Director as described above. The Chair and the Sr. Director of the ORA will sign the report.

Information to be included in the written report include level of study risk, category of review, a summary of the events, previous non-compliance history for PI, Co-I, and/or faculty Sponsor, how event was reported to the IRB, steps (if any) that PI has taken to rectify situation, reasons for IRB suspension or termination, findings of organization and/or IRB, actions taken by the IRB, and future plans. The report will be distributed according to the Reporting Policy detailed in section 2.0.7 below.

2.0.7 Reporting

The IRB enacts the reporting policy when one or more of the following occurs:

1. The IRB determines an event to be an unanticipated problem that represents a significant risk to participants or others; or
2. The IRB makes a determination of serious non-compliance with the federal regulations, Seton Family of Hospitals policies and procedures, and/or IRB determinations;
3. The IRB makes a determination of serious and continuing non-compliance with the federal regulations, Seton Family of Hospitals policies and procedures, and/or IRB determinations; or
4. The IRB suspends or terminates a previously approved research protocol.

The ORA will prepare a report containing background information on the research activity; the event or unanticipated problem in question; the outcomes of the event; any subsequent actions taken by the PI, ORA, or IRB; the personnel involved with the event; the corresponding dates of the event; and/or any additional pertinent information needed. Reports will be reviewed and approved by the Seton IRB Chair. The ORA will ensure that the appropriate reporting steps are completed promptly.

The report is delivered to the PI or project leader and a copy is provided to the following individuals/groups, as deemed necessary by the ORA/IRB:

1. IO;
2. Seton Director of Legal and Litigation;
3. Chair of the PI's Department;
4. IRB Chair;
5. Co-Investigators;
6. Faculty Advisor ;
7. ORA Study File;
8. Director of Sponsored Projects;
9. Sr. Director of ORA;
10. Chair of the Clinical Research Steering Committee (CRSC);
11. Any federal department that has oversight due to funding, conduct, or assurance, including but not limited to, OHRP, NIH, FDA, etc. Note: OHRP is likely to learn of the event before completion of a decision as to whether the event is reportable, the Senior Director of the ORA and IRB Chair will provide OHRP with a preliminary report that describes the situation, indicates the current review of the event by the Board and a time frame for a final, follow-up report;
12. The complainant (when necessary);
13. And any other leadership that the ORA and/or IRB deems necessary.

2.0.8 IRB Resources

The ORA provides primary administrative support to the SIRB and maintains an annual budget containing funding for operating expenses, staff salaries, community IRB member reimbursements, and educational

materials for IRB members. Each year the Sr. Director of the ORA and IO meet to review the current resources and to consider time, space, and staffing needs to determine if a formal budget request should be submitted via the Seton Family of Hospitals normal budgeting processes.

2.1 Clinical Trials Registration

[ClinicalTrials.gov](https://clinicaltrials.gov), a service of the National Institutes of Health (NIH), was developed by the National Library of Medicine (NLM) in collaboration with the Food and Drug Administration (FDA). Its purpose is to “link patients to medical research” by providing information to the general public about clinical research for a range of diseases and conditions. ClinicalTrials.gov encourages registration of all clinical trials with the goal of establishing a comprehensive registry, not only for patients currently looking to participate in ongoing trials, but for patients, researchers, and editors who want to know what interventions have been studied in the past (e.g., for systematic reviews). In line with the FDA Amendments Act of 2007 ([FDAAA Section 801](#) or [U.S. Public Law 110-85](#)), the Seton IRB also encourages and will require registration of applicable trials. Per the U.S. Public Law mentioned above, registration must occur before 21 days after enrollment. The Seton ORA or IRB may require proof of registration as a contingency of the IRB submission being deemed “viable” and ready for IRB review or as a contingency of final IRB approval, respectively.

Further, investigators or sponsors should register clinical trials in the Protocol Registration System (PRS) of ClinicalTrials.gov to comply with the [International Committee of Medical Journal Editors \(ICMJE\) Initiative](#), which requires prior entry of clinical trials in a public registry as a condition for publication. PRS also accepts registration for any IRB-approved trial that conforms to applicable regulations of the appropriate National Health authorities, including interventional and observational trials.

As mentioned before, the FDA Amendments Act of 2007 ([FDAAA Section 801](#) or [U.S. Public Law 110-85](#)) requires a “responsible party” (i.e., the sponsor or designated PI) to register and report results of “applicable clinical trials” involving drugs, biologics, or devices that are subject to FDA regulations. “Applicable clinical trials” generally include interventional studies (with one or more arms) of drugs, biological products, or devices that are subject to FDA regulation, meaning that the trial has one or more sites in the U.S, involves a drug, biologic, or device that is manufactured in the US (or its territories), or is conducted under an investigational new drug application (IND). To add to this definition, the ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. (Note: for more information on ‘applicable clinical trials,’ see [PRS and U.S. Public Law 110-85](#).)

In most cases, the sponsor of the trial will be the ‘responsible party’ for registering the trial. However, in some cases, as outlined below, FDAAA allows the sponsor to delegate all registration and reporting responsibilities to the Principal Investigator (PI).

A PI can be designated by the sponsor as the ‘responsible party’ for registering a clinical trial at ClinicalTrials.gov when:

1. The trial is investigator-initiated;
2. The investigator has access to and control over the data from the clinical trial; or
3. The investigator has the right to publish the results of the clinical trial.

If a PI is responsible for registration, he/she may designate an individual (PRS User) to register the trial(s) and complete registration information by following the steps outlined below to register the clinical trial with the Seton Family of Hospitals. It is ultimately the responsibility of the PI to assure that registration occurs and that the information entered is accurate. The PRS User is also responsible for reviewing the trial information on a periodic basis (typically every six months) and making any needed changes to the registry. Responsible parties are required to post lay summaries of the study protocol and the study results, as well as a description of the quality assurance procedures used throughout the trial.

Follow the general steps below to register your clinical trial and report results:

1. Contact the Seton Institutional Review Board (SIRB) staff in the Office of Research Administration (ORA) at (512) 324-7991. The Director of Sponsored Projects and Clinical Trials as well as SIRB Staff serve as the Protocol Registration System (PRS) Administrators for Seton Family of Hospitals.
2. Request account setup from the SIRB staff in the ORA, and provide full name of trial PI, phone number, and email address.
3. You will receive a user log in name and temporary password via email with instructions for registering a study from www.ClinicalTrials.gov.
4. Access the PRS website: <http://register.clinicaltrials.gov>.
5. The Seton "Organization Name" is: SetonFH.
6. Browse the Main Menu page and follow the instructions for changing the temporary password.
7. View the "Quick Start Guide." All the features required to enter data about a trial are available through the "Standard Functions" menu.
8. Go to Main Menu > Protocol Records > Create, then follow the prompts for creating your registration. As the PI or designee, you are responsible for entering your trial information, ensuring that it is correct, and updating the registry in a timely manner and as required by law.
9. Complete the ClinicalTrials.gov data elements, providing as much accurate, up-to-date information as possible. Submit the completed registration.
10. After you enter the data, a SIRB staff member will review the record before it is released for publication on the ClinicalTrials.gov site.
11. Following system validation and quality assurance review, you can view a record, including its unique identifier (NCT number), at ClinicalTrials.gov within 2 to 5 business days after it is released.
12. Once your record has a NCT number, you will be able to modify it and add results. For more information about registering a clinical trial at ClinicalTrials.gov, see the FAQs at <http://prsinfo.ClinicalTrials.gov> or send e-mail to register@ClinicalTrials.gov.

Per federal mandate, the ClinicalTrials.gov study identification number should be listed in the study's Informed Consent Form (if applicable), along with the following information:

"A description of this clinical trial will be available on <http://www.clinicaltrials.gov>, as required by U.S. law. This web site will not include information that can identify you. At the most, this website will include a summary of the results. You can search the web site at any time. The number used to identify this study is: *[insert clinicaltrials.gov identifier number here]*."

2.2 IRB Meetings

The SIRB holds one regularly scheduled meeting per month, which is predetermined and scheduled in a conference room as determined by the Clinical Education Center at Brackenridge's conference room schedule. These regularly scheduled Full Board meeting dates, along with each of their corresponding submission deadlines, are posted on the ORA website via the [SIRB Meeting Schedule](#). The SIRB also holds a tentative, second monthly meeting only if all Full Board action items are not reviewed and voted on during the regular meeting. Otherwise, the second meeting is not convened and members are notified of the cancellation.

The Meeting Agenda and agenda items are made available to the IRB members approximately one week prior to each scheduled meeting date. The agenda indicates the date, time, and place of the meeting. All IRB members scheduled to attend the meeting are expected to review all materials in sufficient depth to discuss the information at the convened meeting. Primary Reviewers are encouraged to invite investigators to attend the meeting at which their protocol is to be reviewed, should the reviewer feel this would facilitate a better discussion of the study.

Full Board research protocols (all protocols other than exempt or expedited) will be reviewed at fully convened meetings of the IRB at which quorum has been established and includes at least one non-scientific member. For example, if the SIRB roster contains 13 total regular members, at least 7 members must be present, one of whom must be a nonscientific member. A member abstaining from a vote is still counted toward the quorum. For a research protocol to be approved, it must receive the approval of a majority of those members present and voting on the research protocol at the convened meeting. If quorum fails during a meeting; such as, due to a lack of a majority of IRB members being present or an absence of a nonscientific member, including members absent due to a conflicting interest (See Section 3.7), the IRB will not take further actions or votes until the quorum is restored.

Primary and Secondary Reviewers:

Selection: Qualified IRB staff will assign each protocol to a primary and secondary reviewer from the members of the IRB, with a copy provided to all IRB members. Assignment to primary and secondary reviewers shall be made for all new protocols (i.e., initial submissions) that require Full Board Review. Assignment to primary and secondary reviewers shall be made based on scientific and scholarly expertise of reviewers; any vulnerable populations involved in the research and the experience of the reviewers with those populations; and workload. At least one reviewer who has appropriate scientific or scholarly expertise and/or experience with any vulnerable population involved shall be assigned to the review. If the IRB staff cannot identify an IRB member who has the necessary experience, then the IRB Chair or Sr. Director shall solicit consultants from Seton Healthcare or the community with the necessary expertise to assist. Each protocol must be reviewed by at least one voting IRB member.

Written Review: The primary and secondary reviewers will provide written reviews (in the online IRB submission system) of each protocol assigned to them, using the IRB reviewer checklists to guide their review. Each reviewer's comments should be submitted in the online system at least one business day prior to the scheduled meeting. Written comments cannot substitute for a fully convened IRB meeting.

Presentation: During the IRB meeting, the primary reviewer will be responsible for presenting the protocol to the IRB including an overview of the goals, design, study procedures, safety procedures and qualifications of the Investigators and shall lead the IRB members through the completion of the

regulatory criteria for approval, as set forth in the IRB Review Checklist appropriate to the type of review. The primary reviewer also shall present any review comments from any secondary reviewers.

Recommendations: The primary reviewer shall make a recommendation to the Chair/Vice-Chair regarding the action to be taken with regard to the protocol (e.g., Approval, Approval with Stipulations, Tabled (Deferral), or Disapproval), as well as the designation of any special review category (e.g., Prisoner, Pregnant Women, Minors, Ward of State); risk status (Minimal Risk or Greater than Minimal Risk) and corresponding time for the next continuing review to occur; risk of device (as applicable); and grant of a partial or complete Waiver of HIPAA Authorization (as applicable).

If the IRB is reviewing a research protocol involving children as human subjects, then the primary reviewer's review shall include assigning a pediatrics designation, i.e., making a recommendation as to the appropriate risk/benefit category for the research under HHS Regulations 45 CFR §§ 46.403-.407 and/or FDA Regulations 21 CFR §§ 50.51-.54.

Absence of Primary Reviewer at a Meeting: If the primary reviewer is not present at the IRB meeting, the secondary reviewer shall assume his/her duties. If neither the primary nor secondary reviewers are present at the IRB Committee and no other IRB member present has conducted a thorough review, the research protocol shall be Tabled and rescheduled for presentation at the next meeting of the IRB, or alternatively provided to other reviewers for review.

IRB Committee Action: After hearing primary and secondary reviewers, the IRB shall discuss the protocol and entertain a motion and vote on the action that should be taken with regard to the protocol in accordance with the policies outlined in Section 2.3. The IRB office shall notify the PI in writing of the action of the Full Board with regard to the PI's protocol.

In cases where research activities were initially approved under expedited procedures, the decisions reached at the convened meeting shall supersede any decisions made through the Expedited review. All convened IRB meetings shall be conducted under and pursuant to [Robert's Rules of Order](#).

At the discretion of the Chair and/or primary or secondary reviewer, the PI, and/or his/her designees may be invited to attend the meeting for the purpose of additional clarification or discussion. The PI(s) and/or his/her designee(s) is(are) required to leave the meeting for subsequent discussion and voting.

Meetings of the IRB are closed-door meetings, the proceedings are considered confidential. No person attending an IRB meeting (e.g. IRB members, alternate members, ex officio members, ORA staff, or guests) may disclose any information about studies including (but not limited to) contents of files, details of discussions, and the attribution of comments to specific committee members. All persons who attend IRB meetings must sign confidentiality agreements when attending the meetings.

Visitors may be permitted to attend IRB meetings as guests under the following stipulations:

1. The visitor must request permission to attend the IRB meeting a minimum of 2 days in advance of the IRB meeting date;
2. Visitors are required to disclose any potential conflicts of interest prior to attendance and/or must excuse themselves if a potential conflict reveals itself during the course of the meeting;
3. Visitors may not be in attendance during the deliberations pertaining to a study in which they are related to an individual who is a member of the research team (e.g. dependent, spouse, parent);

- or if the visitor serves as a PI, Co-I, or other key personnel on a study; or if the visitor has other potential conflicts of interest (e.g. supervisor's or professor's protocol is being reviewed);
4. Visitors must sign a confidentiality agreement; and
 5. Visitors shall sign the IRB Meeting Sign-In sheet and may be asked to document the purpose of their visit.

When a study is tabled at a meeting (i.e. the majority vote agrees with a motion to table), the study, after the investigators have addressed the IRB requirements, must be returned to a full board IRB meeting for review. The Full Board meeting procedures described above are followed for these protocols. Additional materials distributed to members for tabled studies include the SIRB stipulations letter sent to the PI and any response to those stipulations from the investigators. When possible, the primary reviewer from the previous review will be assigned as the primary reviewer for the study when it is resubmitted for re-consideration.

2.3 IRB Minutes

Minutes of each IRB meeting are recorded electronically, as well as in writing. Minutes are distributed to IRB members in their member packets; and suggestions for revisions are made via email to the ORA up until the day of the meeting. A final review of the minutes and a vote for approval is conducted at the next convened meeting. The IRB Chair or Vice-Chair documents approval of the minutes by signing the official copy of the minutes. Upon approval of the minutes, the original, signed copy is retained in the IRB Meeting Minutes files. A copy of the approved minutes is provided to the IO, informing the IO of all actions taken by the IRB.

Minutes include:

1. Attendance at the meeting for each action (designating any advocates for vulnerable populations that are present, and alternative members replacing primary members):
 - a. 'Members Present' documents the names of IRB members present at any time during the meeting
 - b. 'Members Absent' documents the names of IRB members who never attended the meeting at any time
2. A list of all Full Board studies with the respective information:
 - a. Actions taken and decisions made by the Committee:
 - i. Approved
 - ii. Approved with Stipulations
 - iii. Tabled
 - iv. Disapproved
 - b. Votes will record the number of members voting for, against, and abstaining, and the names of IRB members listed under "Members Present" who are absent from the vote. If a member was absent due to a conflicting interest, the notation "absent due to a conflicting interest," will appear next to the name
 - c. Basis for requiring modifications to the research proposal or consent documents or for disapproving the research proposals
 - d. A summary of the discussion of controversial issues and their resolution
 - e. A summary of discussion of issues pertinent to the protocol
 - f. Determinations required by the regulations along with project specific findings that justify each determination. These determinations include those for waiver or alteration of consent, waiver of consent documentation, research involving children, prisoners, pregnant women, fetuses, and neonates.

- g. Justification for any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample informed consent document
- h. For initial and continuing review, the approval period
- i. The names of IRB members who absented themselves from the meeting due to conflict of interest
- j. The rationale for significant risk/non-significant risk device determinations

Minutes include separate deliberations, actions, and votes for each protocol undergoing initial or continuing review by the convened IRB. The minutes will document the total number of members attending the meeting. In order to document the continued existence of a quorum, vote totals for each action will be recorded in the minutes by listing the number of members originally present, that were absent for this vote only, along with the breakdown of members voting for, against, and abstaining. In order for a protocol to be approved, it must receive the approval of a majority of members present at the meeting. The minutes include the documentation of any potential conflict of interest that an IRB member may have with a particular protocol and indicate that the IRB member was absent from the room for the discussion and vote. IRB minutes reflect decisions and justifications regarding human subjects' research involving vulnerable populations. IRB minutes list all suspended and terminated protocols that occurred during the previous month. ORA staff is assigned the responsibility to monitor quorum at each meeting, to determine vote counts, and to record IRB discussion points for the minutes.

A vote of approval by a member means that the member has determined that:

1. risks to subjects are minimized;
2. risks to subjects are reasonable in relation to anticipated benefits;
3. selection of subjects is equitable;
4. informed consent will be sought from each subject or their legally authorized representative or waived in accordance with applicable guidelines (see section)
5. there are adequate provisions to protect the privacy of subjects and maintain the confidentiality of data; and
6. when some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect their rights and welfare.

A Chair's Report of Expedited and Exempt reviews is submitted to the Full Board, along with any previous Full Board Meeting Minutes that require approval, to inform IRB members of research protocols that have been approved under an Expedited/Exempt review procedure in the previous month. For example, all Expedited and Exempt review actions that occurred in June will be reported at the Full Board meeting in July.

2.4 Approval Timeframes

Approval for Expedited and Full Board studies is one year (not to exceed 365 days). However, the approval period may be shorter if the IRB deems it appropriate.

For Full Board studies, the expiration date of the approval period is one year from the date of the IRB meeting at which the research project initially was approved or approved with stipulations. The effective date at which the approval period begins is the date on which either a) the IRB approved a study with no stipulations at a fully convened meeting; or b) the Chair and/or designee has reviewed and accepted as

satisfactory all changes made by the investigator in response to the IRB's stipulations. The following illustrates examples of this procedure:

1. A study is reviewed at a convened meeting on May 20, 2011 and is approved with no stipulations. The effective date is May 20, 2011 and the expiration date is May 19, 2012.
2. A study is reviewed at a convened meeting on May 20, 2011 and is approved with stipulations that require the investigator to make minor revisions or clarifications. On June 1, 2011, the Chair and/or designee reviews the PI's response to stipulations and determines that the investigator's revisions are satisfactory. The effective date is June 1, 2011 and the expiration date is May 19, 2012.
3. A study is reviewed at a convened meeting on May 20, 2011, and the IRB determines that substantial changes need to be made to the study. The IRB tables the study and requests the investigator significantly revise the protocol. At a convened meeting on July 15, 2011 the IRB reviews the PI's response to stipulations and approves it with stipulations that request the investigator to make additional minor changes. On August 1, 2011, the Chair and/or designee reviews the revised study documents and determines that the stipulations have been met. The effective date is August 1, 2011 and the expiration date is July 14, 2012.

For Expedited studies, the approval period is one year from the date at which the research project initially was approved or approved with stipulations. The effective date at which the approval period begins is the date in which the Chair and/or designee has reviewed and either a) approved with no stipulations; or b) determined that all stipulations were satisfactorily met. The following illustrates examples of this procedure:

1. A study is reviewed by the Chair and/or designee on May 15, 2011, and is approved with no stipulations. The effective date is May 15, 2011 and the expiration date is May 14, 2012.
2. A study is reviewed by the Chair and/or designee on May 15, 2011, and is approved with stipulations. On June 1, 2011, the Chair and/or designee reviews the PI's response to stipulations and determines that the investigator's changes are satisfactory. The effective date is June 1, 2011 and the expiration date is May 14, 2012.
3. A study is reviewed by the Chair and/or designee on May 15, 2011, and the Chair and/or designee determines that substantial changes need to be made to the study. The Chair and/or designee tables the study and requests the investigator significantly revise the protocol. In this case, even with major changes required, the Chair and/or designee still consider the study protocol to meet the criteria for Expedited Review. Otherwise, the Chair and/or designee can send the protocol to the Full Board. On June 1, 2011, the Chair and/or designee reviews the PI's response to stipulations and approves it with stipulations that request the investigator to make additional minor changes. On June 14, 2011, the Chair and/or designee reviews the revised study documents and determines that the stipulations have been met. The effective date is June 14, 2011 and the expiration date is May 31, 2012.

Protocols determined to be Exempt receive effective and expiration dates given in a similar manner to Expedited protocols, with the exception that the Exempt protocols receive an approval period of three years. (See Section 6.3).

In some cases, approvals may be granted for time periods less than one year, or a limited number of subjects over a period not to exceed one year, or additional monitoring may be required. Projects requiring review shorter than annual may include:

1. Experimental therapies in which the clear potential for significant adverse experiences have been identified at the time of review;
2. Non-therapeutic projects based on risk information provided at the time of initial review;
3. Projects in which new information provided during the duration of the study (including at the time of continuing review) indicates a high probability of significant adverse experiences not previously reported;
4. Projects in which local or outside adverse experience reports create new concerns regarding the need for closer project scrutiny; or
5. Projects where the SIRB has concerns with regard to previous or potential serious or continuing noncompliance.

2.5 Expiration and Lapse Notices

As a courtesy, the ORA sends PIs email reminder notices approximately 60 days prior to their study's approval expiration date. Notices list the study title, Clinical Research (CR) number, IRB approval expiration date, and continuing review and closure instructions. The IRB requires PIs to submit a final study closure report if the PI does not intend on continuing research for another year. PIs desiring to continue their research beyond the study approval period must submit a continuing review, utilizing the appropriate online form (see Section 7.0) and all other required documentation.

As close to the study lapse date as possible but not before, the IRB sends the PI a letter to notify them that the study protocol has lapsed and that all research and research-related activities must immediately cease, including enrollment, recruitment, interventions, and interactions with current participants, and data analysis. The letter also lists the study title, CR number, IRB approval expiration date, and instructions for continuing review and closure. The PI has a 30-day grace period from the lapse date to submit a continuing review or final study closure report; however, this is an administrative grace period and all research activity must immediately cease at the lapse date. When a PI does not provide continuing review information to the IRB or the IRB has not approved the protocol by the approval expiration date, interventions and interactions on current participants may continue ONLY when the IRB finds an over-riding safety concern or ethical issue involved such that, it was in the best interest of individual participants. The PI must request this in writing and submit the request to the ORA, who will then promptly forward the request to the IRB Chair and/or designee.

If the PI does not request a continuation or closure within the 30-day grace period, then the IRB sends the PI a formal letter stating the protocol has been administratively closed and the failure to submit a continuation or closure is handled according to Section 6.14, Non-Compliance with IRB Policies, Procedures, or Decisions. The ORA lists the study as administratively closed and stores it accordingly. The IRB Chair's Report lists all suspended and terminated protocols that occurred during the previous month.

2.6 Protocol Files

Any paper copies of protocol files are maintained in locked filing cabinets in the ORA. The locked filing cabinets are maintained within a locked room. Electronic files are maintained on a secure server, behind the Seton firewall, and follow Seton's policies regarding electronic data security. Files are assigned protocol numbers with the format CR-XX-XXX (CR standing for 'Clinical Research,' 'XX' is assigned according to the year that the protocol is initially submitted, 'XXX' is assigned according to the chronological order that the protocol was submitted to the ORA). Each file contains at least the following (where applicable):

1. Seton IRB Action Request Form (paper only);
2. IRB Application;
3. Any supplementary forms, for example: Application for Research Including a Vulnerable Population, Request for Tissue/Data Repository, Request for Waiver of HIPAA Authorization (paper only);
4. Study proposal/protocol (including the DHHS-approved protocol or Sponsor protocol);
5. Recruitment materials (including direct advertising materials);
6. Survey instruments and other data collection sheets;
7. Investigator's brochure/Drug packet inserts;
8. Other materials specific to the proposed study (e.g., Sponsor correspondence with a regulatory agency such as the FDA regarding test item risk, etc.);
9. Informed Consent Document(s) or other consenting/assenting materials;
10. Translator's Declaration;
11. Collaborative Institutional Training Initiative (CITI) Human Subjects Protection Training Certificates for all study personnel;
12. Sign and Dated CVs for Principal and all Co-Investigators;
13. Any correspondence with the IRB, both formal and informal (including all emails), related to the research protocol;
14. Copy of completed Primary Reviewer Checklists including determinations, justification, and findings of the IRB. For initial review of Expedited studies, Reviewer Checklists include the specific permissible category. For initial review of Exempt studies, the specific category of exemption is documented;
15. Copies of scientific evaluations, if any;
16. Official notification of IRB action;
17. Any changes made to the original research proposal, as requested by the IRB;
18. A stamped copy of the approved informed consent/assent form;
19. Applications for Continuing Review and all correspondence and records related to that review;
20. Applications to amend any protocol-related materials and all correspondence and records related to that review;
21. Reports of unanticipated problems and related IRB review and action;
22. Any IRB action regarding non-compliance and related correspondence;
23. Protocol deviations; and
24. Statements of significant new findings provided to participants.

2.7 Consultants

Seton Family of Hospitals authorizes the IRB to request the assistance of a consultant in preparing for discussion of a research protocol in accordance with [45 CFR 46.107](#) and [21 CFR 56.107](#). Any time the IRB, primary reviewer, or ORA staff determines the IRB does not have the necessary scholarly or scientific expertise or experience for sound review, ad hoc consultants may be requested. When requesting additional consultation, the IRB, primary reviewer, or ORA staff may contact the Sr. Director of the ORA or the IRB Chair for a consultant referral. Consultants are independent of the IRB and are selected according to scholarly and scientific expertise. Prior to counsel, consultants must disclose any conflicts of interest according to the conflict of interest policy (see Section 3.9). Consultants with conflicts of interest will be replaced and will not be used in those instances. The person requesting consultation must confirm the consultant does not have any conflict of interest, and this information will be documented in the study file. When requesting additional consultation, the IRB, primary reviewer, or ORA staff may contact the Sr. Director of the ORA or the IRB Chair for a consultant referral.

The IRB, primary reviewer, or ORA will document in the study file and distribute to all IRB members, all counsel received prior to formal IRB protocol review. Consultants are asked to either attend the meetings to present their comments or provide their comments to the IRB in a written report. If consultants attend a meeting, a summary of their findings will be described in the minutes. If consultants provide a written report, a copy of the report will become part of the study file.

Consultants may be called upon to judge the scientific soundness of a research protocol, make a fair and accurate determination of the risk-benefit ratio, review the cultural appropriateness of the informed consent process, and offer additional and unique expertise. However, consultants cannot make any review determinations and may not vote with the IRB; they may only provide counsel.

Legal counsel and advice may be sought at any time, either formally in writing from the IRB to the expert counsel or informally by IRB members or ORA staff during the review of new, ongoing and/or non-compliance cases. Additionally, legal counsel is regularly sought to provide detail on Texas State Law as it pertains to interpretation of [45 CFR 46](#).

2.8 ORA Complaints, Feedback, Concerns, and Issues

All complaints, feedback, concerns, or related issues should be directed to the IRB Chair, as noted in the consent form; please consult Section 1.6 for contact information. Any allegations of noncompliance will be directed to the ORA according to Section 6.14 and adjudicated accordingly. All other complaints will be directed to the IRB Chair. The IRB Chair can direct the IRB to review the complaint or meet with the involved parties and the Sr. Director of the ORA to reach a satisfactory resolution. Complaints will be formally documented with resolutions noted as formal actions in the ORA study file. Investigators may bring to the ORA concerns or recommendations regarding the human research protection program, including the IRB review process.

Section 3: General Research Procedures

3.0 Off-Site and Multi-Site Research

Collaborative research activities at off-site locations are subject to special procedures for coordination of research review and may involve more than one IRB responsible for research oversight. In these cases, the SIRB has established additional procedures to define the responsibilities of each institution, coordinate communication among responsible IRB committees, and manage information obtained in off-site or multi-site research to ensure protection of human subjects.

The Seton Family of Hospitals and other local institutions that routinely collaborate on human research have established agreements that allow the other institutions to rely on the SIRB for the review and continuing oversight of human research either conducted by the institution or covered by the institution's Federal Wide Assurance. In addition, the SIRB may enter into formal agreements with other facilities, which are not legal entities, of the Seton Family of Hospitals to provide research review (i.e., to act as the IRB of record), to rely on other institutions for research review, or to cooperate in review. SIRB enters into these types of arrangements through an [IRB Authorization Agreement](#) (see Section 1.1 for more information).

3.1 Public and/or Published Datasets Not Subject to Human Subjects Review

The IRB recognizes that the analysis of de-identified, publically available data does not constitute human subjects research as defined at [45 CFR 46.102](#) and that it does not require IRB review. Many studies utilize data made available through large data consolidation bureaus and consortiums. To reduce burdens on investigators, the IRB maintains a list of data holders whose archives include only publically available, de-identified data. The IRB had reviewed data procedures of these data holders and recognizes that the data that they provide for analysis does not constitute 'human subjects' information as defined by 45 CFR 46.102 or in the SIRB IRB's policies and procedures.

1. Any changes made to the original public and/or published datasets, accessible without restriction (e.g., password not needed), and containing no readily identifiable, individual information.
 - a. Inter-University Consortium for Political and Social Research (ICPSR)
 - b. U.S. Bureau of the Census
 - c. National Center for Health Statistics
 - d. National Center for Education Statistics
 - e. National Election Studies
2. Public and/or published datasets, accessible without restriction (e.g., password not needed), and containing readily identifiable information and where individuals can reasonably expect this information to be available to the public (examples include letters to the editor, blogs, etc.).
3. Public and/or published datasets, with restrictions to access, that contain data that is presented in aggregate form only (e.g., zip code); thus individuals cannot be identified.
4. In those cases where you must register with a site or organization to gain access, the registration for login and password must be without qualification – anyone could register with this site.

3.2 Process Improvement/Quality Improvement

Making the determination about whether a project meets the definition of a quality improvement project or is a human subjects research project is done by following a systematic set of steps. The Federal government has provided sequenced steps for determining what is research and whether human subjects are involved, thus making it a human subjects research project (and thus necessitating IRB review).

Quality improvement or performance improvement typically does not meet the Federal definition of “research”. While a quality improvement project may be systematic, its boundaries for generalizability is the institution in which the project was implemented. This does not mean that a quality improvement project may not be published in a respective Quality Improvement Journal. A quality improvement project by definition may not be generalized beyond the local boundaries from which it was created.

Seton, like most research institutions, suggests that the individual conducting the project check in advance, with the IRB office to make the correct determinations. This avoids instances of noncompliance, when a project is completed and then incorrectly submitted to the IRB. The IRB can only approve projects in advance (or prospectively). Thus, the IRB never grants approval for a project when it has already been completed, whatever the type of study.

The majority of Quality Improvement (QI) projects do not require review by the IRB. There are however, cases where the project would fall under the purview of the IRB. Projects which qualify as ‘research’ and which involve ‘human subjects,’ as defined in the federal regulations and further explained below, would require IRB review under Seton’s research policies. The most common reason that QI projects require IRB review is that they are projects involving systematic investigations intended to develop generalizable knowledge beyond the boundaries of Seton.

QI may involve systematic, data-guided initiatives or processes designed to enhance health care delivery in a particular setting. QI is intended to use experience to identify effective methods, implement the methods broadly, and evaluate the impact or effect of the implemented changes. As such, QI is an intrinsic part of good clinical practice where lessons learned are used to enhance future healthcare delivery for patients at the institution in which the QI activity is implemented. A QI project may involve implementing a practice to improve the quality of patient care, and collecting data regarding the degree to which implementation of the practice was successful for clinical, practical, or administrative purposes. Process-based QI activities strive to overcome barriers to dissemination and implementation of best practices. Note that these “best practices” represent accepted, evidence-based approaches to caring for patients (such as hand-washing, ordering mammograms for eligible women, or improving glucose control in diabetic patients), rather than experimental/unproven interventions. Results of QI projects could be shared with others within the departments of Seton that they directly involve, either via presentation or publication. QI activities would not be considered human subjects research.

Federal regulations define research as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge” [45 CFR 46.102(d)]. Under this definition, the project must intend at the outset to generate conclusions which can be applied in or be predictive of similar circumstances. Thus, a case study of a single individual would not be considered research.

A human subject is defined in the Federal regulations as a “living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) obtains identifiable private information” [45 CFR 46.102(f)]. Key to this definition is that the information collected is about an identified person and is intended for research.

If the proposed project will involve collecting identifiable information about a living individual and will be used to inform broad policy or generalize findings, then the project must be submitted to the IRB for review. Note that the determination of whether or not a project constitutes research is separate from whether or not the project involves human subjects and only when both definitions are met does the project require IRB review.

The intent to publish is an insufficient criterion for determining whether or not a quality improvement activity involves research. Planning to publish an account of a quality improvement project does not necessarily mean that the project fits the definition of research; people seek to publish descriptions of non-research activities for a variety of reasons, if they believe others may be interested in learning about those activities. Conversely, a quality improvement project may involve research even if there is no intent to publish the results.

Examples:

1. The Pediatric Trauma Registry is required by law to include identifiable information in its database. And by law, identifiable trauma information is sent by Seton to DSHS for collection and analysis. These data transfers do not require IRB review, as they are mandated by law and covered under a separate data sharing agreement for mandated public health programs.
2. A staff person at Dell Children's Hospital wishes to access the Pediatric Trauma Registry and extract personal information from the registry and accompanying patient information from medical records to review (for example) the requirements for "Level 2 Activations" in the Trauma Center in order to examine how efficient and effective the current clinical service system is for determining which children are activated to be released from the hospital vs. admitted to the hospital. Since the purpose of the project is to improve the service at one Hospital and thus is not intended to be generalized beyond Seton, this project would be classified as a QI project and would not need IRB approval.
3. The same staff person at Dell Children's Hospital wishes to access the Pediatric Trauma Registry, by completing a one-time pull of completely de-identified information from the registry for a project in which the sample will be statistically analyzed and reviewed to determine whether certain apriori hypotheses are supported. The staff person plans on presenting these data, if positive, to a national Trauma conference. Does this project need IRB approval prior to data collection? No. While the project met the definition of research, there were no identifiable data, and thus does not meet the Federal definition of human subjects research. (Not QI, not humans subjects research)
4. However, if this same project, using the same variables had included one patient identifier (e.g., medical record number), in order to link the extracted trauma data to medical record data to check these same hypotheses for analysis and generalization at an external Trauma conference, the project would require IRB approval in advance of the data collection. This holds true because the project is conducting a systematic inquiry with intent to generalize beyond the boundaries of Seton and because, private information is included in the data collection.
5. Suppose the staff person described in No. 2 above, decides a year later that the Level 2 Activation Project had some additional potential for generalization. Since the project had been classified as QI, it had not been reviewed by an IRB as either exempt, expedited or full board. What should this staff person do?

Call the ORA office and talk to the SIRB staff. The project should now be submitted either as a prospective study under an expedited IRB category, collecting new data using the same hypotheses, or as a retrospective study without patient identifiers (if possible) (exempt IRB

category 4) utilizing a new data extraction.

The final determination of whether an activity is research requiring IRB review will be made by the SIRB. To obtain an authoritative determination of whether an activity might meet the definition of research with humans, investigators and other Seton associates must consult with the IRB Chair, or Senior Director of the Office of Research Administration.

A helpful suggestion in interpreting the Federal regulations of 45 CFR 46 is understanding what is meant by the word "exempt". Exempt means the research project involves very little risk, and must fit into one of the six exempt categories defined by DHHS. An institution may decide who reviews "exempt" protocols. At Seton, an IRB member is elected to be the designated reviewer for all exempt protocols. Rules for exempt protocols may be found in the SIRB IRB manual (https://www.seton.net/medical_services_and_programs/clinical_research/irb/). Thus, exempt does not mean complete exemption from review or oversight from human research protection guidelines.

Table 1: Examples of What Does and Does Not Require SETON IRB Review and Approval Prior to Initiation of Research.

ACTIVITIES	DESCRIPTION	SUBMISSION REQUIRED TO IRB
Clinical Research	Involves research to increase scientific understanding about normal or abnormal physiology, disease states or development and to evaluate the safety, effectiveness or usefulness of a medical product, procedure, or intervention. Vaccine trials, medical device research and cancer research are all types of clinical research.	YES
Medical Practice	Standard practice, innovative care, or off-label use of FDA-approved drugs, biologics, devices and other articles or substances that are used in the normal course of medical practice, provided the activity does not involve systematic collection of safety or efficacy data, and is limited to prevention, diagnosis, mitigation, treatment, or cure of disease in affected individuals.	NO
Emergency Use of an Investigational Drug or Device	<p>Institutional Policies do not permit research activities to be started, even in an emergency, without prior IRB acknowledgement.</p> <ol style="list-style-type: none"> 1. This does not limit the physician's ability to deliver emergency care. The physician may deliver such care, but the data derived from such care may not be used in any prospectively conceived research. 2. Emergency care involving investigational drugs, devices or biologics must meet the Food and Drug Administration (FDA) criteria. 	IRB Chair or designee notification
Repositories (e.g., data, specimen, etc.), Pre-Review of Clinical Data Sets	Preliminary activities typically designed to help the Investigator refine data collection procedures. This data is to be included in the publication.	YES
	A storage site of mechanism by which identifiable human tissue, blood, genetic material or data are stored or archived for research by multiple investigators or multiple research projects.	YES
	Activities (e.g., review of medical data, queries, etc.) intended only to assess the feasibility of future research. <i>Note that Seton or other "covered entity" might need to obtain researcher certifications for a review preparatory to research for HIPAA compliance purposes.</i>	NO
Humanitarian Use Device (HUD)	Clinical and investigational use of a HUD device.	YES
Epidemiological Research	Focuses on health outcomes, interventions, disease states and conclusions about cost-effectiveness, efficacy, efficiency, interventions, or delivery of services to affected populations. This research may be conducted through surveillance, monitoring, and	YES

	reporting programs. Other methods are retrospective review of medical, public health and/or other records.	
Research Involving Only Decedents	Research involving only data or tissue obtained from individuals who are deceased prior to the conduct of the research. There must not be any interaction or intervention with living individuals, or collection of private data or specimens associated with living individuals. Under HIPAA regulations, researchers within the Seton or other "covered entity" must obtain a HIPAA waiver of authorization for review of identifiable protected health information (PHI).	NO <i>(contact Privacy Officer for HIPAA requirements)</i>
Standard Diagnostic or Therapeutic Procedures	The collection of data about a series of established and accepted diagnostic or therapeutic procedures, or instructional methods for dissemination or contribution to generalizable knowledge. (See Case Report for exceptions)	YES
	An alteration in patient care or assignment for research purposes.	YES
	A diagnostic procedure added to a standard treatment for the purpose of research.	YES
	An established and accepted diagnostic, therapeutic procedure or instructional method, performed only for the benefit of a patient or student but not for the purposes of research. (See Case Studies)	NO
Case Report - Clinical	Report about three or less clinical experiences or observations identified in the course of clinical care, provided that FDA regulations requiring IRB approval do not apply such as use of: articles (e.g., drugs, devices, and biologics) that have not been approved for use in humans; articles requiring exemption from FDA oversight; articles under an IND/IDE. Case reports are generally done by retrospective review of medical records and highlights a unique treatment, case or outcome.	NO
Case Report - Other	Report about experiences or observations associated with three or less individuals.	NO
Quality Assurance and Quality Improvement Activities - Clinical or Procedures	Systematic, data-guided activities designed to implement promising ways to improve clinical care, patient safety and health care operations. The activity is designed to bring about immediate positive changes in the delivery of health care, programs, or business practices at Seton. There must be no plans to disseminate the knowledge beyond Seton.	NO
Quality Assurance and Quality Improvement Activities - Non-Clinical	Data collected with the limited intent of evaluating and improving existing services and programs or for developing new services or programs at Seton. There must be no plans to disseminate the knowledge beyond Seton. Examples include teaching evaluations or customer service surveys.	NO
Innovative Procedures, Treatment, or Instructional Methods	Systematic investigation of innovations in diagnostic, therapeutic procedure or instructional method in multiple participants [more than three (3)]. The investigation is designed to test a hypothesis, permit conclusions to be drawn, and thereby develop or	YES

	contribute to generalizable knowledge.	
	The use of innovative interventions that are designed solely to enhance the wellbeing of an individual patient or client and have a reasonable expectation of success. The intent of the intervention is to provide diagnosis, preventive treatment, or therapy to the particular individual.	NO <i>(unless FDA regulations requiring IRB approval apply such as use of: articles (e.g., drugs, devices, biologics) that have not been approved for use in humans; articles requiring exemption from FDA oversight; articles under an IND/IDE)</i>
Pilot Studies	Pilot studies involving human subjects are considered human subjects research.	YES
Research Using Publicly Available Data Sets	Use of publicly available data sets that do not include information that can be used to identify individuals. "Publicly available" is defined as information shared without conditions on use. This may include data sets that require payment of a fee to gain access to the data.	NO
Research on Organizations	Information gathering about organizations, including information about operations, budgets, etc. from organizational spokespersons or data sources. Does not include identifiable private information about individual members, employees, or staff of the organization.	NO
Community Service Projects	Donated service or activity that is performed by someone or a group of people solely for the benefit of the public or its institutions.	NO <i>(but if human subjects data are collected during the activity to be used for research protocols, submission is required to the IRB)</i>
Secondary use of research data	Analysis of data gathered for a previous research protocol not related to current proposal and the data are de-identified. De-identified means removal of the 18 identifiers recognized by the HIPAA regulations which can be found under the HIPAA De-identification Certification Form at the following link: http://www.research.Setony.edu/ori/MedicalFullReviewApplication.htm#HIPAA	NO <i>(but if data has direct or indirect identifiers, submission is required to the IRB)</i>
Behavioral and Social Sciences Research	Focuses on individual and group behavior, mental processes, or social constructs and usually generates data by means of surveys, interviews, observations, studies of existing records, and experimental designs involving exposure to some type of stimulus or environmental intervention.	YES

<p>Student Practicum and Internship (Professional schools within SETON which actively seek opportunities for their students to become involved in "real world" activities or work assignments that will introduce them to and, in some cases, provide practical experiences in their chosen profession)</p>	<p>A practicum/internship that falls within the work scope of a local, state, or federal agency (e.g. Public Health Agency) or employment by private industry involving data collection for non-research purposes. No <i>a priori</i> research design or intent.</p>	<p>NO <i>(but professional standards apply)</i></p>
	<p>Use of or access to human subjects data previously collected for non-research purposes (perhaps through a circumstance like the one above) in a systematic investigation designed to contribute to generalizable knowledge, one indicator of which is publication.</p>	<p>YES</p>
	<p>Independent research project not falling within the scope of a previously approved project.</p>	<p>YES</p>
	<p>Participation with or providing services to a SETON PI conducting IRB-approved research. No work outside the scope of the IRB approval.</p>	<p>YES <i>(Modification to protocol to add student if providing research assistance at level of study personnel)</i></p>
<p>Classroom Assignments/ Research Methods Classes</p>	<p>Activities designed for educational purposes that teach research methods or demonstrate course concepts. The activities are not intended to create new knowledge or contribute to generalizable knowledge (e.g. published or disseminated at a capstone or conference).</p>	<p>NO <i>(but instructors have an obligation to ensure students meet professional and ethical standards)</i></p>
<p>Internet Research</p>	<p>Research involving online interactions with human subjects where identifiers are known or can be ascertained such as email addresses, certain websites and bulletin boards. Also includes data collected where an individual cannot be directly identified and data are collected through intervention or interaction with research subjects</p>	<p>YES</p>
	<p>Research involving online interactions with/data collection from human subject internet community members that may expect a level of privacy and confidentiality such as vulnerable populations (HIV patients, alcoholics anonymous, sexual abuse survivors etc.). Also includes data collected where an individual cannot be directly identified and data are collected through intervention or interaction with research subjects.</p>	<p>YES</p>

*Excerpted from The University of Michigan IRB website

The following information is guidance from the Office of Human Research Protections, the Federal office that provides compliance for 45 CFR 46. It is provided as additional information to the researcher as they develop their research project and make determinations about whether their project is a QI project or a research project that requires IRB review. The ORA office houses the Seton IRB and is available to answer such questions at all times, particularly through the electronic IRB TOPAZ submission system.

Quality Improvement Activities - FAQs:

[How does HHS view quality improvement activities in relation to the regulations for human research](#)

[subject protections?](#)

Protecting human subjects during research activities is critical and has been at the forefront of HHS activities for decades. In addition, HHS is committed to taking every appropriate opportunity to measure and improve the quality of care for patients. These two important goals typically do not intersect, since most quality improvement efforts are not research subject to the HHS protection of human subjects' regulations. However, in some cases quality improvement activities are designed to accomplish a research purpose as well as the purpose of improving the quality of care, and in these cases the regulations for the protection of subjects in research (45 CFR part 46) may apply.

To determine whether these regulations apply to a particular quality improvement activity, the following questions should be addressed in order:

- (1) Does the activity involve *research* ([45 CFR 46.102\(d\)](#));
- (2) Does the research activity involve human subjects ([45 CFR 46.102\(f\)](#));
- (3) Does the human subjects research qualify for an exemption ([45 CFR 46.101\(b\)](#)); and
- (4) Is the non-exempt human subjects research conducted or supported by HHS or otherwise covered by an applicable FWA approved by OHRP.

For those quality improvement activities that are subject to these regulations, the regulations provide great flexibility in how the regulated community can comply. Other laws or regulations may apply to quality improvement activities independent of whether the HHS regulations for the protection of human subjects in research apply.

[Do the HHS regulations for the protection of human subjects in research \(45 CFR part 46\) apply to quality improvement activities conducted by one or more institutions whose purposes are limited to: \(a\) implementing a practice to improve the quality of patient care, and \(b\) collecting patient or provider data regarding the implementation of the practice for clinical, practical, or administrative purposes?](#)

No, such activities do not satisfy the definition of “research” under [45 CFR 46.102\(d\)](#), which is “...a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge...” Therefore the HHS regulations for the protection of human subjects do not apply to such quality improvement activities, and there is no requirement under these regulations for such activities to undergo review by an IRB, or for these activities to be conducted with provider or patient informed consent.

Examples of implementing a practice and collecting patient or provider data for non-research clinical or administrative purposes include:

- A radiology clinic uses a database to help monitor and forecast radiation dosimetry. This practice has been demonstrated to reduce over-exposure incidents in patients having multiple procedures. Patient data are collected from medical records and entered into the database. The database is later analyzed to determine if over-exposures have decreased as expected.
- A group of affiliated hospitals implements a procedure known to reduce pharmacy prescription error rates, and collects prescription information from medical charts to assess adherence to the procedure and determine whether medication error rates have decreased as expected.
- A clinic increasingly utilized by geriatric patients implements a widely accepted capacity assessment as part of routine standard of care in order to identify patients requiring special services and staff expertise. The clinic expects to audit patient charts in order to see if the assessments are performed with appropriate patients, and will implement additional in-service training of clinic staff regarding the use of the capacity assessment in geriatric patients if it finds that the assessments are not being administered routinely.

[Do quality improvement activities fall under the HHS regulations for the protection of human subjects in](#)

[research \(45 CFR part 46\) if their purposes are limited to: \(a\) delivering healthcare, and \(b\) measuring and reporting provider performance data for clinical, practical, or administrative uses?](#)

No, such quality improvement activities do not satisfy the definition of “research” under 45 CFR 46.102(d), which is “...a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge...” Therefore the HHS regulations for the protection of human subjects do not apply to such quality improvement activities, and there is no requirement under these regulations for such activities to undergo review by an IRB, or for these activities to be conducted with provider or patient informed consent.

The clinical, practical, or administrative uses for such performance measurements and reporting could include, for example, helping the public make more informed choices regarding health care providers by communicating data regarding physician-specific surgical recovery data or infection rates. Other practical or administrative uses of such data might be to enable insurance companies or health maintenance organizations to make higher performing sites preferred providers, or to allow other third parties to create incentives rewarding better performance.

[Can I analyze data that are not individually identifiable, such as medication databases stripped of individual patient identifiers, for research purposes **without** having to apply the HHS protection of human subjects regulations?](#)

Yes, whether or not these activities are research, they do not involve “human subjects.” The regulation defines a “human subject” as “a living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information....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.” Thus, if the research project includes the analysis of data for which the investigators cannot readily ascertain the identity of the subjects and the investigators did not obtain the data through an interaction or intervention with living individuals for the purposes of the research, the analyses do not involve human subjects and do not have to comply with the HHS protection of human subjects regulations.

(See *OHRP Guidance on Research Involving Coded Private Information or Biological Specimens*, October 2008; available at <http://www.hhs.gov/ohrp/policy/cdebiol.pdf>.)

[Are there types of quality improvement efforts that are considered to be research that are subject to HHS human subjects regulations?](#)

Yes, in certain cases, a quality improvement project may constitute non-exempt human subjects research conducted or supported by HHS or otherwise covered by an applicable FWA. For example, if a project involves introducing an untested clinical intervention for purposes which include not only improving the quality of care but also collecting information about patient outcomes for the purpose of establishing scientific evidence to determine how well the intervention achieves its intended results, that quality improvement project may also constitute nonexempt human subjects research under the HHS regulations.

[If I plan to carry out a quality improvement project and publish the results, does the intent to publish make my quality improvement project fit the regulatory definition of research?](#)

No, the intent to publish is an insufficient criterion for determining whether a quality improvement activity involves research. The regulatory definition under 45 CFR 46.102(d) is “*Research* means a systematic

investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.” Planning to publish an account of a quality improvement project does not necessarily mean that the project fits the definition of research; people seek to publish descriptions of nonresearch activities for a variety of reasons, if they believe others may be interested in learning about those activities. Conversely, a quality improvement project may involve research even if there is no intent to publish the results.

[Does a quality improvement project that involves research need to be reviewed by an IRB?](#)

Yes, in some cases. IRB review is needed if the research involves human subjects, is not exempt, and is conducted or supported by HHS or otherwise covered by an applicable FWA.

See exempt categories at: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.101>.

[Does IRB review of a quality improvement project that is also non-exempt human subjects research always need to be carried out at a convened IRB meeting?](#)

No, if the human subjects research activity involves no more than minimal risk and fits one or more of the categories of research eligible for expedited review, the IRB chair or another member designated by the IRB chair may conduct the review.

The categories of research eligible for expedited review are available at:

<http://www.hhs.gov/ohrp/policy/expedited98.html>.

[If a quality improvement project involves non-exempt research with human subjects, do I always need to obtain informed consent from all subjects \(patients and/or providers\) involved in the research?](#)

No, the HHS regulations protecting human subjects allow an IRB to waive the requirements for obtaining informed consent of the subjects of the research when

- (a) The risk to the subjects is minimal,
- (b) Subjects’ rights and welfare will not be adversely affected by the waiver,
- (c) Conducting the research without the waiver is not practicable, and
- (d) If appropriate, subjects are provided with additional pertinent information after their participation ([45 CFR 46.116\(d\)](#)).

Other applicable regulations or laws may require the informed consent of individuals in such projects independent of the HHS regulations for the protection of human subjects in research.

[If a quality improvement project is human subjects research requiring IRB review, do I need to obtain separate IRB approval from every institution engaged in the project?](#)

No, not if certain conditions are met. The HHS protection of human subjects regulations allow one IRB to review and approve research that will be conducted at multiple institutions. An institution has the option of relying upon IRB review from another institution by designating that IRB on its FWA and submitting the revised FWA to OHRP, and having an IRB Authorization Agreement with the other institution.

See <http://www.hhs.gov/ohrp/assurances/> for information on FWAs and IRB Authorization Agreements. <http://answers.hhs.gov/ohrp/categories/1569>

3.3 Case Reports

Federal regulations [45 CFR 46.102\(d\)](#) and [45 CFR 164.501](#) define research as a systematic

investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. The review of medical records for publication of a single case report or a case series involving data from up to three patients is not considered by the SIRB to be research involving human subjects. Therefore such a report of medical cases does not require SIRB review and approval due to the fact that reporting such a small series of patients does not involve a systematic investigation to develop or contribute to generalizable knowledge.

The SIRB regards such limited case report preparation as an educational activity, and thus it is permissible under the Health Insurance Portability and Accountability Act ([HIPAA](#)) as a part of health care operations [[45 CFR 164.501](#)]. Although the use of protected health information to prepare the paper does not require SIRB review, the author of a case report must comply with HIPAA. Ideally, the author of the article will obtain the signed authorization of the subject, or the subject's legally authorized representative if the subject is deceased, to use the subject's information in the article. If it is not possible to obtain authorization, the author should be aware that one of the identifiers described by HIPAA as requiring written authorization is, "Any other unique identifying number, characteristic, or code...." Moreover, HIPAA requires that, at the time of publication, "[t]he covered entity does not have actual knowledge that the information could be used alone or in combination with other information to identify an individual who is a subject of the information."

Investigators who wish to publish case report data with HIPAA identifiers will need to obtain from the patient a signed HIPAA compliant authorization. This authorization does not need to be submitted to the IRB for review.

If an investigator wishes to have the project assessed by the SIRB to see if it meets the definition of a case report, the investigator should contact the SIRB. If the project qualifies as a case report, the SIRB will send to the investigator a formal letter containing the following information:

Thank you for your recent submission to the Office of Research Administration (ORA) concerning a case report you wish to publish. The submission was reviewed on [*Date of Review*] and it was determined that the above-referenced project is indeed a case report or case series limited to three cases and is NOT considered human subjects research, as defined under 45 CFR 46.102. This determination only applies to the complete submission that was received and reviewed by the ORA ([*Date of Viable Submission*]). Changes to the project may alter the determination.

The ORA has determined that a case report does not produce generalizable knowledge, nor is it an investigation of an FDA-regulated product. Therefore, Seton Institutional Review Board (SIRB) review is not required for this activity.

Please note that if you are utilizing protected health information (PHI) for this project, you must continue to comply with Health Insurance Portability and Accountability Act (HIPAA) regulations. Ideally, the author of the publication/presentation will obtain the signed authorization of the subject, or the subject's legally authorized representative if the subject is deceased, to use the subject's information in the publication/presentation. If it is not possible to obtain authorization, the author should be aware that one of the identifiers described by HIPAA as requiring written authorization is, "Any other unique identifying number, characteristic, or code...." Moreover, HIPAA requires that, at the time of publication, "[t]he covered entity does not have actual knowledge that the information could be used alone or in combination with other information to identify an individual who is a subject of the information."

3.4 Not Human Subjects Research

As outlined in [45 CFR 46.102](#), certain research does not meet the definition of human subjects research and does not require the review and approval of the SIRB. This includes research on quality improvement studies and case reports (defined in Section 3.3). Projects that are not human subjects research are not governed by federal regulations for the protection of human subjects [\[45 CFR Part 46\]](#). However, if the person initiating the project desires a formal determination from the ORA of Not Human Subjects Research, that person may submit a Not Human Subjects Research Form to the ORA, and the ORA will review the proposed project and will make a determination.

Investigators with questions regarding Not Human Subjects Research and whether or not research should be submitted to the SIRB for review should contact the ORA for guidance. Conducting human subjects research without prior IRB approval may be determined to be serious noncompliance, leading to serious penalties by federal authorities. Investigators are highly encouraged to have the final determination as to whether a project constitutes human subject research or not, be made by the ORA.

If the project qualifies as a Not Human Subjects Research, the ORA will send to the investigator a formal letter containing the following information:

Thank you for your recent submission to the Office of Research Administration (ORA). Your request was reviewed by [*ORA Reviewer*] on [*Date of Review*]. The above-referenced project was determined to be Not Human Subjects Research, as defined under 45 CFR 46.102. Therefore, review by the Seton Institutional Review Board (SIRB) is not required.

Please note that this determination only applies to the complete submission that was received and reviewed by the ORA. Changes to the project may alter the determination. Additionally, if you are utilizing protected health information (PHI) for this project, you must continue to comply with Health Insurance Portability and Accountability Act (HIPAA) regulations.

3.5 Guidelines for Research Protocols Requiring Collection and Storage of Genetic Material

IRB approval must be obtained in most cases in which research activities include the use of data from records or stored specimens (blood, urine, tissue, saliva, tumor, and other human products) on which genetic-related research; such as identification and location of specific genes, study of gene products, inherited human traits, or identification and analysis of DNA mutations, may be performed. Health care information records (including financial records, pharmacy records, x-rays, CT scans, MRIs, and other images and recordings), diagnostic specimens, pathological specimens and residual specimens are treated as health care information.

When creating a tissue bank for genetic research purposes, specimens will be processed for storage, catalogued, and placed in a secured facility at the Seton Family of Hospitals, or another site as defined in research protocol and contract. All identifying information, including name and any identifying numbers, will be removed from the specimen and will not be retained. As a result, it should be impossible to connect the donor with the specimen. Some basic information such as age, gender, and diagnosis may be retained with the specimen. The specimen may be stored indefinitely.

The consent form must clearly state that the specimen was donated for medical research purposes. Donors are not entitled to compensation from any commercial use of the products or derived products from the specimen. The consent form should also indicate if the specimen may be used for purposes and research that has not yet been determined. These studies may involve genetic research. Genetic research is about finding the specific location of genes on chromosomes, learning how genes work, and

developing treatments and cures for diseases which are genetically based. The consent form should include a section for the participant to choose whether or not to allow the specimen to be used in genetic research.

3.5.1 Biospecimens and Data Repository Research

Data and specimen repositories are used to store data and/or specimens for future research use. Repositories typically include the collection, storage, and later distribution of information and/or biological specimens for future use. Activities of repositories include 1) the collection of materials, 2) the repository storage and data management, and 3) the use by recipient investigators. According to [45 CFR 46.102\(f\)](#) obtaining identifiable private information or identifiable specimens for research purposes constitutes human subjects research. Obtaining identifiable private information or identifiable specimens includes, but is not limited to:

1. Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that have been provided to investigators from any source; and
2. Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that was already in possession of the investigator.

[45 CFR 46.102\(f\)](#) considers private information or specimens to be individually identifiable when they can be linked to specific individuals by the investigator(s) either directly or indirectly through a coding system. Private information and specimens are not considered to be individually identifiable when they cannot be linked to specific individuals by the investigator(s); either directly or indirectly through a coding system. According to [45 CFR 46.102\(f\)](#) research involving only coded private information or specimens is not considered human subjects research, if the following conditions are met:

1. The private information or specimens were not collected specifically for the currently proposed research project through an interaction with living individuals; and
2. The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
 - a. The investigators and the holder of the key enter into an agreement prohibiting the release of the key to investigators under any circumstances, until the individuals are deceased (note that this is not an agreement that requires SIRB review)
 - b. There are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to investigators under any circumstance, until the individual is deceased; or
 - c. There are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased

The investigator should contact the ORA to determine whether or not the research involves human subjects, and thus, is required to be submitted to the SIRB for review. This policy applies to human subject research repositories established by a Seton Family of Hospitals employee or housed at a Seton Family of Hospitals facility for the purpose of storing data and/or specimens for future research purposes.

1. Any repository holding identifiable or coded data/specimens for research purposes must comply with the SIRB policies and procedures.
2. The collection and storage of specimens/data becomes a research repository when there is a specific intention for the data/specimens to be used repeatedly for research purposes, or stored for future research or shared with other investigators.

- a. The prospective collection and storage of data/specimens for defined research purposes (including holding samples to “batch” them for assays), as part of a single IRB-approved protocol is not considered a repository.
 - b. If there is no explicit plan to destroy the data/specimens when the specific original research project ends, the investigator may maintain the data/specimens under continued IRB approval for uses as approved in the original protocol.
 - c. Once a use is desired beyond the primary research goals of the original protocol, the PI must establish an IRB approved research repository protocol for any future research uses or submit data/specimens into an existing IRB-approved repository.
3. All research repositories, except those qualifying as non-human subjects research, requires review and approval by the IRB.
 - a. Non-Human Subjects Research – this is an activity that doesn’t meet the definition of human subject or research:
 - i. Research projects that are originally deemed non-human subjects (NHS) research and converted to a repository are considered NHS repositories.
 - ii. Data/specimens that are de-identified as part of the original research protocol will likely be deemed NHS repositories.
 - iii. A request for determination should be sought to have the IRB confirm the NHS status.
 - b. Exempt Repositories – these meet the regulatory definition of being exempt from the full requirement of IRB oversight:
 - i. For repositories that are exempt, continuing oversight by the IRB is limited to renewals every three years.
 - ii. Repositories will not be found to be exempt if the data/specimens retain any identifier or link that would permit anyone to identify, directly or indirectly, the person whose data/specimens are stored.
 - c. Non-Exempt Repositories:
 - i. The operation of any non-exempt research repository requires standard continued oversight by the IRB.
 - ii. Creating a repository specific protocol will be required for the review.
 - iii. The IRB will review and approve the repository protocol, specifying the conditions under which data and specimens may be accepted into the repositories, how they will be securely stored, and the procedures under which they will be shared in order to ensure that adequate measures are employed to protect the privacy of subjects, maintain confidentiality of the data and the integrity of specimens.
 4. Revisions to a repository protocol must be approved by the IRB prior to implementation.
 5. Research repositories require consent or authorization by participants for the storage and future use of their data/specimens or a waiver of consent and/or authorization by the IRB.
 6. Requests by a recipient investigator to access identifiable data and/or specimens from any existing non-exempt research repository require IRB approval. The PI must comply with all requirements of the repository and terms of any usage and/or submittal agreements.
 7. Research repositories will be required to provide a summary report to the IRB of all collections, releases or destruction of data/specimens from the repository at each continuing review.

The following are the procedures for submitting an application for IRB approval of a research repository:

1. Completion of the online submission form.
2. Any existing study that is completed, but has collected data and/or specimens for future research purposes, may choose to convert the study to a repository via a modification of continuing review application utilizing the Study Status Report Form.

3. It is recommended that a request for determination be sought from the SIRB should there be any questions of IRB oversight requirements.
4. If the database/repository is maintained at a Seton Family of Hospitals facility, a separate repository protocol must be submitted for the database/repository itself.
5. If the database/repository is maintained outside of a Seton Family of Hospitals facility and managed by a non-Seton Family of Hospitals employee, the SIRB must approve, at minimum, the collection protocol, the consent process, and the submittal agreement. This can be done as a new application or an amendment to an existing study. However, not all submittals meet the requirements for engagement in human subjects' research and a request for determination may be sought.
6. Requesting Data/Specimens from a Repository
 - a. When an investigator is requesting coded or identifiable data from an established repository, a study submission is required, either as a new study or as a modification to an existing study. The SIRB must approve, at a minimum the protocol, data collection tools, the usage agreement, consent process, and IRB approval of the repository from which the request is being made.
 - b. For anonymous and some coded data, a request for determination should be submitted.
7. All repository protocols must include information regarding the following:
 - a. Purpose of the repository
 - b. Data/Specimens to be included - describe the data/specimens to be included, their sources, and the process of acquisition. If some of the data/specimens have been or are collected at sites outside of a Seton Family of Hospitals facility for storage at a Seton Family of Hospitals facility, include a collection plan. Indicate conditions under which data/specimens may be accepted. Confirm that documentation of local IRB approval will be provided to the SIRB for each site contributing data/specimens to the Seton Family of Hospitals database/repository.
8. Description of how consent and authorization has been or will be obtained from subjects, or why waiver of consent/authorization is justified.

3.6 Confidentiality

Whenever researchers promise participants that their responses and data will be maintained in confidence, all research project members (investigators, coordinators, assistants, etc.) are required to prevent accidental and intentional breaches of confidentiality. In most cases, confidentiality can be assured by following fairly simple practices (e.g., substituting codes for identifiers, removing survey cover sheets that contain names and addresses, limiting access to identified data, and/or storing research records in locked cabinets). However, all measures used to assure confidentiality of data needs to be understood by all research staff before research is initiated, and followed once research is initiated.

Confidentiality procedures must be described in research applications that come before the SIRB. Researchers should recognize that the assurance of confidentiality includes keeping the identity of participants confidential. Researchers proposing projects that will address sensitive, stigmatizing, or illegal information/data must explicitly outline the steps they will take to assure any information linking participants to the study is maintained in confidence. The requirement of signed consent forms can be waived in sensitive studies, if the consent document is the only written record linking the participant to the project and a breach of confidentiality presents the principal risk of harm anticipated in that research (see Section 5.6).

If there is any chance that data or participants' identities might be sought by law enforcement agencies or

subpoenaed by court, a grant of confidentiality should be obtained. Under Public Health Act 301(d), researchers, prior to the initiation of the research project, may request grants of confidentiality to protect against forced data and participant identify disclosures. These grants provide protection for specific research projects where protection is judged necessary to achieve the research objectives. If you believe your research project may require a grant of confidentiality, please contact the ORA.

3.7 Privacy

When participants voluntarily permit investigators access to themselves, they exercise their right to privacy. Privacy is the right to authorize or decline access. It should not depend upon the participant's ability to exert control over another's access. Thus, an incapacitated adult or infant is unable to control access to their privacy; but regardless, still has a right to privacy. The informed consent process should disclose any risks to privacy and how investigators specifically plan to protect privacy. Investigators are required to follow the privacy protections outlined in Seton Family of Hospitals' Administrative Policy 5000.05. The IRB reviews studies to ensure adequate privacy protections and prevent unnecessary invasions of privacy. Privacy is best protected by making sure the research is designed in a way that participants will be comfortable with. Investigators must maintain the confidentiality of all private and identifiable information unless disclosure is mandated according to federal, state, or local law.

3.8 Protecting Participants' Health Information

Even in those circumstances where an exemption to the signed consent requirement applies, a signed authorization from the research participant, permitting the use and disclosure of his or her Protected Health Information (PHI), will still be required, unless specifically waived by the IRB. Confidentiality is best maintained by anonymous data collection. In the event that the [Health Insurance Portability and Accountability Act \(HIPAA\) Privacy Rule](#) is more restrictive than the procedures described in the consent requirements, the more restrictive rule must be followed.

3.9 Conflict of Interest

All investigators, study personnel, consultants, and IRB members are required to disclose any conflicts of interest according to the Seton Family of Hospitals Financial Conflicts of Interest (COI) policy 1000.46. Conflicts of potential interest that might affect the protection of participants are prohibited unless a management plan is in place that prevents the conflict of interests from affecting the protection of participants. Management plans that are considered include: partial or complete divestment, limiting involvement of the conflicted individual, additional oversight or disclosure. Disclosure alone cannot be used to manage conflicts of interest that might affect the protection of participants. Consultants found to have a conflict of interest will not serve as consultants for the study under review. When made aware of a possible conflict, the IRB formally refers to the Seton Research Conflict of Interest Committee, which in turn determines if formal COI management strategies are needed.

If required, the Chair of the COI Committee will prepare a draft COI Management Plan for submission to the COI Committee for review. The Chair will work with the investigator/researcher to further develop a COI Management Plan. When finalized, the Management Plan will be submitted to the IRB for review and approval. Under no circumstances will research be approved until the IRB has reviewed and approved the Management Plan.

In cases in which the COI committee identifies a situation involving possible institutional conflict of interest, such cases will be sent to the Institutional Compliance Officer for review and disposition.

Institutional conflicts of interest are handled according to Seton Family of Hospitals' COI policy 1000.46.

Should an IRB member declare involvement in a research protocol under review by the IRB, or state a conflict of interest with the research proposal, the member(s):

1. Are excluded from discussion and voting except to provide information requested by the IRB;
2. Leave the meeting room for discussion and voting; and
3. Are not counted towards quorum.

3.10 Record Retention and Destruction Requirements

The IRB collects, prepares, and maintains adequate documentation of IRB activities. All records will be accessible for inspection and copying by authorized representatives of OHRP, DHHS, FDA, Sponsors, institutional officials, and internal auditors at reasonable times and in a reasonable manner.

It is required that all physical IRB files follow this retention and destruction policy:

1. Periodically, physical files of inactivated (closed, withdrawn, not human subjects research determinations, etc.) protocols are sent to the warehouse for storage.
2. The files to be archived are logged into a tracking database (which tracks the box number for each file) and the boxes containing the files are sealed.
3. A request to store the files is generated with a destruction date (three years after the inactivation date of the last study in the box which was inactivated).
4. The request is sent to the warehouse, whose staff transports the files and stores them.
5. Files are destroyed after 3 years per the ORA's request.

Types of documents in files include:

1. Initially submitted application, protocol, consent form(s), and any recruitment materials.
2. Applications, reports, and records of continuing review activities and correspondence with noted frequency for continuing review.
3. Progress reports submitted by investigators.
4. Reports of injuries to subjects.
5. Scientific evaluations of protocols (if available) if performed by someone outside the IRB.
6. DHHS protocols, if applicable.
7. DHHS sample consent forms, if applicable.
8. All reviewed documents and determinations for research with vulnerable populations (i.e., pregnant women, fetuses, neonates, prisoners, children, decisionally impaired adults).
9. Protocol deviations, noncompliance, unanticipated problems (internal and external) reports, and amendment requests.
10. Statements of significant new findings provided to subjects.
11. Exemption determinations with specific category of exemption, when applicable.
12. Waiver of consent requests and documentation of review.
13. All correspondence between the investigator and the IRB.
14. Submitted audit reports.
15. Completed Reviewers checklists and other ORA forms or documents.
16. All documentation of reports and disposition of incidents of noncompliance.

Per [45 CFR 46.115\(a\)\(2\)](#) the IRB meeting minutes are recorded in writing (see Section 2.2 for detailed

information). Minutes of the IRB meetings are destroyed when all protocols referenced in the minutes have met retention requirements.

The PI, or individual designated as appropriate by the PI, shall maintain, in a designated location, all records relating to conducted research for at least 3 years after completion of the research. All records must be accessible for inspection and copying by authorized representatives at reasonable times and in a reasonable manner. Signed consent/assent forms are to be available for inspection by authorized officials of the Seton Family of Hospitals, the IRB, DHHS, FDA (as appropriate), regulatory agencies, and/or sponsors, as applicable to the research protocol in question. Should a PI depart from the Seton Family of Hospitals prior to completion of the research protocol, the PI is responsible for initiating mutually satisfactory arrangements with their department and the Seton Family of Hospitals as to the disposition of the research documents.

3.11 Guidelines on Payment of ‘Finder’s Fees’ for Research Subject Recruitment

Finder’s fees and bonus payments are generally associated with clinical trials and are offered by the sponsor of the research as an incentive to enhance recruitment. The SIRB does not permit the payment of finder’s fees and/or bonus payments (monetary or in kind) in any form, due to the potential that such a practice could be perceived as causing undue influence and bordering on unethical research subject recruitment.

3.12 Guidelines on Compensation for Research Subjects

The guidelines outlined below are meant to assist investigators in determining a reasonable amount of compensation that can be given to research participants and also place boundaries on what is and is not considered reasonable. The ‘reasonableness’ of a particular sum of money or other form of payment should be based upon the time involved, the inconvenience to the subject, and reimbursement for expenses incurred while participating; and should not be so large as to constitute a form of undue influence or coercion.

During the initial review of a research protocol, the IRB is required to review both the amount of compensation proposed and the method and timing of disbursement to assure that neither are coercive nor present undue influence. The following are some additional guidelines:

1. Any compensation should not be contingent upon the subject completing the study, but should accrue as the study progresses.
2. Unless it creates undue inconvenience or a coercive practice, compensation to subjects who withdraw from the study should be made at the time with which they would have completed the study, had they not withdrawn.
3. Compensation given as a ‘bonus’ or incentive for completing the study is acceptable to the IRB, providing the amount is not coercive. The IRB is responsible for determining if the incentive amount is not so large as to be coercive or represent undue influence.
4. The amount of compensation should be clearly set forth in the informed consent document.

3.13 Guidelines on Research Advertisement Content

The IRB must review and approve advertisements (including letters, emails, flyers, ads, etc.) that will be used to recruit subjects for a specific research study. Generally, advertisements used to recruit research subjects should be limited to information that a potential subject would need to determine if they are

eligible and interested in participating. More specifically, the ads may include information such as:

1. Name and address of the research facility;
2. The condition or disease that will be the focus of the research;
3. Purpose of the research, with reference to the fact that the study is investigational;
4. Summary of criteria for eligibility to participate;
5. Time and other commitments that will be required of the subject;
6. Location of the study and the office to contact for further information.

The advertisements should not:

1. Contain explicit or implicit claims of safety and efficacy or equivalency or superiority to approved procedures or treatments;
2. Emphasize the amount of reimbursement that subjects will receive. The ads may say that reimbursement for time, travel, etc., will be given;
3. Promise a favorable outcome or benefit;
4. Include exculpatory language;
5. Promise 'free treatment' when the intent was only to say participants would not be charged for taking part in the investigation;
6. For FDA-regulated research, advertisements should not:
 - a. Make claims, either explicitly or implicitly, about the drug, biologic or device under investigation that were inconsistent with FDA labeling;
 - b. Use terms such as 'new treatment', 'new medication', or 'new drug' without explaining that the test article was investigational;
 - c. Allow compensation for participation in a trial offered by a sponsor to include a coupon for a discount on the purchase price of the product once it had been approved for marketing.

Advertisements conforming to the above guidelines may be approved for any advertising format (e.g., posted flyers, newspapers, internet advertisements, radio/television, and slides shown prior to films at movie theatres). The IRB must review the final copy of printed advertisements to evaluate the relative size of type used and other visual effects. To avoid multiple requests for IRB review and approval, investigators should specify in their original request all advertising formats that are anticipated.

All advertisements should follow Seton Family of Hospitals' Human Resources Policy 300.11.

3.14 Equitable Subject Recruitment

The IRB will only approve studies that demonstrate equitable subject recruitment, taking into account the purposes for the research and the setting in which it will be conducted. The IRB evaluates all research applications to verify that investigators have demonstrated equitable selection and recruitment (distributive justice) of all research subjects and have made every effort to ensure diversity of subject selection. In particular, the IRB evaluates any special problems that may occur with the proposed research involving vulnerable populations, such as children, prisoners, pregnant women, cognitively-impaired individuals, Seton staff, and economically or educationally disadvantaged persons. The IRB ensures that proposed sampling efforts do not favor some classes of participants solely due to ease of availability, compromised positions, or manipulability. IRB reviewers also require researchers to make every effort to include women and members of minority groups, if appropriate to the research purpose and beneficial to the subjects.

Section 4: Training in Human Subjects Protections

4.0 Background

To increase the federal commitment to the protection of human research participants, several new initiatives to strengthen government oversight of research with human subjects were announced by Department of Health and Human Services (DHHS) Secretary Shalala on May 30, 2000. On October 1, 2000, the National Institutes of Health (NIH) required education on the protection of human research participants for all investigators submitting NIH applications for grants or proposals for contracts or receiving new or non-competing awards for research involving human subjects. Before funds can be awarded for competing applications or contract proposals involving human subjects, investigators must provide a description of education completed in the protection of human subjects for each individual identified as “key personnel” in the proposed research.

For further information on the NIH policy, also see [Required Education in the Protection of Human Research Participants](#) and [Frequently Asked Questions for the Requirement for Education on the Protection of Human Subjects](#).

In addition to the federal commitment to the protection of human research participants, the Seton Institutional Review Board (SIRB) and the Seton Office of Research Administration (ORA) agree that a sound understanding and working knowledge of the ethical principles, legal requirements, regulatory requirements, professional standards, and institutional policies and procedures, are needed by persons involved in the design, conduct, review and/or oversight of human research conducted at or supported by Seton Family of Hospitals. Such individuals also are obligated to have a thorough understanding of the basic principles of conducting ethical human research and to stay current with evolving issues related to the conduct of human research and the protection of individuals who choose to participate in such research.

4.1 Required Training in Human Subject Protections

The SIRB, in accordance with federal requirements, good clinical practices, and the SIRB/ORA mission statement, requires Human Subjects Protection (HSP) training for all research personnel who are actively involved with clinical research within the Seton Family of Hospitals. This includes IRB members and staff, and research personnel (i.e., SIRB Members, Principal Investigators (PIs), Co-Investigators, Collaborators, Research Coordinators, Research Assistants, Research Nurses, Data Managers, Students, those consenting research participants, those recruiting research participants, etc.) Research personnel include all individuals who serve as members of the research team and/or who participate in the design, conduct, ethical review, and/or oversight of human research in the Seton Family of Hospitals.

All research personnel, including those who are not initially involved with a study but are later added to a research team, must complete HSP training through the [Collaborative Institutional Training Initiative \(CITI\)](#) web-based courses in human research subjects' protections. CITI training is a series of modules that can be completed at any time from any location with Internet access. Researchers are to complete the Basic/Refresher Course – Human Subjects Research Curriculum for the learner group that best applies to their role in the study. For example, Investigators are to complete the Basic/Refresher Course – Human Subjects Research Curriculum for Investigators. Research Coordinators are to complete the Basic/Refresher Course – Human Subjects Research Curriculum for Research Coordinators, as well as the CITI Good Clinical Practice (GCP) Course.

The completion of these applicable CITI courses is required prior to study initiation and submission to the SIRB. If CITI training is not completed by a researcher, ANY protocol which lists that person as key personnel cannot be reviewed and approved by the SIRB. Additional instructions on registration for the CITI program and the completion of these courses can be found at the following website:

http://www.seton.net/medical_services_and_programs/clinical_research/training_requirements_citi_program.

The core required modules that are included in the Basic/Refresher Course – Human Subjects Research Curriculum consist of:

1. Belmont Report and CITI Course Introduction
2. Basic Institutional Review Board (IRB) Regulations and Review Process
3. Informed Consent
4. Research and HIPAA Privacy Protections
5. Conflicts of Interest in Research Involving Human Subjects

Each learner group may contain additional modules to provide further training and information pertaining to that learner group. Modules may be added or removed to better suit the needs of research personnel, as decided by collaboration between the IRB Chair, Sr. Director of the ORA, IRB Manager, IRB Project Coordinators, and other institutional administrators within the CITI program.

As long as there are reciprocity agreements in place between the Seton IRB, the University of Texas at Austin (UT – Austin) IRB, and the University of Texas Southwestern (UTSW) IRB, completion of these institutions' (UT – Austin and UTSW) required HSP training(s) are accepted in lieu of the Seton IRB's CITI training requirements. The Seton IRB's CITI training requirements and the UT – Austin IRB or UTSW IRB's HSP training requirements are the only acceptable forms of HSP training.

4.1.1 ORA Staff Training

All staff members within the ORA – including those who directly support the SIRB and those who support other areas of research – will be oriented and trained with Human Subjects Protections, which includes completion of CITI on-line training modules. Staff members are required to complete the modules for the Basic/Refresher Course on Human Subjects Curriculum as well as the CITI Good Clinical Practice (GCP) Course.

4.1.2 Seton Institutional Review Board Member Training

All new IRB members and IRB member alternates are required to complete an orientation regarding their roles and responsibilities in the review of human subjects research prior to their participating as a voting member of the IRB. Orientation is conducted by the IRB Chair and/or Sr. Director of the ORA and/or the IRB Manager and/or the IRB Project Coordinator, and encompasses all of the following areas and member responsibilities:

1. Ethical foundations of IRB review;
2. Application of ethical principles to IRB review;
3. Seton IRB and ORA Policies and Procedures;
4. Federal regulations ([45 CFR 46](#)), guidance, and information on any relevant state laws;
5. Review criteria as set forth in [45 CFR 46.111](#);

6. Information on IRB submission and meeting schedules;
7. Types of IRB review;
8. Review procedures and expectations;
9. Checklists to aid in the review of protocols;
10. Data safety and security;
11. Economic considerations related to study participation;
12. Adverse event and unanticipated event considerations;
13. Conflict of Interest and protocol violations/noncompliance;
14. Information on HIPAA compliance;
15. FDA regulations ([21 CFR 50](#) and [21 CFR 56](#));
16. Information on clinical trials registration;
17. Information on multi-center trials;
18. Information on data and tissue repositories;
19. Information on Certificates of Confidentiality;
20. ORA website information and resources;
21. Organization of the ORA and explanation of various types/levels of support provided.

SIRB new member orientations may be scheduled individually or in groups, as necessary. Members are provided with written materials to support the learning/orientation objectives. These supporting materials, such as member handbooks, FDA issued guidances, checklists, etc., can be provided to the SIRB Members to serve as reference materials for the above-listed items. In addition, SIRB members must document that they have completed the CITI training for IRB Members.

4.2 Continuing Education

All active research personnel are required to complete the CITI training at least once every three years to stay current in issues and regulations regarding human research. Investigators and research personnel should track these deadlines and ensure submission of any renewed human subjects training certificates are received by the IRB prior to the study's annual renewal date in order to avoid a study lapse.

4.2.1 Continuing Education for IRB Members and IRB Staff

Continuing education material(s) are distributed at the one regularly scheduled IRB meeting each month, in the form of OHRP/FDA issued guidance documents, current events, checklists, periodicals, blogs, editorials, summaries of meetings, meeting transcripts, reports, and/or journal articles. (See Section 2.2 for IRB Meetings schedule) Other forms of continuing education may be utilized as determined by the Sr. Director of the ORA. The alternate forms include – but are not limited to – invitations to group forums, conferences, webinars, presentations, educational retreats, lectures, and guest speakers.

4.2.2 Continuing Education for Investigators and Research Staff

Continuing education material(s) and/or information are periodically distributed to the research community via the ORA Newsletter. Other forms of continuing education for Investigators and Research Staff may be utilized as determined by the Sr. Director of the ORA. The alternate forms include – but are not limited to – invitations to group forums, conferences, webinars, presentations, educational retreats, lectures, and guest speakers.

4.2.3 Continuing Education for IRB Chair and Institutional Official

The IRB Chair and the Institutional Official (IO) have the responsibility to remain current with developments in the field of human research protections. Attendance at local, regional, and national conferences, networking with peers at other institutions, review of the literature, and review of issues presented in the press all serve to maintain currency of knowledge. These leaders are expected to participate in conferences and peer networking on a regular basis. The Institution provides budgetary support for journal subscriptions and conference attendance.

4.2.4 Documentation of Continuing Education

CITI training records are maintained in all IRB files for each research personnel that are involved with a study. (Please see section 2.6 for more information on Protocol Files) CITI training records for IRB Members are maintained in a designated binder containing all IRB Member records. An online database of CITI training records is also maintained and accessible by IRB Coordinators at anytime. Completion of CITI training is made available online for free to the research community and verified by the IRB staff at the time of protocol submission. (See Section 6.0 for Requirements for Initial IRB Review)

The continuing education material(s) that are distributed at the one regularly scheduled IRB meeting each month are documented in the Meeting Agenda and Meeting Minutes for that IRB meeting accordingly. Additionally, IRB members and staff are asked to provide their signature on the *Education Sign-In Sheet* attesting to their receipt and acknowledgement of the continuing education materials that were provided.

The continuing education material(s) and/or information that are periodically distributed to the research community via the ORA Newsletter are documented via a copy of the Newsletter. An archive of the Newsletters is maintained by IRB staff.

Section 5: Informed Consent and Assent of Research Participants

5.0 Informed Consent

Informed consent is an ongoing communication process between the researchers and subjects. Informed consent is central to the research process and is based on the ethical principles of respect for persons, beneficence, and justice. Informed consent assures that prospective human subjects will understand the nature of the research and can knowledgeably and voluntarily decide whether or not to participate. If the PI has a relationship with potential subjects (physician-patient, instructor-student, employer-employee), care should be taken to avoid recruitment methods that may be seen as coercive due to the special relationship between parties.

Only adults with sufficient capacity to consent can provide legally effective informed consent. The consent document should be written using language that is understandable to the subject. The potential subject or legally authorized representative (LAR) must be given adequate time to review the consent, ask questions, and make an informed decision.

Children and those individuals who are not competent to provide consent should be given the opportunity to assent in order to participate in the research project. Assent is a knowledgeable agreement to participate in the research project. The assent document should be written using language that is understandable to the subject.

Except as described in Sections 5.6 and 5.7 below, PIs may not enroll human subjects in research unless they have obtained the legally effective, written, informed consent of the subject or the subject's legally authorized representative prior to enrollment of the subject in the research. Investigators are responsible for ensuring that the subjects, or their representatives, are given sufficient opportunity to consider whether or not to participate and must seek to avoid coercion or undue influence. The IRB is responsible for evaluating the informed consent process. The IRB may request to observe the informed consent process to ensure adequate consent when the research involves particularly vulnerable populations. Information given to potential subjects or their representatives must be in a language that is understandable to the subject or representative. No process of obtaining consent may include exculpatory language through which subjects waive any of their legal rights or releases or appear to release the investigator, sponsor, or institution or its agents from liability for negligence. The consent process must provide sufficient opportunity to consider whether to participate. The PI must completely describe the consent process in the study protocol.

Occasionally, the institutional setting in which the consent is sought will pose the possibility of coercion or undue influence. Conducting research at institutions that provide services to subjects may be perceived as implying that continued service is dependent upon participation in the research. Patients in the hospital or clinical setting may be concerned that refusal to participate will affect their standard treatment. These institutional pressures should be addressed in the research design. The protocol must adequately preserve the right to refuse participation.

There are many other examples of possible sources of undue influence on subjects. It may not be possible to remove all sources of undue influence, but the PI must examine each project to assure the elimination of coercion and minimization of other undue influences. The requirement to obtain informed consent should be seen as not only a legal obligation, but also as an ethical obligation. The research design must adequately address how informed consent will be obtained and what information will be given to prospective subjects. IRBs must look at the issues of coercion and undue influence in each

proposal and insist on protocols where the circumstances of the consent process minimize the possibility of coercion and undue influence to participate.

5.1 Elements of Informed Consent / Assent Forms

Informed consent/assent¹² templates with sample consent/assent language can be found on the ORA web page at www.seton.net/research. The sample consent/assent forms contain the basic required elements in language that is appropriate for the respective age groups. The following are the basic required elements of consent (from [45 CFR Part 46.116](#)):

1. Statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
2. A description of any reasonably foreseeable risks or discomforts to the subject;
3. A description of any benefits to the subject or to persons that may reasonably be expected from the research;
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained; if the research is subject to Food and Drug Administration (FDA) regulation, the statement also must note the possibility that the FDA will inspect the records.
6. For research involving more than minimal risk ("Minimal Risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in the participant's daily life or during the performance of routine physical or psychological examinations or tests [[45 CFR 46.102\(i\)](#) and [21 CFR 50.3\(k\)](#)]). In research involving prisoners, minimal risk is also defined as the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons. An explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Whenever appropriate, one or more of the following elements of information shall also be provided to each subject:

1. If the risks of any research procedure are not well known, for example because of limited experience in humans: A statement that the particular treatment or procedure may involve risks to the participant which are currently unforeseeable;

¹² Assent is the affirmative agreement by a child, or an adult who lacks full decision-making capacity, to participate in a research or clinical investigation. Mere failure to object or absent affirmative agreement may not be construed as assent [[45 CFR 46.402\(b\)](#) and [21 CFR 50.3\(n\)](#)].

2. If the research includes women of child bearing potential or pregnant women, and the effects of any research procedures on embryos and fetuses is not well known: A statement that the particular treatment or procedure may involve risks to the embryo or fetus, if the participant is or may become pregnant, which are currently unforeseeable.
3. If there are anticipated circumstances under which the participant's participation will be terminated by the investigator without regard to the participant's consent: Anticipated circumstances under which participation may be terminated by the investigator without the participant's consent.
4. If there are costs to the participant that may result from participation in the research: Additional costs associated with study participation.
5. If there are adverse consequences (e.g., physical, social, economic, legal, or psychological) of a participant's decision to withdraw from the research: Consequences of a participant's decision to withdraw from the research.
6. If there are adverse consequences (e.g., physical, social, economic, legal, or psychological) of a participant's decision to withdraw from the research: Procedures for an orderly termination of participation
7. If significant new findings during the course of the research that may relate to the participant's willingness to continue participation are possible: Statement that new findings developed during the course of the research that may relate to the participant's willingness to continue in the research study will be provided to the participant.
8. If the approximate number of participants involved in the study might be relevant to a decision to take part in the research: Approximate number of participants involved in the study
9. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
10. A description of the clinical trial available on <http://www.clinicaltrials.gov>, as required by U.S. law and that this web site will not include information that can identify the participants. At the most, the website will include a summary of the participants' results and that they can search the web site at anytime.

The informed consent requirements in this policy are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed in order for informed consent to be legally effective. The IRB also provides a [Brief Informed Consent Form Template](#) that may be used in research studies, as deemed appropriate (i.e. studies that are no more than minimal risk).

5.2 Obtaining and Documenting Informed Consent of Participants Who Do Not Speak English

Federal regulations require that consent information be presented in language understandable to the subject [[45 CFR 46.116](#)]. Subjects who do not speak English should be presented with a consent document written in a language understandable to them. Study documents (including informed consent/assent forms and scripts) are to be translated by a certified translator, or translated documents are to be reviewed and authenticated by a certified translator. The IRB also provides a [Translator Declaration](#) for use in certifying translations.

Except in cases where informed consent requirements have been waived or altered, the consent form for non-English speakers may be either of the following (as determined appropriate by the IRB):

1. A written consent document that embodies the elements of informed consent required by [45 CFR 46.116](#). This form may be read to the participant or the participant's legally authorized

representative, but in any event, the investigator shall give either the participant or the representative adequate opportunity to read it before it is signed. When a translated consent is used, the PI or member of the research team must ensure that the participant's questions can be answered in a language that the patient or the patient's representative understands. The preferred process is that consent be obtained by a bilingual member of the research team. In the instance that no member of the research team is fluent in the participant's language, the consent may be obtained with the assistance of a certified translator who is bilingual and is familiar with the medical procedures used in the protocol, so that the participant's questions can be answered in the language of the participant. The PI or another member of the research team must be present to ensure that the participant's questions about the study are answered at the time the consent is discussed. The signature line for the 'person obtaining consent' should be modified to indicate that the person obtaining the consent was bilingual (e.g. Signature of Bilingual Person Obtaining Consent) or there should be some indication of this on the informed consent document; or

2. A short form written consent document stating that the elements of informed consent required by [45 CFR 46.116](#) have been presented orally to the participant or the participant's legally authorized representative (LAR). When this method is used, there shall be a witness to the oral presentation. The witness should be fluent in both English and the language of the participant. The researcher must submit for approval a written summary of what is to be said to the subject or the LAR. The IRB-approved English language consent document may serve as the summary document. Only the short form document is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the participant or the representative, in addition to a copy of the short form.

The IRB will consider the research study, the stage/phase in which the research study is in, the research subject population, and any other related factors to decide which of these options is the most appropriate.

5.3 Additional Consent Information for Different Types of Studies

1. Studies involving blood samples: The consent form should contain a statement such as, "Blood samples will be obtained by venipuncture. This method involves inserting a needle into a vein in the arm and withdrawing a sample of blood. It is routinely used to obtain blood for physical examinations. Venipuncture is accompanied by minor discomfort at the site of the needle entry and may result in slight bruising and a feeling of faintness. In this study a trained technician will obtain a 30 milliliters (about 2 tablespoonfuls) sample of your blood that will be analyzed for..."
2. Studies involving blood, tissue, or body fluid for possible genetic research: If the research involves the use of a subject's blood, tissue or body fluid for current or future genetic research, the researcher should modify the consent form to explain subjects' rights, including:
 - a. the fact that the specimens will be maintained without identifiers;
 - b. the risk level to the subject if they agree to participate;
 - c. where the specimens will be stored;
 - d. who owns the specimens; and
 - e. how the specimens will be used in the future.
3. Studies that involve physical risk: The Seton Family of Hospitals does not have a plan to provide facilities or insurance to cover research-related injuries. If the study involves physical risk, assess the risk and add a statement such as, "There is no plan to provide treatment for research related injury and no plan to provide payment in the event of a medical problem." If emergency treatment

for research related injuries is arranged by (for example) having a medical doctor available for emergency treatment, that should be stated, but a disclaimer for extended care should be put into the consent form, such as “You will be charged for continuing medical care and hospitalization for research-related injuries. There is no plan to provide financial compensation.”

4. Studies that involve a risk to a fetus: The female participant must be informed of the risk and the methods to be used (such as a pregnancy test) to minimize the risk in accordance with the Seton Family of Hospitals approved [Model Language for IRB Consent Clauses Regarding the Use of Contraception](#), provided on the ORA website.
5. Studies that involve drugs: The participants must be given a statement of known side effects, warned about possible drug interactions (including interactions with alcohol), and warned about activities that may be dangerous (such as driving with a drug that has a sedative effect).
6. Studies that involve psychological risk: The principles that apply to studies that involve psychological risk or mental stress are similar to those that involve physical risk. Participants should be informed of the risk and told that there is no plan to provide treatment. They should be given the names and telephone numbers of agencies that may alleviate their mental concerns, such as a crisis hot line. If the PI or the faculty sponsor of a student investigator is qualified to treat mental health problems, that person may be listed as a resource.
7. Studies that involve sensitive topics: Participants should be told that some of the questions are of a personal or sensitive nature and should be given examples of the topics or questions. They should also be told that they can skip a question if they do not wish to answer it. If questionnaires or interviews may generate reports of child physical or sexual abuse, the participant must be informed that the researcher is legally required to report this information to Child Protective Services. If the questionnaire or interview may generate reports that the participant plans to harm him or herself or others, the participant must be told that the investigator is ethically required to report that information to the local police department. Information about the legal obligations to report abuse and threats of harm to oneself or others may be omitted if the responses are anonymous. In the event that the Privacy Rule is more restrictive than the procedures described in the consent requirements, the more restrictive rule must be followed.
8. Studies that involve deception: Deception should be employed only when there are no viable alternative procedures. Where deception is a necessary part of an experiment, the IRB will generally require that a preliminary consent be obtained, in which the investigator informs the subject of the research. After the experiment, the subject should be informed of the deception and its purpose. The IRB recognizes that there may be rare instances in which no consent can be obtained or debriefing done. Deception requires that a PI obtain formal approval of a [Waiver or Alteration of Informed Consent](#), due to only the preliminary consent being used.
9. Studies that involve audio or video recordings: Participants must be told:
 - a. that the interviews or sessions will be audio or videotaped;
 - b. that the media to be used will be coded so that no personally identifying information is visible on them;
 - c. that the recordings will be kept in a secure place (e.g., a locked file cabinet in the PIs office, which is locked);
 - d. that recordings will be heard or viewed only for research purposes by the investigator and his or her associates; and
 - e. that recordings will be erased after they are transcribed or coded.

If the PI wishes to keep the recordings because of the requirements of his/her professional organization with respect to data or because the researcher may wish to review them for additional analyses at a later time, the statement about erasing them should be omitted and replaced with a statement that recordings will be retained for possible future analysis. If the researcher wishes to present the recordings at a convention or to use them for other educational

purposes, he/she should get special permission to do so by adding, after the signature lines on the consent form, the following statement, "We may wish to present some of the tapes from this study at scientific conventions or as demonstrations in classrooms. Please sign below if you are willing to allow us to do so with the tape of your performance." Additionally, a second signature line should be added with the preface, "I hereby give permission for the video (audio) tape made for this research study to be also used for educational purposes." This procedure makes it possible for a participant to agree to being taped for research purposes and to maintain the confidentiality of the information on that tape.

10. Studies that involve monetary or other compensation: The amount and type of the stipends or other compensations and the requirements to earn them must be clearly specified. If the study extends over a period of time, it is acceptable to reward a participant with a bonus if he or she completes all the interim components of the study; however, the participant must be paid for each component, and the bonus should not be greater than 50% of the total compensation.
11. Cover Letters: Cover letters, rather than consent forms, may be used for some minimal-risk research with adults such as survey or questionnaire research on non-sensitive topics. The cover letter should state the purpose of the survey, the expected number of respondents, a description of the topic of the survey and the content of the questions on the survey, a statement about confidentiality or anonymity, that participation is voluntary, a statement about how the participant may obtain additional information about the study and that he or she need not sign it, because responding to the survey indicates a willingness to participate in the study. The cover letter should also state that a decision not to participate will not affect, "... Your current or future relationships with (names of relevant entities, such as Seton Family of Hospitals)." The participant should be allowed to keep the cover letter. In the event that a cover letter is used, it must confirm to the authorization procedures required by Health Insurance Portability and Accountability Act ([HIPAA](#)).

5.4 Waiver of Authorization for Use and Disclosure of Personal Health Information (PHI)

To use or disclose PHI without authorization by the research participant, all of the following must be true or present:

1. Documentation that a Waiver of HIPAA Authorization has been approved by the IRB. This provision of the rule might be used, for example to conduct retrospective chart reviews, when researchers are unable to use de-identified information; or
2. Where researchers represent:
 - a. that the research is only for purposes of preparing a research protocol or use similar uses preparatory to research;
 - b. that he or she will not remove any PHI from the covered entity; and
 - c. that PHI is necessary for the research purpose.
3. To disclose PHI of decedents, where the researcher represents that the use or disclosure of PHI is:
 - a. solely for research on the PHI of decedents;
 - b. necessary for the research; and
 - c. documentation of the death of the individuals about whom PHI is sought and provided.

In addition, in order to use or disclose PHI without authorization by the research participant, the researcher is required to obtain:

1. Documentation of the following information:
 - a. a statement identifying the IRB and the date on which the amendment or waiver of authorization was approved;
 - b. a brief description of the protected health information for which use or access has been determined to be necessary by the IRB;
 - c. a statement that the amendment or waiver of authorization has been reviewed and approved under either normal or expedited review procedures following the requirements of the Common Rule, including the normal review procedures;
 - d. a statement that the IRB has determined that the authorization may be altered or waived, in whole or in part, indicating:
 - i. The use or disclosure of protected health information involves no more than minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
 1. an adequate plan to protect the identifiers from improper use and disclosure;
 2. an adequate plan to destroy the 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; and
 3. adequate written assurances that the protected health information will not be re-used or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by the Privacy Rule;
 - ii. The research could not be practically conducted without access to, and use of, the protected health information;
2. Documentation of the amendment or waiver of authorization must be signed by the chair or other member, as designated by the chair of the IRB, as applicable;
3. Prior to the review of preparatory research, the IRB will obtain from the researcher representations that:
 - a. use or disclosure is sought solely to review protected health information as necessary to prepare a research proposal or for similar purposes of preparatory research;
 - b. no protected health information is to be removed from the covered entity by the researcher in the course of the review; and
 - c. the protected health information for which use or access is sought is necessary for research purposes;
4. Prior to research using information of decedent(s), the IRB will obtain from the researcher:
 - a. representations that the use or disclosure is sought solely for research on the protected health information of decedents;
 - b. documentation, at the request of the IRB, of the death of such individuals; and
 - c. representation that the protected health information, for which use or disclosure is sought is necessary for the research purposes;

Personnel receiving a request from an individual or entity for use or disclosure of protected health information will determine whether the requesting individual is a person with whom the IRB has a knowing relationship. All personnel will follow appropriate policies and procedures for verifying the identity and authority of individuals requesting protected health information.

Once it is determined that use or disclosure is appropriate, personnel with appropriate access clearance will access the protected health information using proper access and authorization procedures. The requested protected health information will be delivered to the requesting individual in a secure and confidential manner, such that the information cannot be accessed by employees or other persons who do not have appropriate access clearance to that information. All personnel will appropriately document the request and delivery of the protected health information. In the event that the identity and legal authority of an individual or entity requesting protected health information cannot be verified, staff will refrain from disclosing the requested information and report the case to Seton Family of Hospitals Privacy Officer. Knowledge of a violation or potential violation of this policy must be reported to the Seton Family of Hospitals Privacy Officer.

5.5 Documentation of Informed Consent

Federal regulations governing the use of human subjects in research activities require written documentation of informed consent unless the research meets the criteria for Waiver of Documentation of Consent. The participant and investigator should sign and date the IRB approved consent form.

Confusion sometimes arises as to who can obtain consent and who can be designated to sign the consent form. The following are the acceptable methods for documentation of informed consent of human research subjects at Seton Family of Hospitals:

1. The IRB must be made aware of the person(s) who will be conducting the consent interviews. These faculty/staff members should be listed in the IRB application, and unless indicated otherwise, are the only personnel allowed to obtain consent.
2. Each subject (or their legally authorized representative) must be provided adequate time to read and review the consent form, in addition to being advised of the procedures, risks, potential benefit, alternatives to participation, etc. This is frequently accomplished using the consent form as an outline for the interview process.
3. After completing the consent interview and assuring that the subject (or their representative) has no further questions and agrees to participate in the research activity, the interviewer should instruct the subject (or their representative) to sign and date the consent form in the appropriate spaces.
4. The person conducting the consent interview must then sign and date the consent form in the appropriate spaces (PI or appropriately trained and designated study personnel). It is assumed that in most cases, all persons signing the consent form will do so at the conclusion of the consent interview.
5. Each subject (or their representative) must be given a copy of the signed consent form. The original consent form should be filed in such a manner as to ensure immediate retrieval when required by auditing entities, e.g., FDA, IRB, or sponsor monitors.
6. The regulations are clear that written documentation of informed consent is required, unless waived. Therefore, obtaining consent from an authorized third party via the telephone is not acceptable unless the IRB waives the requirement to document the informed consent process.
7. The regulations also include provisions for approval of a waiver or amendment of part or all of the consent process. The IRB will consider written requests for waiver or amendment of the process when accompanied by sufficient justification.
8. Obtaining informed consent from subjects must be accomplished prior to performing any research activity involving those subjects; and must be done using only an IRB approved and stamped consent form with the current approval dates. Written requests for

amendments to an existing consent form must be approved prior to implementation, at which time the IRB office will provide a formal approval letter of the amendment to the consent form and newly stamped consent forms with the new approval dates.

9. In some instances, the IRB will approve the use of the [Brief Informed Consent Form Template](#) for minimal risk studies.

Upon receipt of an IRB approved consent form, all old versions should be filed away to prevent inadvertent use of an outdated consent form. Copies of the most recently approved consent form may be made and should be used until replaced by an amended consent form. The consent form must be reviewed at least annually as part of the continuing review process.

5.6 Waiver of Documentation of Informed Consent

The IRB can waive the requirement that the consent process include a signed consent form. Investigators desiring to not have a signed consent form must still provide participants with a consent document disclosing all the required elements necessary for informed consent. In such cases, the IRB encourages investigators to use the consent templates and remove the signature section. Investigators are free to format the consent document, as necessary. According to [45 CFR 46.117](#) and/or [21 CFR 56.109\(c\)\(1\)](#), an IRB may waive the requirement for the PI to obtain a signed consent form for some or all subjects if it finds:

1. The research presents no more than minimal risk; and
2. The research involves procedures that do not require written consent when performed outside of a research setting [[45 CFR 46.117](#); [21 CFR 56.109\(c\)\(1\)](#)].

OR

1. The principle risks are those associated with a breach of confidentiality concerning the subject's participation in the research;
2. The consent document is the only record linking the subject with the research [[45 CFR 46.117](#)];
3. Each participant will be asked whether the participant wants documentation linking the participant with the research, and the participant's wishes will govern; and
4. The study is not FDA regulated.

5.7 Waiver of Informed Consent

The IRB may waive the requirements for obtaining informed consent or approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent listed in section 5.1, provided that all of the following conditions are met:

1. The research involves no more than minimal risk to the subjects;
2. The waiver or amendment will not adversely affect the rights and welfare of the subjects;
3. The research could not practicably be carried out without the waiver or amendment;
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation; and
5. The study is not FDA regulated.

Section 6: Review Mechanisms and Outcomes

6.0 Requirements for Initial IRB Review

Applications are initially screened in the Seton Office of Research Administration (ORA) for completeness before forwarding to the designated Institutional Review Board (IRB) reviewer or fully convened meeting of the Seton Institutional Review Board (SIRB), also referred to as Full Board, for review. Once a submission has been received by the ORA and is deemed viable, it is assigned a unique Clinical Research (CR) number. The date that the submission is received is also recorded. A complete submission for IRB review includes, but is not limited to, the following items, as applicable:

1. A complete original IRB Application (electronic) with Principal Investigator (PI)'s e-signature signing off on PI Assurance Statement (required);
2. IRB Approval Letters for extramural research (if applicable);
3. Other materials specific to the proposed study (e.g., sponsor correspondence with a regulatory agency such as the FDA regarding test item risk, etc.) (if applicable);
4. A research proposal/protocol describing the rationale for the study, research questions to be answered, methods, procedures, data analysis plan, and other required information (see the [Topics to Address in the Research Proposal Template](#)). The research proposal must contain all of the required information as outlined in the research proposal template (required);
5. Sponsor Protocol or Main Site Protocol (if applicable);
6. DHHS sample protocol (if applicable);
7. DHHS sample consent document (if applicable);
8. Case Report Forms (if applicable);
9. Data collection sheets (if applicable);
10. If the study involves the use of questionnaires, surveys or similar instruments, copies must be submitted (if applicable);
11. Investigator's brochure/Drug packet inserts (if applicable);
12. Recruitment materials (including direct advertising materials, flyers, posters, web-pages, email messages, letters, etc.) (if applicable);
13. Translator's Declaration for any translated documents (if applicable);
14. An informed consent document *or* justification for Waiver of Informed Consent or Waiver of Documentation of Informed Consent (required);
15. Assent documents (if applicable);
16. Collaborative Institutional Training Initiative (CITI) Human Subjects Protection Training Certificates for all study personnel (See Section 4.1 for more information for Training In Human Subjects Protections) (required);
17. Sign and Dated CVs for Principal and all Co-Investigators (required).

All forms and documents that require a signature from the PI must contain the PI's own original or electronic signature. If any part of the application is incomplete or otherwise not fully prepared for review, a viability email will be sent to the PI requesting the necessary changes. If the PI does not fulfill the requirements requested in the viability email within 30 days of the date of submission, the submission may be withdrawn by the ORA. Once a complete packet of information has been received, it is considered viable and ready for IRB review. The date that the submission becomes viable is recorded by the ORA. The unique CR number remains with the study and is not reassigned to a different study.

6.1 Submission Schedule Requirements

For Full Board studies, there is one regularly scheduled IRB meeting each month. (Please see Section 2.2 for more information on IRB Meetings schedules.) Investigators shall be responsible for ensuring that all Full Board protocols are submitted to the ORA and signed into the ORA submission log by the 3rd Friday of the current month in order for the protocol to be reviewed at the next month's Full Board meeting. (For example, a new Full Board study should be submitted to the ORA and viable by December 20, 2013, in order to be reviewed at the Full Board Meeting on January 14, 2014.) This is in the case of a complete and viable submission. Otherwise, the expected time to review is extended until the submission is viable.

For Expedited and Exempt studies, investigators shall be responsible for ensuring that all of these research protocols are submitted to the ORA and signed into the ORA submission log by the Friday of the current week in order for the submission to be reviewed by an IRB Reviewer the following week. This is in the case of a complete and viable submission. Otherwise, the expected time to review is extended until the submission is viable.

These deadlines for submissions will hold true each week/month unless otherwise determined by the IRB Coordinator(s), in correspondence with the PI and/or research coordinator.

6.2 Initial Evaluation of Submitted Projects

Once the ORA receives a human research project application, the IRB Coordinator(s), in collaboration with the IRB Chair and/or designee, review the application verifying that the PI requested the appropriate level of review: Exempt, Expedited, or Full Board; and that all required documentation has been submitted. Any further questions about the appropriate review level, applicability of the definition of human research, jurisdiction of IRB, or otherwise related to the necessity of IRB review are directed to the Sr. Director of the ORA and/or IRB Chair directly. All projects involving the use of investigational drugs, investigational devices, or investigational biologics for which an IND/IDE is required must receive Full Board review.

6.3 Exempt Research Review Process

Federal regulations identify specific categories of research activities that are exempt from certain federal regulations on the protection of human subjects in research. It is important to note that while a project may be exempt from the regulations, the ethical principles of conducting research with human subjects still apply. The investigator is still responsible for knowing and adhering to the ethical principles of human subject research.

At the Seton Family of Hospitals, the investigator may not make the determination of Exempt status. This is in compliance with the Terms of the Federal Wide Assurance (FWA) that requires written procedures for "Verifying, by a qualified person or persons other than the investigator or research team, whether proposed human subject research activities qualify for exemption from the requirements of the Common Rule." It is the policy of the Seton Family of Hospitals that the IRB Chair and/or designee will make the determination whether a protocol meets the criteria for exemption from federal research regulations. To request Exempt status, investigators should submit an initial application to the ORA selecting Exempt as the level of review. Once a complete application and all required information have been received, the IRB Chair and/or designee will make a final determination of Exempt status. The determination requires that the research activity meets the criteria for Exempt status and meets the criteria for protection of research

participants in Exempt research. The ORA will then issue a letter of Exempt designation to the investigator.

Exempt protocols will be approved for a three-year period. Before the end of the three-year approval period, the ORA will request a study status update from the Investigator. This will serve as a continuing review of the study. Amendments to the study protocol are required to be reviewed and approved by the SIRB in order to determine if the amendment changes the exempt determination of the study. The IRB Chair and/or designee will make this determination. The investigator is also responsible for informing the IRB immediately of any adverse or unexpected events that would alter the exempt status, as well as when the research is completed.

6.3.1 Criteria for Exempt Status

The criteria used for the determination of Exempt status follow all applicable federal regulations including:

- [45 CFR 46.101\(b\)\(1\) through \(6\)](#);
- [45 CFR 46.301\(a\)](#);
- [45 CFR 46.306\(a\) and \(b\)](#);
- [45 CFR 46.401\(b\)](#); and
- [21 CFR 56.104](#).

These criteria are applied to all research regardless of funding or funding source. The regulations identify specific categories of Exempt research activities and also identify when there are exceptions. To be classified as Exempt, the research:

1. Must involve only procedures or be a type of study listed in one or more of the Exempt Categories (listed below in Section 6.3.4. Categories of Research that May be Reviewed by the IRB through an Exempt Review Procedure);
2. Cannot involve children being surveyed, interviewed, or interactively publicly observed (see Section 6.3.2 Involving Children in Exempt Research);
3. Cannot involve prisoners as research subjects (see Section 6.3.3 Involving Prisoners in Exempt Research);
4. Cannot be greater than minimal risk*; and
5. Cannot be FDA-regulated; except for Category 6.

“Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” This is in accordance with [45 CFR 46.102\(j\)](#).

If a specific research activity meets the Exemption criteria for one applicable regulation but not another, the research activity will not be given Exempt status, but will be processed under procedures for Expedited or Full Board Review as appropriate.

6.3.2 Involving Children in Exempt Research

Research involving children cannot be classified as Exempt if the research involves:

1. Surveys;

2. Interview procedures; or
3. Observations of public behavior in which the investigator participates in the activities being observed.

Research involving children can be classified as Exempt if the research involves only educational tests and observation of public behavior where the investigator does not participate in the activities being observed and meets the other conditions of [45 CFR 46.101\(b\)\(2\)](#). The regulations require additional protections for research involving children. The only Exempt Category below (see Section 6.3.4) that applies to children as research subjects is Exempt Category 2. This category applies to research involving children as subjects only under specific conditions as specified in [45 CFR 46.401\(b\)](#): “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.” This is in accordance with [45 CFR 46.401\(b\)](#).

6.3.3 Involving Prisoners in Exempt Research

The federal regulations on exemptions listed above do not apply to research involving prisoners. Research involving prisoners as subjects is never exempt from the regulations. “The regulations in this subpart are applicable to all biomedical and behavioral research conducted or supported by the Department of Health and Human Services (DHHS) involving prisoners as subjects.” [45 CFR 46.301\(a\)](#) “Except as provided in paragraph (a) of this section, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as subjects.” This is in accordance with [45 CFR 46.306\(b\)](#).

6.3.4 Categories of Research that May be Reviewed by the IRB through an Exempt Review Procedure

As outlined in [CFR 46.101\(b\)](#), following are the categories of research that may be reviewed by the IRB through an Exempt Review Procedure:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as:
 - a. research on regular and special education instructional strategies, or
 - b. research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
 - a. information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
 - b. 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 subject's financial standing, employability, or reputation.
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 category number 2 above, if:
 - a. the human subjects are elected or appointed public officials or candidates for public

- office; or
 - b. federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
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. To qualify for this exemption, the data, documents, records, or specimens must be in existence before the project begins.
 5. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:
 - a. public benefit or service programs;
 - b. procedures for obtaining benefits or services under those programs;
 - c. possible changes in or alternatives to those programs or procedures; or
 - d. possible changes in methods or levels of payment for benefits or services under those programs.
 6. Taste and food quality evaluation and consumer acceptance studies,
 - a. if wholesome foods without additives are consumed; or
 - b. 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.

6.3.5 Procedures for Exempt Determination

The Investigator must submit an initial application to the ORA selecting Exempt as the level of review. With the initial application, the PI must also submit the PI Assurance Statement acknowledging they have read and accepted the responsibility to protect research participants. Once a complete application and all required information have been received, the IRB Chair and/or designee will make a final determination of Exempt status, consulting with the Sr. Director of the ORA, as appropriate.

If the project is determined to meet the criteria for Exempt and if the PI Assurance Statement has been received, the ORA will issue a letter of Exempt designation to the investigator.

If the project is determined to not meet the criteria for Exempt, the IRB chair and/or designee will then request additional information as needed, and initiate the relevant Expedited or Full Board review process as appropriate. If the project is determined to meet the criteria for Expedited Review (See Section 6.4.1 Categories of Research that may be Reviewed by the IRB through an Expedited Review Procedure), the IRB Chair and/or designee can complete the Expedited review process after receiving the information necessary. If the project is determined to require Full Board review, the IRB Coordinator will determine if the study can be added to the next Full Board Meeting agenda; and the IRB Chair and IRB Coordinator will assign an appropriate Primary Reviewer.

Processing of complete applications for Exempt determination is estimated to take 7 working days or more, though the ORA works to process submissions as rapidly as possible. Processing time increases if the application is incomplete (not viable) or if the IRB Staff must request additional information and/or clarifications.

6.4 Expedited Research Review Process

Protocols determined to be no more than minimal risk and do not qualify under any Exempt category, may be considered for Expedited review. Expedited review shall be conducted by the IRB chair and/or designee. The Chair and/or designee may approve projects as submitted or require modifications prior to approval (in the form of explicit stipulations). The IRB member(s) conducting the Expedited review may exercise all of the authorities of the full IRB except that the reviewer(s) may not disapprove the research. Protocols that cannot be approved by the Chair and/or designee are referred to the Full Board for review.

6.4.1 Categories of Research that may be Reviewed by The IRB Through an Expedited Review Procedure

If the proposed research is minimal risk and it is of a type of research that falls into one of the categories of research listed below and published in the Federal Register by HHS and FDA, the Chair (or an experienced designated reviewer) may review and approve the research. 'Minimal risk' means "that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests", under [45 CFR 46.102\(I\)](#).

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.

The categories in this list apply regardless of the age of subjects, except as noted. The Expedited review procedure may not be used:

1. 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; or
2. for classified research involving human subjects.

IRBs are reminded that the standard requirements for informed consent (or its waiver, amendment, or exception) apply, regardless of the type of review, Expedited or convened, utilized by the IRB. Categories one (1) through seven (7) below pertain to both initial and continuing IRB review.

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 Part 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 Part 812](#)) is not required; or
 - ii. the medical device is cleared or 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:

- f. from healthy, non-pregnant 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
 - g. 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.
 - 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;
 - d. excreta and external secretions (including sweat);
 - e. uncannulated saliva collected, either in an unstimulated fashion or stimulated by chewing
 - f. gumbase or wax or by applying a dilute citric solution to the tongue;
 - g. placenta removed at delivery;
 - h. amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
 - i. supra- and sub-gingival 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;
 - j. mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
 - k. 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 include:
 - 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, doppler blood flow, and echocardiography;
 - e. 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 non-research purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS 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 HHS 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:
 - a. 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
 - b. Where no subjects have been enrolled and no additional risks have been identified; or
 - c. 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 two (2) through eight (8) 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.

Even when the above criteria are met, the IRB Chair and/or designee retain(s) the right to require Full Board review when warranted by the nature of the research and/or where the IRB Chair and/or designee has/have concerns with regards to subject safety, rights, or welfare.

Minor modification to the protocol, consent documents, recruitment materials, etc., defined as a modification that does not increase the risk or decrease the potential benefit to participants; does not involve the addition of procedures involving more than minimal risk to participants; and all added procedures fall under the Categories 1-7, as described above, can be reviewed through the Expedited Review procedure.

6.5 Greater Than Minimal Risk Protocols - Full Board

All submissions for initial review, continuing review, review of modifications to previously approved research, review of protocol deviations, review of adverse events, etc. that have been determined by the IRB Chair and/or designee to not be eligible for Exemption from IRB review or review through Expedited Review procedures (i.e., failing to meet the criteria defined in Section 6.3.1 or 6.4.1), by regulation, must be reviewed and approved at a fully convened meeting of the IRB. The IRB adheres to the following process to facilitate the thorough review of each protocol according to federal regulations (45 CFR 46 and 21 CFR 50 and 56):

After a submission is determined to be viable, IRB Staff provide a complete copy of the submission to each IRB member at the IRB meeting as well as each reviewer of the protocol in advance of the meeting. Each person who receives the protocol is asked to review the protocol and the supporting documentation in detail.

The IRB Chair and/or designee assist(s) IRB Staff to assign primary reviewers in advance of a full board meeting when necessary. The IRB Chair, at his/her discretion, may serve as the Primary Reviewer of a submission. In selecting the Primary Reviewer, consideration is given to the individual's knowledge of the subject area embodied in the study protocol. If, in the opinion of the IRB Chair, the IRB membership does

not include someone with the relevant scientific or scholarly expertise to conduct an in-depth review of a particular protocol, the Chair may invite a non-voting consultant with the appropriate expertise to attend the meeting as the primary reviewer and/or submit his/her review to the ORA prior to the Full Board meeting. The IRB Chair and ORA make every effort to identify reviewers based upon expertise, relevance, interest, and possible conflict of interests.

Each reviewer is responsible for completing the [Primary Reviewer Checklist](#) and returning it to ORA. Prior to the IRB meeting, the reviewers may correspond with the investigator(s) to resolve any questions with assistance from the ORA to mediate discussion. Furthermore, any IRB member may contact the investigator, co-investigators, other IRB members, or outside sources as necessary to ensure a thorough evaluation of risks and benefits of the proposed research. The [Primary Reviewer Checklist](#) documents regulatory determinations and protocol specific findings and is maintained with the IRB files. Investigator-initiated studies may also require a Scientific Reviewer, whose review is documented in the Meeting Minutes and the IRB file. The IRB meets at least once a month to review and discuss each protocol. The Primary Reviewer (if not present, their alternate) presents the new study to the Board following the format of the [Primary Reviewer Checklist](#) and raises any additional points for discussion. After completion of all individual discussions during the fully convened meeting, each protocol is voted upon for one of four possible dispositions (described below).

Following are details regarding the potential IRB actions:

1. Approved – Accepted and endorsed as written with no conditions.
2. Approved with Stipulations (Conditions) – Accepted and endorsed with explicit minor changes or simple concurrence of the principal investigator. All stipulations requested of the PI (ORA sends a formal letter to the PI notifying the PI of the stipulations) must be completed and documented prior to beginning the research. For these stipulations, the IRB Chair and/or designee can review and approve the research through an Expedited Review procedure ensuring that the PI has sufficiently responded to the IRB's requests. The PI has a designated time period, not to exceed 90 days, in which to respond to the revisions requested. If the PI does not respond in the designated time period, the application may be withdrawn and returned. If the PI wishes to conduct a study that has been withdrawn, he/she must submit a new application, incorporating the revisions/clarifications requested from the previous IRB review. The Response to Stipulations submission must contain a cover letter detailing how the PI has addressed each of the stipulations outlined by the IRB as well as tracked changes and clean copies of all revised documents, if any. The study protocol receives final approval when all required changes have been submitted and approved.
3. Tabled (or Deferred) – If the protocol, consent form, or other materials have deficiencies that prevent accurate determination of risks and benefits or requires significant clarifications, modifications or conditions that, when met or addressed, require Full IRB review and approval of the PI's responses and revisions, the study will be tabled. The deficiencies will be specified to the PI (ORA sends a formal letter to the PI notifying the PI of the stipulations), and on occasion the PI is asked to attend the Full Board meeting in order to clarify the points in question. If a study has been tabled, the PI is responsible for submitting a response to the stipulations to the ORA within 90 days. If the PI does not respond in the designated time period, the application may be withdrawn and returned. If the PI wishes to conduct a study that has been withdrawn, he/she must submit a new application, incorporating the revisions/clarifications requested from the previous IRB review. The Response to Stipulations submission must contain a cover letter detailing how the PI has addressed each of the tabled conditions outlined by the IRB as well as tracked changes and clean copies of all revised documents, if any. The study protocol receives final approval when all required changes have been submitted and approved.

4. Disapproved – When the IRB votes for disapproval, the protocol describes a research activity that is deemed to have risks which outweigh potential benefits or the protocol is significantly deficient in several major areas. A PI has the right to appeal the disapproval of his research protocol to the Board and ask to have the decision reconsidered. PIs may submit a written response to the IRB for a protocol that is disapproved or tabled. The written response will be reviewed by the IRB. The IRB can invite the investigator to the IRB meeting if the IRB has additional questions for the investigator. The IRB will reconsider its decision. The second decision is final.

The PI is notified of the IRB determination within 7 days of the IRB meeting unless other situations cause a delay in this correspondence. Letters are sent to the PI through electronic mail, and must pick up the original copies from the ORA in person.

Upon receipt of final approval by the IRB, IRB staff stamp the final, approved Informed Consent Document(s) and other materials, as needed with the date of SIRB approval and the date of expiration. A formal letter is sent to the PI and research coordinator, if any, of the approval. The letter includes all versions and version dates of the documents (e.g., protocols, consent form(s), etc.) that were reviewed and approved by the SIRB. Additionally, the letter reminds investigators that any changes in research activity may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to subjects.

6.6 Facilitated Review Process

The Central Institutional Review Board (CIRB) facilitated review process can streamline local IRB reviews for national multi-center cancer treatment trials. Under the facilitated review process, the Seton Institutional Review Board (SIRB) can download CIRB reviews from a confidential webpage and decide whether or not to use the CIRB's review for a particular protocol.

Once an investigator at an institution decides to submit the study for IRB review, the local IRB Chair and/or designee performs a 'facilitated review' using the CIRB documents. If there are no concerns about local context, the SIRB Chair and/or designee can decide to accept the CIRB review, in lieu of a full board review. In this case, CIRB becomes the IRB of record for that particular study and performs all future continuing reviews, amendment reviews, and reviews of serious adverse events for the life of the study. The SIRB Chair and/or designee retain the option *not* to accept CIRB review and can choose to conduct a Full Board review, when deemed appropriate.

CIRB Procedures:

1. As outlined in the NCI CIRB [Standard Operating Procedures](#), the CIRB receives the protocol, the informed consent document(s), and a completed CIRB application and, when appropriate, an investigator drug brochure from the Cooperative Group via the Protocol Information Office at NCI. The CIRB staff clarifies any initial issues with the Study Chair of the Cooperative Group, designates the next meeting date for review, and assigns primary reviewers (two for the Adult CIRB and three for the Pediatric CIRB). The CIRB Chair decides if additional expertise (e.g., a consultant) needs to be brought into the review process.
2. The [CIRB members](#) meet at least once a month. At the meetings the Board members discuss the protocol and may consult by telephone with the Study Chair to explore any concerns they may have.

3. Per the NCI CIRB Standard Operating Procedures, the Board takes one of the following actions for each protocol: approve, approve pending modification, table, or disapprove. Any non-approval is followed up with communication with the Study Chair to resolve, wherever possible, outstanding issues identified by the Board.
4. After approval or disapproval, the Study Chair of the Cooperative Group is formally notified.
5. For each protocol, the CIRB's primary reviews, minutes, notification letters, and any other correspondence are posted in a separate section of this web site for participating institutions to access.
6. In addition to conducting initial reviews, the CIRB conducts Continuing Reviews and reviews of Serious Adverse Events (SAEs), Data Safety Monitoring Board (DSMB) reports, protocol amendments, national subject recruiting materials, etc. These actions are also posted on the web site for prompt access by participating institutions.

SIRB Procedures:

1. A local investigator who wishes to enroll subjects in a CIRB-approved study downloads the Local IRB Facilitated Review Packet and any other documents that may be requested from the [Participant-Side](#) of this website and submits these documents to the SIRB.
2. The SIRB designates at least one voting member of the IRB to conduct the 'facilitated review' of the study that the investigator submitted. The role of the person(s) is to determine whether there are local concerns that need to be addressed and whether to accept the CIRB Review. Local IRBs (i.e., SIRB) comply with [OHRP Guidance Document](#) that, "...an institution relying upon another institution's IRB has a responsibility to ensure that the particular characteristics of its local research context are considered through subsequent review by appropriate designated institutional officials, such as the Chairperson and/or other members of its local IRB."
3. The designated person(s) examines the materials provided by the IRB Coordinator(s), and/or such other information as they may seek, so they can decide whether a particular protocol and informed consent documents are acceptable and whether they are appropriate in their local context.
4. SIRB has the option to accept the CIRB approval "as is", accept it with de minimus modifications or they may decide not to accept the CIRB review and require that the investigator submit the protocol for Full Board review at their site. If the designated person(s) do not accept the CIRB review they may still utilize CIRB written materials as resources for their local process.
5. Local template additions to the informed consent dealing with state and local law, institutional requirements, or IRB policies may be added to the local consent form. No CIRB approved information may be deleted from the informed consent document. SIRB may also make minor word substitutions or additions in the informed consent document, particularly to facilitate better comprehension by the local population, as long as the proposed changes do not alter the meaning of the CIRB approved contents. Additional risks may be added to the informed consent document. Revisions/changes to the local consent form other than those described above require Full Board review at the local level; facilitated review may not be used, and the CIRB cannot serve as the IRB of record for the study at the local site.
6. SIRB will notify the Central IRB Operation's Office each time it accepts the CIRB review of a study. Clicking on the 'Facilitated Review Acceptance' button/link within the main menu for each study and completing the Facilitated Review Acceptance Form does this. In order for the CIRB to become the Official IRB of Record for the site for a particular study, this form needs to be

completed and submitted by the ORA. A separate form must be submitted for each study review that is accepted.

The study team personnel will notify SIRB when there are any actions taken on the study (e.g., an SAE report provoking a change in the consent form, an approved protocol amendment, a change in the protocol/informed consent resulting from the Continuing Review, etc.).

6.7 Emergent Use of an Unapproved Investigational Device

Nothing in this policy is intended to prevent a physician from preserving life. For example, if in the physician's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to conform to the policies as outlined (e.g., IRB notification, obtaining an independent physician's determination), the clinical investigator should make the determination and then, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must then notify the IRB within 5 working days after the use of the test article.

Emergent use of an unapproved investigational device requires an Investigational Device Exemption (IDE) when an IDE for the device does not exist, the proposed use is not approved under an existing IDE, or the physician or institution is not approved under the IDE. However, since the FDA has stated that it has not objected if a physician chooses to use an unapproved device in such an emergent situation, provided that the physician later justifies to FDA that an emergency actually existed, SIRB policy allows for this circumstance.

Clinical investigations require prior IRB review and approval. Exemption from prior review and approval by the IRB is allowed in emergent use cases in accordance with FDA [21 CFR 56.104\(c\)](#).

1. Whether or not the exception applies:
 - a. Emergent use must meet criteria as a clinical investigation of a test article for emergent use on a human participant in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval and the situation necessitates the use of the investigational article. AND
 - b. Prior notification by the physician is required. The physician must notify the IRB Chair, or physician member concerning the emergent use of the investigational test article.
2. Where the exemption applies, the exception allows for one emergent use of a test article without prospective IRB review.
3. Where the exemption does not apply, IRB approval must be by a convened IRB. However, although the FDA regulations do not provide for Expedited IRB approval in emergent situations, a letter may be sent to the sponsor, a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of [21 CFR 56.104\(c\)](#), if sufficient time does not exist to organize a convened IRB meeting. This is not an "IRB approval." The acknowledgment letter is only intended to be acceptable to manufacturers to allow shipment of the product to proceed.

Informed consent is required for emergent use of an unapproved Investigational Device. Exceptions may be allowed. The IRB may approve an exception to informed consent if the physician and a physician who is not otherwise participating in the clinical investigation may certify in writing stipulations as noted in [21 CFR 50.23\(a\)](#).

6.7.1 Procedures for Emergent Use of an Unapproved Investigational Device

This procedure begins when a physician identifies the need for the emergent use of an unapproved Investigational Device. The three specific protections listed below require special consideration; however, this procedure ends when the IRB has reviewed the follow-up/final report information on the use of the unapproved Investigational Device.

1. Whether an IDE is required (whether previously existing or an emergent IDE is obtained);
2. notwithstanding which IDE is obtained/used, whether Exemption from prior IRB approval may be allowed and;
3. notwithstanding the circumstances in either one (1) or two (2) above, whether Exception from Informed Consent may be allowed.

Before using an investigational device in an emergency, the physician must:

1. Identify whether an IDE already exists.
 - a. If an IDE clinical investigation is active within the Seton Family of Hospitals, the physician should contact the PI of that clinical investigation to determine whether the intended subject meets enrollment criteria:
 - i. If the subject meets inclusion/exclusion criteria, the PI (or Co-Investigator) on the approved IDE study enrolls the subject and initiates the investigational device protocol.
 - ii. If the physician finds the intended subject does not meet criteria of an existing study protocol active at the Seton Family of Hospitals, the physician should contact the PI on the study in question and determine whether that PI is willing to consider the use of the device to represent the case of a deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such deviation shall be reported to the FDA and SIRB within 5-working days after the sponsor learns of it.
 2. If an IDE clinical investigation is NOT active within the Seton Family of Hospitals:
 - a. The physician may be allowed to use the device in an emergency if the sponsor/company can cover the emergent use under their IDE or the physician can obtain an emergent IDE from the FDA. In either case, the physician must contact the manufacturer.
 - b. The manufacturer determines whether the device can be made available for the emergent use under a company IDE. If so, the physician must submit the following information directly to the IRB Chair for review and confirmation and convened IRB review and approval (when possible) for emergent use of a test article in a single subject:
 - i. [*Request for Emergent Use of an Investigational Drug, Device, and Biologic*](#);
 - ii. Copy of the informed consent form (obtaining informed consent from the patient or a legal representative is expected if possible); If the physician proposes to administer the test article in emergent use situations without informed consent, the request to the IRB Chair should include a statement by the physician and a physician who is not otherwise participating in the clinical investigation certifying in writing that all of the following conditions are met:
 1. the subject is confronted by a life-threatening situation necessitating the use of the test article;
 2. Informed consent cannot be obtained because of an inability to communicate with or obtain legally effective consent from the subject;
 3. Time is insufficient to obtain consent from the subject's legal

- representative; and
4. There is no alternative method of approved or generally recognized therapy available that will provide an equal or greater likelihood of saving the subject's life.
 5. If the immediate use of the test article without informed consent is, in the investigator's opinion, required to preserve the life of the subject and time is not sufficient to obtain the independent determination by a nonparticipating physician then the independent evaluation must be included in writing in the five working days report.
 6. Completed **PI Assurance Statement**, if possible, but the IRB Chair may accept it post-administration. The physician must include the words "EMERGENT USE" and the name of the test article in the title listed in the submission.

If the IRB Chair is not available during the notification of the emergent use, the physician should submit the information listed to the ORA. In the event that a physician submits an emergent use request to the ORA, ORA staff forwards the materials to the IRB Chair, or physician member, as available. The IRB Chair or physician member assesses the request to determine whether it meets the regulatory requirements for emergent use and the ORA along with physician IRB member responds to the physician in writing. The IRB Chair or physician IRB member may determine that the physician can proceed or may withhold confirmation.

If the need for an investigational device represents an emergent situation that does not allow time for submission of an IDE:

1. The physician must determine that criteria as described above have been met, assess the potential for benefits from the unapproved use of the device, and have substantial reason to believe that benefits will exist. The physician may not conclude that an "emergency" exists in advance of the time when treatment may be needed based solely on the expectation that IDE approval procedures may require more time than is available. Physicians should be aware that FDA expects them to exercise reasonable foresight with respect to potential emergencies and to make appropriate arrangements under the IDE procedures far enough in advance to avoid creating a situation in which such arrangements are impracticable.
2. The physician will need to contact the manufacturer. The physician must advise the device developer to notify the Center for Devices and Radiological Health (CDRH), Program Operation Staff by telephone (301-594-1190) immediately after shipment is made. Note: an unapproved device may not be shipped in anticipation of an emergency. During nights and weekends, contact the FDA Office of Emergent Operations (HFA-615) at 301-443-1240.
3. The SIRB, in line with the expectations of the FDA, would expect the physician to follow as many subject protection procedures as possible. These include:
 - a. obtaining an independent assessment by an uninvolved physician;
 - b. notifying institutional officials as specified by institutional policies;
 - c. obtaining authorization from the IDE holder, if an approved IDE for the device exists.
 - d. notifying the IRB, as outlined above.

Within five working days after the emergent use (with or without prior IRB approval), the physician must:

1. Submit the [Request for Emergent Use](#) Form;
2. Conduct an evaluation of the likelihood of a similar need for the device occurring again, and if

future use is likely, immediately initiate efforts to obtain IRB approval and an approved IDE for the device's subsequent use;

3. If an IDE for the use does exist, notify the sponsor of the emergent use, or notify the FDA of the emergent use (CDRH Program Operation Staff 301-594-1190) and provide FDA with a written summary of the conditions constituting the emergent, subject protection measures, and results (essentially the contents of the report to the IRB in number 1 above).

In accord with FDA regulations, any subsequent emergent use of the device may not occur unless the physician or another person obtains approval of an IDE for the device and its use. If an IDE application for subsequent use has been filed with FDA and FDA disapproves the IDE application, the device may not be used even if the circumstances constituting an emergency exist. (Note: FDA has stated that developers of devices that could be used in emergencies should anticipate the likelihood of emergent use and should obtain an approved IDE for such uses.)

According to Department of Health and Human Services (DHHS) regulations, research involving human participants must receive IRB review and approval by a convened IRB, except where Expedited Review is specifically permitted, prior to initiation of the research, under [45 CFR 46.103\(b\)](#). Physicians do, however, retain the authority to provide emergent medical care to their patients, under [45 CFR 46.116\(f\)](#). In line with previous statements from DHHS, whenever emergent care is initiated without prior IRB review and approval, the patient may not be considered to be a research subject. Such emergent care may not be claimed as research, nor may the outcome of such care be included in any report of a research activity. DHHS regulations for the protection of human subjects do not permit research activities to be started, even in an emergent, without prior IRB review and approval. Investigators may not aggregate such data with research data, even if the emergent protocol is identical to that of a research protocol subsequently approved by the IRB, nor may the investigator include the outcome of such care in any report of a research activity.

At a next convened meeting of the IRB, IRB staff will inform the IRB that the IRB Chair and/or physician member has/have assessed a request for emergent use using the regulatory definition, and the committee verifies the following criteria for emergent use:

1. The subject was confronted by a life-threatening situation necessitating the use of the investigational drug, biologic, or device;
2. No alternative method of approved or generally recognized therapy was available that provides an equal or greater likelihood of saving the subject's life; and
3. Time was not sufficient to obtain IRB approval.

If an investigator fails to submit a request involving emergent use of an investigational test article to the IRB Chair and/or ORA for review and confirmation or to the convened IRB prior to initiation, the IRB retrospectively reviews the situation to determine if the test article administration met the regulatory definition and whether failure to comply with this policy meets the IRB definition of noncompliance (see Section 6.14). Details concerning documenting the use of the emergent use test article will be documented in the minutes and reported according to this policy. After emergent use of a test article is approved or reported to the IRB the use is reported in accordance with the Reporting Policy and Procedure (see Section 2.0.7).

Treatment Use IDE: If the need for an investigational device does not represent an emergent situation, the FDA may authorize shipment for a serious or immediately life-threatening disease or condition in patients for whom no comparable or satisfactory alternative device or other therapy is available, under a

treatment IDE.

1. A protocol for an investigational device meets the criteria for a treatment IDE if:
 - a. The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;
 - b. There is no comparable or satisfactory alternative device or other therapy available to treat or diagnose that stage of the disease or condition in the intended patient population;
 - c. The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or such clinical trials have been completed; and
 - d. The sponsor of the investigation is actively pursuing marketing approval/clearance of the investigational device with due diligence.
2. If the device is to be sold, the price to be charged must be based on manufacturing and handling costs only.
3. Treatment use of an investigational device is evaluated following criteria in the Initial IRB Review of a Research Proposal Involving Human Subjects. In this case, this policy and procedure does not apply.

6.8 Emergent Use of an Unapproved Investigational Drug

Nothing in this policy is intended to prevent a physician from preserving life. For example, if in the physician's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to conform to the policies as outlined (e.g., IRB notification, obtaining an independent physician's determination), the clinical investigator should make the determination and then, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must then notify the IRB within 5 working days after the use of the test article.

Use of an unapproved investigational drug or biologic requires an IND. Several mechanisms are available and described in the procedures section below to enable investigators to meet this requirement when emergent use is necessary which may include obtaining a telephonic emergent IND from the FDA.

Clinical investigations require prior IRB review and approval. Exemption from prior review and approval by the IRB is allowed in emergent use cases in accordance with FDA [21 CFR 56.104\(c\)](#).

1. Whether or not the exception applies:
 - a. emergent use must meet criteria as a clinical investigation of a test article for emergent use on a human participant in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval and the situation necessitates the use of the investigational article; and
 - b. prior notification by the physician is required. The physician must notify the IRB Chair, or physician member concerning the emergent use of the investigational test article.

Where the exemption applies, the exception allows for one emergent use of a test article without prospective IRB review.

2. Where the exemption does not apply, IRB approval must be by a convened IRB. However, although the FDA regulations do not provide for expedited IRB approval in emergent situations, a letter may be sent to the sponsor, a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of [21 CFR 56.104\(c\)](#), if sufficient time does not

exist to organize a convened IRB meeting. This is not an "IRB approval," the acknowledgment letter is only intended to be acceptable to manufacturers to allow shipment of the product to proceed.

Informed consent is required for emergent use of an unapproved investigational drug or biologic. Exceptions may be allowed. The IRB may approve an exception to informed consent if the physician and a physician who is not otherwise participating in the clinical investigation may certify in writing stipulations as noted in [21 CFR 50.23\(a\)](#).

6.8.1 Procedures for Emergent Use of an Unapproved Investigational Drug

This procedure begins when a physician identifying the need for the emergent use of an unapproved Investigational Drug or Biologic. The three specific protections below require special consideration; however, this procedure ends when the IRB has reviewed the follow-up/final report information on the use of the unapproved Investigational Drug or Biologic.

1. Whether an IND is required (whether previously existing or an emergent IND is obtained);
2. notwithstanding which IND is obtained/used, whether Exemption from prior IRB approval may be allowed; and
3. notwithstanding the circumstances in either of the previous two, whether Exception from Informed Consent may be allowed.

When IRB review and approval is sought prior to use of the test article and before administering the investigational drug:

1. The physician must identify if an available IND exists or obtain an Emergent IND from the FDA.
 - a. If the physician finds the intended subject meets criteria of an existing study protocol open at the institution, the physician contacts the PI on the study in question and the PI or Co-Investigator on the study in question enrolls the subject and initiates the investigational drug treatment.
2. If an approved study protocol does not exist the physician may either contact the manufacturer who may be able to allow use under an existing company IND or contact the FDA. In either case, the physician must contact the manufacturer.
 - a. The manufacturer determines whether the drug or biologic can be made available for the emergent use under a company IND. If so, the physician compiles the necessary documentation and follows the submission procedures above.
 - b. If the need for an investigational drug or biologic represents an emergent situation that does not allow time for submission of an IND, the physician must contact the FDA who may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means.

Product: Drug
Office/Division to Contact: Drug Information Branch
Contact number: 301-827-4573

Product: Biological blood products
Office of Blood Research and Review
Contact number: 301-827-3518

Product: Biological vaccine products
Office/Division to Contact: Office of Vaccines Research and Review
Contact number: 301-827-0648

Product: Biological therapeutic products
Office/Division to Contact: Office of Therapeutics Research and Review
Contact number: 301-594-2860

On nights and weekends
Office/Division to Contact: Division of Emergent and Epidemiological Operations
Contact number: 301-443-1240

If the FDA does not authorize shipment of the test article in advance of the IND submission in the form of an Emergent IND, they may authorize shipment for a serious or immediately life-threatening disease condition in patients for whom no comparable or satisfactory alternative drug or other therapy is available under a treatment IND.

For a request for emergent use of a test article in a single subject, the physician must submit the [Request for Emergent Use](#) Form directly to the ORA for review and approval by the IRB Chair or physician member and, when time permits, convened IRB review. The IRB Chair or physician member assesses the request to determine whether it meets the regulatory requirements for emergent use and the ORA along with physician IRB member responds to the physician in writing. The IRB Chair or physician IRB member may determine that the physician can proceed or may withhold confirmation.

For notification of an emergent use, within five working days after administration, the physician must the [Request for Emergent Use](#) Form directly to the ORA for review and approval by the convened IRB.

Details concerning the documented emergent use of a test article will be included in the SIRB minutes per policy. Reporting of this information will follow the SIRB Reporting Policy and Procedure (see Section 2.0.7).

In accord with FDA regulations, any subsequent emergent use of the drug may not occur unless the physician or another person obtains approval of an IND for the drug and its use. If an IND application for subsequent use has been filed with FDA and FDA disapproves the IND application, the drug may not be used even if the circumstances constituting an emergent exist.

According to Department of Health and Human Services (DHHS) regulations, research involving human participants must receive IRB review and approval by a convened IRB, except where Expedited Review is specifically permitted, prior to initiation of the research, under [45 CFR 46.103\(b\)](#). Physicians do, however, retain the authority to provide emergent medical care to their patients, under [45 CFR 46.116\(f\)](#). In line with previous statements from DHHS, whenever emergent care is initiated without prior IRB review and approval, the patient may not be considered to be a research subject. Such emergent care may not be claimed as research, nor may the outcome of such care be included in any report of a research activity. DHHS regulations for the protection of human subjects do not permit research activities to be started, even in an emergent, without prior IRB review and approval. Investigators may not aggregate such data with research data, even if the emergent protocol is identical to that of a research protocol subsequently approved by the IRB, nor may the investigator include the outcome of such care in any report of a research activity.

A protocol for an investigational drug meets the criteria for a treatment IND if:

1. The drug is intended to treat a serious or immediately life-threatening disease;
2. There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population;
3. The drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and
4. The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.

For a drug intended to treat a serious disease, the Commissioner may deny a request for treatment use under a treatment protocol or treatment IND if there is insufficient evidence of safety and effectiveness to support such use.

For a drug intended to treat an immediately life-threatening disease, the Commissioner may deny a request for treatment use of an investigational drug under a treatment protocol or treatment IND if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug:

1. May be effective for its intended use in its intended patient population; or
2. Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.

Treatment use of an investigational drug is evaluated following criteria in the Requirements for Initial IRB Review Procedure if the sponsor has not applied for a waiver of local IRB review under the treatment IND. The waiver may be approved if it can be shown to be in the best interest of the subjects, and if a satisfactory alternate mechanism for assuring the protection of human subjects is available, e.g., review by a central IRB. Such a waiver does not apply to the informed consent requirement. The IRB may still opt to review a study even if FDA has granted a waiver; therefore, in the event of a waiver of local IRB review the physician must still contact the IRB Chair directly as noted above.

6.9 Planned Emergent Research / Exception from Informed Consent Requirements

The IRB determines and documents whether the research is subject to FDA regulations. If FDA-regulated, the IRB reviews the study in accordance with [21 CFR 50.24](#) and DHHS published waiver. If not FDA regulated, the IRB reviews the study in accordance with the DHHS published waiver.

The IRB documents and reports to OHRP planned emergent research, not subject to FDA regulations, that is approved under the requirements of the DHHS Secretarial waiver under [45 CFR 46.101\(j\)](#) that permits a waiver of the general requirements for obtaining informed consent in a limited class of research in emergent settings. The IRB does not approve this waiver for research involving prisoners [[subpart C of 45 CFR 46](#)], research involving fetuses, pregnant women, and human in vitro fertilization [[subpart B of 45 CFR 46](#)], or any Veterans Affairs (VA) research.

The following procedure occurs during initial review of research:

1. The convened IRB determines whether the research activity is subject to [21 CFR 50](#). If the research is FDA regulated, the IRB follows the FDA regulatory criteria to allow an exception to the

requirement to obtain consent [[21 CFR 50.24](#)] and DHHS criteria as follows:

- a. The IRB may approve the planned emergent research without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the research) finds and documents each of the following: (Note: additional guidance related to the required determinations is provided in the [FDA Information Sheet on Exception from Consent in Emergent Research](#)):
 - i. The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions. (all three must be true)
 - ii. Obtaining informed consent is not feasible because (all three must be true):
 1. The subjects will not be able to give their informed consent as a result of their medical condition;
 2. The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
 3. There is no reasonable way to prospectively identify the individuals likely to become eligible for participation in the clinical investigation.
 - iii. Participation in the research holds out the prospect of direct benefit to the subjects because (all three must be true):
 1. Subjects are facing a life-threatening situation that necessitates intervention;
 2. Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
 3. Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
 - iv. The clinical investigation could not practicably be carried out without the waiver.
 - v. The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has provided a plan to attempt to contact a legally authorized representative for each subject within that window of time and, if feasible, to ask the legally authorized representative contacted for consent within that window rather than proceeding without consent.
 - vi. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with FDA and HHS regulations. The procedures for obtaining informed consent and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible:
 1. Consent in an emergent setting may require a short form consent
 2. Procedure if subject regains competence within the therapeutic window
 3. Provisions for language barrier
 - vii. The IRB application will provide details for implementing the following additional protections of the rights and welfare of the subjects, including, at least:
 1. Community consultation:

- a. The PI's plan for consultation with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;
 - b. The IRB will determine whether it is appropriate for the IRB to carry out community consultation in addition to that performed by the investigator.
2. The PI's plan for public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
3. Community consultation and public disclosure should engage the affected communities in discussion about the proposed research, with the possibility of appropriate modification to the design and/or conduct of the study as a possible outcome. The plan for consultation and disclosure should consider the following:
 - a. Use of radio/TV advertisements, talk shows, etc.
 - b. Press releases - newspaper, press interviews,
 - c. Community meetings/gatherings
 - d. Civic groups, churches, minorities organizations, public officials
 - e. Target groups more likely to be involved
 - f. Include information related to procedures for opting out
4. The PI's plan for public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
5. The PI's plan to establish an independent data monitoring committee to exercise oversight of the clinical investigation;
6. The PI's plan to contact the subject's family member who is not a legally authorized representative to determine whether he or she objects to the subject's participation, if feasible. The plan is applicable in situations when obtaining informed consent from the subject is not feasible and a legally authorized representative is not reasonably available. The plan will be implemented within the therapeutic window defined in the proposal. (Family member is defined by DHHS rules as any one of the following legally competent persons: spouse; parents; children (including adopted children); brothers; sisters; and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.)
7. The PI's plan to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member,:
 - a. Of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document.
 - b. that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
8. The plans provided above will include:

- a. provisions for situations when a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible, and
 - b. if a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.
- 9. Evidence that the study will be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies the research may include subjects who are unable to consent. (The requirement for a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists). The initial IRB application for this research may not be submitted as an amendment under 21 CFR 312.30 or 812.35.
- b. The IRB determinations of this section are documented in the IRB record and retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with 21 CFR 56.115(b).
- c. If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided above or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.
- 2. If the research is not FDA-regulated, the IRB follows the DHHS regulatory criteria to waive the requirement to obtain consent using the criteria listed above with the following exceptions:
 - a. The reference to applicable FDA regulations in section 1(a)(vi) above,
 - b. The requirement for IND/IDE in section 1(a)(vi)(1)(a) above
 - c. The record retention schedule in section 1(b) above
 - d. The sponsor's responsibilities for notifying the FDA in section 1(c) above.
- 3. Continuing Review. The investigator will summarize efforts made to contact legally authorized representatives and family members in the annual progress report

6.10 Humanitarian Use Device (HUD)

SIRB recognizes that humanitarian device exemption (HDE) approval by the FDA is based on safety and probable benefit and does not consider HUD use to represent research. If research is performed with the HUD as the object of the investigation, the project must be submitted as human research.

Principal Investigators may collect safety and effectiveness data to support Pre-Market Approval (PMA) for an HDE-approved indication without submitting to the FDA for an IDE. Collecting safety or effectiveness data to support a PMA for an indication not approved under the existing HDE requires prior submission to the FDA for an IDE and cannot be approved under this policy. IRB review should occur under the Requirements for Initial IRB Review Procedure (with the exception of requiring a research

informed consent form where the project is not being submitted as human research). Use of an HUD for an indication not approved under the existing HDE where the IRB has determined there is no intention or plan to collect safety or effectiveness data to support a PMA for that new indication does not require an IDE.

All requests for use of an HUD under an HDE must be initially reviewed and approved by the convened IRB unless used in an emergency as follows:

1. A physician in an emergent situation determines that IRB approval for the use of the HUD at the facility cannot be obtained in time to prevent serious harm or death to a patient
2. The physician must report the emergent use within five days; provide written notification of the use to the IRB chair person including identification of the patient involved, the date of the use, and the reason for the use [[21 CFR 814.124](#)].

Use of a consent form is not required by the federal regulations, however, it is permitted. The IRB does not require a research informed consent form where the project is not being submitted as human research. It is generally advisable to obtain consent for the use of a HUD, if the Principal Investigator would obtain consent for other similar clinical procedures, if the need for the HUD can be anticipated, and the clinical situation will permit obtaining consent.

Continuing review of the use of an HUD under an HDE must be reviewed and approved no less frequently than annually by the IRB and may be reviewed through an Expedited Review procedure, if determined appropriate by the IRB. All requests for alterations to the IRB approved use of an HUD under an HDE must be reviewed and approved by the IRB and may be reviewed through an Expedited Review procedure.

The physician requesting approval for use of the HUD (hereafter referred to as the Principal Investigator (PI)) submits all documents as applicable listed in the Requirements for Initial IRB Review Policy (see Section 6.0). The submission must also include any of the following applicable items:

1. a copy of the HDE approval order;
2. a description of the device;
3. the product labeling;
4. the patient information packet that may accompany the HUD;
5. a sample consent form for the use of the HUD if required by the IRB or sponsor; and
6. a summary of how the physician proposes to use the device, including:
 - a. a description of any screening procedures,
 - b. the HUD procedure, and
 - c. any patient follow-up visits, tests or procedures.

Upon receipt of the application, ORA staff screens the application and documentation for completeness and accuracy and forwards to the convened IRB for review. The Board members receive access to a copy of the submission. The Board will ensure that Principal Investigators are qualified through training and expertise to use the device. For many HDEs, the HDE holder is required to provide training on the use of the device prior to the Principal Investigator using the device. Such requirements would be specified in the HDE approval order, available at [CDRH Humanitarian Device Exemption Summaries of Safety and Possible Benefit](#) (select the HDE number). A list of approved HDEs may be found at [CDRH Humanitarian Device Exemption Summaries of Safety and Possible Benefit](#).

The IRB considers the following, as applicable:

1. Additional information needed to determine HUD or HDE status;
2. Required revisions needed to qualify for approval;
3. How the HUD may be used (within approved labeling, outside approved labeling where there is no intention or plan to collect safety or effectiveness data to support a PMA for that new indication);
4. Where the use of the HUD may take place;
5. Who may use the HUD (Individuals, departments, hospitals, etc);
6. Whether or not additional IRB approval is needed prior to use on each patient;
7. Determination that the activity does not qualify for approval with rationale for the determination and recommendations for submission of full review human research application where applicable;
8. Approved for implementation (general comments or suggestions may be included but not required for approval).

If the PI has concerns regarding the IRB decision/recommendations for changes in the use of the HUD, he/she may submit the concerns to the IRB including a justification for changing the IRB decision. The PI may send the request to the IRB Chair and/or designee for final resolution. The ORA records all determinations concerning the use of an HUD under an HDE.

Any changes to the activities described in the initial request to use the HUD must be reviewed by the IRB prior to implementing (except where necessary to eliminate apparent immediate hazards to the patient). The PI must submit the proposed changes to the ORA by utilizing the Amendment Form. The IRB Chair and/or designee will determine whether the change alters the determination that the device may be used under the HDE in place. If the changes do not affect the HDE determination and are acceptable, the IRB Chair and/or designee documents the determination in the IRB record and the ORA notifies the local PI. If the changes do affect the determination such that the device will no longer be eligible for use of an HUD under an HDE, the ORA contacts the local PI that requested the use of the HUD and develops a plan to either withdraw the change or submit the study as human research under the appropriate review process (Expedited or Full Board Review).

[21 CFR 814.126\(a\)](#) requires HDE medical device reports (MDRs) that are submitted to FDA in compliance with the requirements of part 803 of this chapter also be submitted to the IRB of record. The IRB Chair and/or designee will review all MDRs submitted directly to the IRB from manufacturers. MDRs requiring immediate action are forwarded to the IRB Chair, IRB Director, and/or Full Board for consideration of suspension or termination.

Filing MDR reports does not necessarily mean that the product caused or contributed to the event. Many reports are incomplete and do not provide enough information to rule in or out a relationship between the event and the device. The IRB Chair and/or designee will send a letter advising the PI that the IRB has received the MDRs and that further evaluation by the local PI that requested the use of the HUD may be required. If the events are determined to require immediate local action the PI may be required to submit an amendment. If the events do not require immediate local action the PI will submit a list and summary of all MDRs, adverse events and unanticipated problems. Any death or other serious adverse event occurring within 30 days of the use of the device must be reported to the IRB, regardless of the relationship of the event to the use of the device.

The IRB requires Investigators to submit an HDE Progress Report and any applicable attachments for continuing review, utilizing the HUD Status Report Form. Continuing Review may be completed by

Expedited procedure, if decided on by the Full Board. At Continuing Review, the IRB Chair and/or designee will consider the risk and benefit information available and any Medical Device Reporting (MDR) reports.

6.11 Expanded Access / Treatment Use of an Unapproved Investigational Drug/Device / Compassionate Use

Nothing in this policy is intended to prevent a physician from preserving life, for example, if in the investigator's opinion, immediate use of the test article is required to preserve the patient's life, and if time is not sufficient to conform to the policies as outlined in ORA policies (e.g., Emergent use procedures such as IRB notification, obtaining an independent physician's determination or Treatment Use of an Unapproved Investigational Drug (Including Single Patient Use) Policy and Procedure), the clinical investigator should make the determination and then follow the procedures outlined in the Emergent Use of an Unapproved Investigational Drug Policy and Procedure, e.g., within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation, then notify the IRB within 5 working days after the use of the test article [[21 CFR 50.23\(c\)](#)].

This policy, in accord with FDA recommendations, seeks a balance between administrative burden and ensuring patient safety and welfare and does not seek to be a deterrent to obtaining access to investigational drugs for treatment use. For single patients, physicians will generally be relying heavily on the sponsor's IND and minimal additional information that should be readily available to the physician in the course of the care of that patient is all that is required by the FDA and therefore a similar package with minor variations will be required by the IRB. For small group (multi-patient) INDs the SIRB will make all reasonable efforts to follow FDA recommendations regarding the use of centralized IRBs and standardized documentation across sites to minimize the administrative burden. Full Treatment Protocols will likely be submitted in the usual manner with the understanding that at some point an emergent may arise calling for invoking the Emergent Use of an Unapproved Investigational Drug Policy and Procedure. In all cases, sponsors and sponsor-investigators must comply with all applicable responsibilities under all applicable regulations.

Use of an unapproved investigational drug or biologic requires an IND. Several mechanisms are available. As mentioned above, emergent use may be necessary at any point during submission of any type of Expanded Access Treatment Protocol or request and other mechanisms to enable investigators to meet this requirement which may include obtaining a telephonic emergent IND from the FDA. If the physician determines criteria are not met for submitting a request for an emergent IND or if the FDA does not authorize shipment of the test article in advance of the IND submission in the form of an Emergent IND the FDA may authorize shipment for those patients with a serious disease or condition, regardless of whether the patient would currently be considered seriously ill with that disease or condition as treatment use under a single patient IND, small group treatment IND or a full protocol treatment IND (other mechanisms include: open label protocol or open protocol IND, group C treatment IND, or under the FDA's Parallel Track policy.) In all other cases a standard submission to the FDA for an IND may be required. Only the three most common forms of treatment IND, single patient IND, small group treatment IND or a full protocol treatment IND will be thoroughly discussed under this policy since all other treatment use can be submitted under the Requirements for Initial IRB Review Procedure.

Single patient treatment IND, multi-patient (small group) treatment IND and full treatment use protocol:

1. All of these Treatment Use requests for an investigational drug or biologic must meet the criteria

for a Treatment IND, Single patient IND. The FDA considers the use to meet criteria if:

- a. The drug is intended to treat a serious or immediately life-threatening disease;
 - b. There is no comparable or satisfactory alternative drug or other therapy to diagnose, monitor or treat the disease or condition;
 - c. The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and
 - d. Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.
 - e. Expanded access use may begin 30 days after FDA receives the protocol or upon earlier notification by FDA that use may begin. However, it is also possible that the FDA may place any expanded access IND or protocol on clinical hold as described in 312.42.
 - f. For a drug intended to treat an immediately life-threatening disease, the Commissioner of the FDA may deny a request for treatment use of an investigational drug under a treatment protocol or treatment IND if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug: (i) May be effective for its intended use in its intended patient population; or (ii) Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.
2. Additional criteria for each specific type of Expanded Access Investigational Drug Use:
- a. Single patient, including emergent use (see the Emergent Use of an Unapproved Investigational Drug Policy and Procedure).
 - i. If the drug is the subject of an existing IND, the expanded access submission may be made by the sponsor or by a licensed physician.
 - ii. A sponsor may satisfy the submission requirements by amending its existing IND to include a protocol for individual patient expanded access.
 - iii. A licensed physician may satisfy the submission requirements by obtaining from the sponsor permission for FDA to refer to any information in the IND that would be needed to support the expanded access request (right of reference) and by providing any other required information not contained in the IND (usually only the information specific to the individual patient).
 - b. Small Group (Intermediate-size population), including emergent use (see the Emergent Use of an Unapproved Investigational Drug Policy and Procedure).
 - c. FDA may ask a sponsor to consolidate expanded access under this section when the agency has received a significant number of requests for individual patient expanded access to an investigational drug for the same use. Need for expanded access. Expanded access under this section may be needed in the following situations:
 - i. Drug not being developed. The drug is not being developed, for example, because the disease or condition is so rare that the sponsor is unable to recruit patients for a clinical trial.
 - ii. Drug being developed. The drug is being studied in a clinical trial, but patients requesting the drug for expanded access use are unable to participate in the trial. For example, patients may not be able to participate in the trial because they have a different disease or stage of disease than the one being studied or otherwise do not meet the enrollment criteria, because enrollment in the trial is closed, or because the trial site is not geographically accessible.

- iii. Approved or related drug. (i) The drug is an approved drug product that is no longer marketed for safety reasons or is unavailable through marketing due to failure to meet the conditions of the approved application, or (ii) The drug contains the same active moiety as an approved drug product that is unavailable through marketing due to failure to meet the conditions of the approved application or a drug shortage. Criteria. The criteria in [21 CFR 312.305\(a\)](#) must be met; and FDA must determine that: (1) There is enough evidence that the drug is safe at the dose and duration proposed for expanded access use to justify a clinical trial of the drug in the approximate number of patients expected to receive the drug under expanded access; and (2) There is at least preliminary clinical evidence of effectiveness of the drug, or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population.
- iv. Full Treatment Protocol, including if necessary while awaiting approval an emergent use (see the Emergent Use of an Unapproved Investigational Drug Policy and Procedure).
 - 1. FDA may permit an investigational drug to be used for widespread treatment use.
 - 2. The drug is being investigated in a controlled clinical trial under an IND designed to support a marketing application for the expanded access use, or All clinical trials of the drug have been completed; and
 - 3. Marketing status. The sponsor is actively pursuing marketing approval of the drug for the expanded access use with due diligence; and
 - 4. Evidence. When the expanded access use is for a serious disease or condition, there is sufficient clinical evidence of safety and effectiveness to support the expanded access use. Such evidence would ordinarily consist of data from phase 3 trials, but could consist of compelling data from completed phase 2 trials; or When the expanded access use is for an immediately life-threatening disease or condition, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk of illness or injury. This evidence would ordinarily consist of clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence.
- 3. Other Treatment Use INDs for Investigational Drugs and Biologics that do not require special processing outside the scope of the Requirements for Initial IRB Review Procedure.
 - a. Open Label Protocol Or Open Protocol IND: These are usually uncontrolled studies, carried out to obtain additional safety data (Phase 3 studies). They are typically used when the controlled trial has ended and treatment is continued so that the subjects and the controls may continue to receive the benefits of the investigational drug until marketing approval is obtained. These studies require prospective Institutional Review Board (IRB) review and informed consent and are submitted under the Requirements for Initial IRB Review Procedure.
 - b. Group C Treatment IND: "Group C" treatment IND was established by agreement between FDA and the National Cancer Institute (NCI). The Group C program is a means for the distribution of investigational agents to oncologists for the treatment of cancer under protocols outside the controlled clinical trial. Group C drugs are generally Phase 3

study drugs that have shown evidence of relative and reproducible efficacy in a specific tumor type. They can generally be administered by properly trained physicians without the need for specialized supportive care facilities. Group C drugs are distributed only by the National Institutes of Health under NCI protocols. Although treatment is the primary objective and patients treated under Group C guidelines are not part of a clinical trial, safety and effectiveness data are collected. The usage of a Group C drug is described in the FDA's "Guideline Protocol" document. Because administration of Group C drugs is not done with research intent, FDA has generally granted a waiver from the IRB review requirements [21 CFR 56.105]. Even though FDA has granted a waiver for these drugs, the SIRB still chooses to conduct a review under this policy and procedure. The Guideline Protocol contains an FDA-approved informed consent document which must be used if there has been no local IRB review; however, although the SIRB chooses to conduct a local review the FDA-approved informed consent may still be used. Local review will occur under the Requirements for Initial IRB Review Procedure.

- c. Parallel Track: The FDA Agency's Parallel Track policy [57 FR 13250] permits wider access to promising new drugs for AIDS/HIV related diseases under a separate "expanded access" protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. It provides an administrative system that expands the availability of drugs for treating AIDS/HIV. These studies require prospective IRB review and informed consent and are submitted under the Requirements for Initial IRB Review Procedure. Physicians and sponsors are responsible for meeting all responsibilities under applicable regulations and may be required to submit to additional safeguards (additional monitoring, reporting, etc.) by the FDA during the IND review or by the IRB during IRB review.
4. Treatment Use Protocols require prior IRB review and approval. "A Waiver of Local IRB Review" is allowed under FDA [21 CFR 56.105]. The FDA may approve a waiver of local IRB review if it can be shown to be in the best interest of the subject(s), and if a satisfactory alternate mechanism for assuring the protection of human subjects is available, e.g., review by a central IRB. Such a waiver does not apply to the informed consent requirement. The SIRB still opts to review such studies even when FDA has granted a waiver; therefore, in the event of a waiver of local IRB review the physician must still contact the IRB (Office, Sr. Director, Director, or Chair) directly as soon as possible.
 - a. Whether or not the waiver applies:
 - i. Treatment use must meet criteria for a treatment IND and must provide sufficient data to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.
 - ii. Prior notification by the physician is required. The physician must notify the IRB Chair, alternate chair or designated physician member concerning the proposed treatment use of the investigational drug or biologic.
 - b. Where the waiver applies, the SIRB makes no exception to local review requirements unless there is an existing agreement in place with the central IRB.
 - c. Where the waiver does not apply or the SIRB has not entered into the applicable agreements necessary with the central IRB in question, IRB approval must be by a convened IRB. [However, although the FDA regulations do not provide for expedited IRB approval in treatment use or emergent situations, the physician should keep in mind that a letter may be sent to the sponsor as described in the Emergent Use of an Unapproved Investigational Drug Policy and Procedure, if sufficient time does not exist to organize a

convened IRB meeting and the condition of the patient changes such that criteria for emergent use are now met, the letter would include a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of [21 CFR 56.104\(c\)](#). This is not an 'IRB approval,' the acknowledgment letter is only intended to be acceptable to manufacturers to allow shipment of the product to proceed as described in Emergent Use of an Unapproved Investigational Drug Policy and Procedure.]

5. Treatment Use Protocols require Informed consent. FDA regulations note that treatment use of an investigational drug is conditioned on the sponsor and investigators complying with the safeguards of the IND process, including the regulations governing informed consent ([21 CFR part 50](#)).

This procedure starts upon a physician identifying the need for the treatment use of an Unapproved Investigational Drug or Biologic. Treatment use of an investigational drug is conditioned on the sponsor and investigators complying with the safeguards of the IND process (whether previously existing or a treatment IND/single patient IND is obtained), including the regulations governing informed consent ([21 CFR part 50](#)) and institutional review boards ([21 CFR part 56](#)), Waiver of Local IRB Review may be allowed, and the applicable provisions of [21 CFR 312](#), including distribution of the drug through qualified experts, maintenance of adequate manufacturing facilities, and submission of IND safety reports. This procedure ends when the IRB has reviewed the information provided by the physician on the treatment use of the Unapproved Investigational Drug or Biologic in the form of a Treatment Use Protocol (as submitted to the FDA) or as a full SIRB Submission packet under the Requirements for Initial IRB Review Procedure.

When IRB review and approval is sought for a Treatment Use Protocol and before administering the investigational drug:

1. the physician must identify an available IND or the physician or the sponsor must obtain a Single, Multiple-Patient or Full Treatment IND or a standard IND from the FDA:
 - a. If the physician finds the intended patient meets criteria of an existing study protocol open at the institution in question:
 - i. The physician contacts the PI on the study in question
 - ii. The PI on the study in question may enroll the subject and initiate the investigational drug treatment or the local physician may opt to open the study at this location through the normal submission process.
 - b. If an approved study protocol does not exist or if the subject does not meet enrollment criteria for an existing study, the physician may either contact the manufacturer who may be able to allow use under an existing company Treatment IND or contact the FDA for a Single, Multiple-Patient or Full Treatment IND. In either case, the manufacturer must be contacted.
 - i. The manufacturer determines whether the drug or biologic can be made available for the treatment use under a company Treatment IND. If so, the physician compiles the necessary documentation and follows the submission procedures as noted above.
 - ii. If the need for an investigational drug or biologic represents an emergent situation that does not allow time for submission of an IND or if the FDA does not authorize shipment of the test article under a Single, Multiple-Patient or Full Treatment IND, the physician may choose proceed as described in the Emergent Use of an Unapproved Investigational Drug Policy and Procedure if criteria as an

emergent are met.

2. The physician must submit the following information to the IRB for convened IRB review and approval for a Treatment Use Protocol (If the sponsor has not applied for a waiver of local IRB review under the treatment IND (such a waiver must be accepted by the SIRB under applicable agreements):
 - a. A full submission package as described in Requirements for Initial IRB Review Procedure.
 - b. Or alternately the IRB Chair, Sr. Director, or Director may allow the physician to submit to the convened IRB, the completed package sent to the FDA for approval of the Treatment IND or Single Patient Use IND.

When Waiver of Local IRB review is sought and before administering the investigational drug:

1. The physician must still identify an available IND or obtain a Treatment IND or Single Patient Use IND from the FDA (This will likely have been done prior to a satisfactory alternate mechanism for assuring the protection of human subjects was obtained, e.g., review by a central IRB.)
2. The physician must still contact the IRB Chair, Sr. Director, or Director concerning the planned treatment use of a test article in the following manner:
 - a. A written memorandum, email, or telephone call summary of explanation which justifies administration of the test article is required;
 - b. A copy of the informed consent form may still be required;
 - c. Applicable agreements must be in place

6.12 Use of Email for Collecting Board Member Votes

The use of e-mail for Board votes are limited to those items that do not need to be handled in a confidential manner. Possible items requiring a vote by Board members that could be handled through an e-vote mechanism include:

1. Consideration of new regular or alternate members to the SIRB;
2. Minor revisions of policies previously approved by the SIRB;
3. New policies that have been discussed at a meeting of the SIRB but that required revision before final vote;
4. Forms (revised or new) that have been presented at a meeting of the SIRB, but that required revision before final vote; or
5. Planned changes in the Board meeting schedule.

Action items that fit this policy will be distributed by e-mail to the regular members of the SIRB and designated by use of the term "e-vote" in the email subject line. Information on the action item will be provided in the body of the e-mail and/or in an attachment. A response will be required within 7 working days (ex. send e-mail on Monday, vote closes at the end of Tuesday in the following week). The majority vote determines the outcome of the action item.

6.13 Appeal of Decisions Made by the Institutional Review Board

Approvals, favorable actions, and recommendations made by the IRB are subject to review and further restriction by the institutional administration (Sr. Vice President for Medical Affairs, President). For example, protocols could be approved by the IRB on a scientific and ethical basis, but be restricted or disapproved by institutional administration due to the potential for adverse public/community reaction.

Protocol disapproval, restrictions or conditions imposed by the IRB upon any activity involving human subjects cannot be rescinded or removed except by subsequent action of the IRB. Investigators may appeal tabled and disapproved studies. A PI has the right to appeal the disapproval of his research protocol to the Board and asked to have the decision reconsidered. Investigators may submit a written response to the IRB for a protocol that is disapproved or tabled. The written response will be reviewed by the IRB. The IRB will invite the investigator to the IRB meeting if the IRB has additional questions for the investigator. The IRB will reconsider its decision. The second decision is final.

6.14 Noncompliance with IRB Policies, Procedures, or Decisions

Human subjects research that deviates from the policies, procedures, stipulations, decisions, state, or federal law is noncompliant and subject to further inquiry by the IRB and ORA. All reports and complaints of noncompliance should be directed to the ORA (via email, phone, mail, or in person). The ORA will immediately investigate all allegations of noncompliance. If necessary, the ORA will send the investigator(s) in question a notice requesting the immediate suspension of all specified research activities while the issue of noncompliance is reviewed, consistent with Federal Regulations [45 CFR Part 46.113](#). This initial notice will also include a statement detailing the rationale for the IRB's action. There are categories of noncompliance: general, serious, and continuing.

Definitions:

1. **General Noncompliance:** Any deviation from SIRB policies and procedures, federal regulations, or state law is 'noncompliance.' Failure to follow requirements and determinations of the IRB is also considered 'noncompliance.'
2. **Serious Noncompliance:** All Noncompliance substantially affecting participants' rights and/or welfare, or impacting upon the risks or benefits is serious noncompliance.
3. **Continuing Noncompliance:** Is a pattern of noncompliance that indicates an inability or unwillingness to comply with the regulations or the requirements of the IRB.
4. **Allegation of Noncompliance:** An unproven assertion of non-compliance.
5. **Finding of Noncompliance:** Noncompliance that is true in fact. A finding of noncompliance may exist because there is clear evidence, an admission, or an investigation into an allegation has determined the allegation to be true.

All noncompliance will be brought to the attention of the Sr. Director of the ORA. If the general noncompliance is clearly neither serious nor continuing and there is a corrective action plan that can be readily implemented to prevent recurrence, then the matter may be noted in the IRB file and no further action is needed (for example, failure to sign the application or lost consent forms). Otherwise, the Sr. Director will refer allegations and findings of noncompliance to undergo an evaluation by an ad-hoc SIRB Noncompliance Sub-Committee, selected by the SIRB Chair. This sub-committee, composed of two members of the SIRB and one staff member from the ORA, will review the nature of the noncompliance and make a recommendation based on each specific case. When allegations are substantiated, the sub-committee considers the following recommendations: modifying the research protocol; modifying the consent process; contacting past or current participants with additional information (for current participants whenever that information might affect their willingness to continue to take part in the research); re-consenting participants; modifying the approval period; suspension; termination; or utilizing a peer review process; and other actions deemed necessary. The SIRB Noncompliance Sub-Committee will also recommend whether the noncompliance was serious or continuing. The sub-committee issues the recommendations to the IRB for a vote.

The IRB will review the recommendation(s) of the IRB Noncompliance Sub-Committee at a convened meeting. All IRB members will be provided with a copy of the approved protocol, current consent documents, and the report of the IRB noncompliance sub-committee along, with any supporting documents. A member of the IRB noncompliance sub-committee will serve as a primary reviewer. The relevant IRB files, if any, will be made available at the meeting. The IRB may accept, modify, or reject the sub-committee's recommendation(s). The IRB will then assess whether the incident of noncompliance was serious and/or continuing. If necessary, the IRB may request additional information before issuing determinations. The IRB reserves the right to request any appropriate additional consultation and expertise to resolve noncompliance. Deliberations and determinations of the convened IRB will be fully documented in the minutes. All cases of noncompliance which the IRB determines to be serious or continuing noncompliance will be reported according to the Reporting Policy (see Section 2.0.7).

Section 7: Additional Review Items

7.0 Continuing Review Procedure

Any research activity (including Exempt, Expedited, and Full Board) involving the use of human subjects that has received initial review and approval by an Institutional Review Board (IRB) is subject to continuing review and approval. Time intervals for such reviews shall be made at the discretion of the IRB but shall occur no less than annually, for Expedited and Full Board approvals.

Principal Investigators (PI) should submit a continuing review when:

1. Research is ongoing;
2. The remaining research activities are limited to data collection; or
3. The research remains active for long-term follow-up of participants despite the protocol being permanently closed to the enrollment of new participants and all participants having completed all research related interventions, or for the analysis of identifiable data.

Continuing review may stop only when:

1. The research is permanently closed to the enrollment of new participants; and
2. All participants have completed all research-related interventions; and
3. Collection and analysis of private identifiable information has completed.

Full Board and Expedited studies require the following be submitted for continuing review:

1. **Study Status Report Form;**
2. A current copy of the consent form(s);
3. A current copy of the assent form(s);
4. A current copy of the research protocol on file; and
5. All other additional documents and materials, including questionnaires, recruitment materials, and scripts.

Any revisions to the previously approved consent process, the protocol, recruitment, enrollment, or other study related activity are to be submitted as an amendment. The PI must submit an amendment with updated copies of the revised consent process and form, protocol, recruitment, enrollment, or other study activity or procedure. All changes should be clearly indicated in a tracked changes format or highlighted. The PI must submit renewal letters from cooperating IRBs, as relevant. If the site(s) in question did not have an IRB of record and thus submitted an official letter granting permission for the investigator to conduct the research, then a second letter is not required.

PIs are required to complete the **Study Status Report Form** for continuing review applications. IRB staff provides the designated IRB reviewer with: the continuing review form, the current protocol, consent forms, and other submitted documents. The designated reviewer is expected to review these materials in depth. Each Full Board continuing review is assigned to an appropriate primary reviewer (no conflict of interests) by the IRB chair and the reviewer completes the **Primary Reviewer Checklist for Continuing Review**. Continuing reviews for Expedited and Exempt studies are reviewed by the IRB Chair or a delegated IRB reviewer. Continuing reviews ensure that current informed consent documents are accurate and complete. Reviewers are required to ensure that the submitted informed consent

documents and protocols are accurate and complete. Reviewers will compare the continuing review materials with the prior years' submission materials to verify accuracy and precision before making a final determination. Then the IRB may vote to 'Approve' for continuation, if explicit clarifications are required, 'Approved with stipulations,' if general clarifications and issues are required, 'Table,' or 'Disapprove' if the IRB can no longer approve research. When necessary the IRB may disapprove continuing reviews. No research protocol may continue until final approval for continuation is granted.

Full Board studies are subject to agenda deadlines and will be reviewed accordingly. Continuing review approval periods are one year or less from the day of formal re-approval, unless otherwise necessitated. Continuing reviews submitted prior to their expiration date but not formally reviewed and approved by the expiration date are expired and all research and research related activity must cease until formal IRB re-approval. Human Research Protection Program (HRPP) provides PIs a 30-day grace period after the expiration date to submit a continuing review; however, during this time all research and research related activities must cease.

The IRB has the authority to observe or appoint a third-party to observe research conduct, including consent procedures. It may also consider whether a study requires independent verification from sources other than the PI to ensure that no material changes have occurred since the last IRB approval. The IRB will require verification of the information provided for continuing review when:

1. Continuing review materials appear inconsistent or inaccurate compared to prior applications or records and discrepancies cannot be resolved via communication with the PI;
2. The IRB determines that such actions are useful as part of a corrective action plan for any unanticipated problem or event;
3. Complex projects involving unusual levels or types of risks to subjects;
4. Projects involving vulnerable populations;
5. Projects conducted by an investigator who previously failed to comply with IRB determinations; or
6. Projects where the continuing review application or reports from other sources have indicated that changes may have occurred without IRB approval.

If the findings of such investigations during the continuing review process warrant corrective actions, the IRB may suspend or terminate a research project to ensure the quality of research. Continuing review materials (reviewer checklist, research determinations, and specific protocol findings) are stored in the IRB files.

Investigators are required to submit an application for continuing review by the Seton Institutional Review Board (SIRB) before the approval expiration date as follows:

- For protocols approved under Expedited review procedures, the documents must be submitted to the Office of Research Administration (ORA) no less than two weeks before the expiration date;
- For protocols approved under Full Board review procedures, the documents must be submitted to the ORA no less than four weeks before the expiration date.

It is the responsibility of the PI to know when any given study requires renewal and to initiate that process. If the PI does not respond within 30 days, then the IRB will administratively terminate the study. At that point, the study no longer has IRB approval. Participants who are enrolled in a study that has been terminated may no longer receive care under that study protocol, no new participants may be enrolled, no

further data can be collected under that study protocol, and no further data analysis can be performed.

Continuing Review Submissions must include any significant findings that become known in the course of the research that might affect the willingness of subjects to continue to participate in the study. Depending on the protocol status, the following materials must be submitted for continuing review:

	Currently Enrolling Participants	Closed to Enrollment, Open for Intervention, and/or Data Collection	Open ONLY for Data Analysis
Study Status Report	X	X	X
Summary of Study Progress	X	X	X
Updated and Signed CV of PI and Co-Investigators (If needed)	X	X	X
Updated Study Personnel	X	X	X
Current version of the most recently approved protocol on file	X	X	X
Report of Significant New Findings	X	X	X
Copy of the most recently approved consent form	X	-	-
Copy of Recruitment materials	X	-	-

The PI may determine that all protocol activities are completed; including final data analysis. The PI may close the study by submitting a Study Status Report Form and final study progress report. The Study Status Report Form and application must be approved by the SIRB prior to the annual expiration date.

Once the ORA receives a continuing review application, the IRB Coordinator(s), in collaboration with the IRB Chair and/or designee, review the application making the determination as to Full Board review or Expedited review, for the following:

- A protocol initially reviewed by Expedited review is considered eligible for Expedited continuing review, as long as during the course of the study, the risks of the study have not increased (Expedited Categories 1-7).
- A protocol initially reviewed by the Full Board will continue to receive full board review unless the Chair or his/her IRB member designee determines that the study meets the specific criteria for expedited review as outlined [\[45 CFR 46.110\]](#) and [\[21 CFR 56.110\]](#): Expedited Category 8]:

- The research is permanently closed to the enrollment of new subjects (all subjects have completed all research-related interventions; and the research remains active only for long-term follow-up of subjects);
 - No subjects have ever been enrolled and no additional risks are identified; or
 - Where the remaining research activities are limited to data analysis.
- A protocol initially reviewed by the Full Board, but the SIRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified (Expedited Category 9).

For projects undergoing continuing review, the SIRB may approve, conditionally approve pending required actions on the part of the investigator, defer approval pending significant actions on the part of the investigator, or disapprove the protocol. Investigators are notified in writing of the decision of the SIRB and any changes required.

7.1 More Frequently Than Annual Continuing Review

There are times when the risks associated with a particular protocol are such that continuing review should take place more frequently than annually. In these cases, the IRB will specify that the PI report to the IRB either at a shorter time interval or after a specified number of subjects (e.g., after each subject or after 3 subjects) are enrolled. The PI's reports must describe the observed effects of the research activities and/or how the subject(s) responded to the research interventions. The determination will be recorded in the IRB minutes and approval letters; and the reports will be provided to the IRB, by the ORA, when they are submitted.

The IRB may require a more frequent annual review because of any of the following:

1. Noncompliance history;
2. Marginal Risk / Benefit Ratio;
3. As necessitated by protocol; or
4. Quality Assurance & Improvement (QA&I) recommendation

7.2 Protocol Amendments

All amendments, modifications, or changes (Exempt, Expedited, and Full Board) to protocols or consent forms must be requested and reviewed and approved, as appropriate, by the SIRB under the same procedure as for initial review, prior to making any changes in study procedures. Requests must be made on the Amendment Form describing what modifications are desired, why the changes are required, and if the changes pose any additional risks to the subjects. PIs are required to submit the Amendment Form along with updated research documents along with documents indicating all changes in tracked changes format. A summary of changes document (e.g., containing a table clearly listing all changes – old language versus new language) may be acceptable at the discretion of the ORA/IRB. However, the tracked changes document is preferred and may be specifically requested for by the ORA/IRB.

When amendments, modifications, or changes are reviewed by the convened IRB, all IRB members will be provided with a copy of all documents submitted by the investigator. Minor changes to the protocol or consent forms may be administratively approved according to [45 CFR 46.110\(b\)\(2\)](#). SIRB uses the

Expedited review procedure to review minor changes in previously approved research. Minor changes are defined as changes that involve minimal risk procedures and/or do not increase the risk or decrease the potential benefit to subjects, do not involve one or more of the regulatory criteria, and may include Categories 1-7 [[45 CFR 46.110\(a\)](#)]. Typical changes include changes in key personnel, non-significant changes in sample size, an addition of a questionnaire that does not include sensitive or controversial questions, a change in the compensation schedule, an addition of a site, etc.

Minor amendments submitted to SIRB will be forwarded to the IRB Chair or Chair's designee for review and approval. At the Chair's or Chair's designee discretion the amendment may be reviewed by the full convened IRB. Changes considered to be more than minor must be reviewed at a convened IRB meeting.

Investigators are responsible for reporting promptly to the SIRB proposed changes in a research activity. Changes in research during the period for which SIRB approval has already been given shall not be initiated by research investigators without SIRB review and approval, except when necessary to eliminate apparent immediate hazards to the subject. If this occurs, the investigator is required to promptly notify the IRB of these instances by submitting written documentation to the ORA. The IRB reviews this documentation to determine if the modification made to eliminate apparent immediate hazards to the subject was consistent with ensuring the subject's continued welfare.

During the course of a study, researchers may become aware of new information that would impact a subject's decision to participate, or continue participating in the research study. For example, interim analyses of data may identify a trend which impacts the safety of subjects, or may identify early efficacy (benefit) of one of the interventions under study. In addition, results from other research studies or changes in standards of practice or care may affect conduct of a study and would need to be communicated to research subjects. Investigators must report any new information that may impact the willingness of subjects to participate to the SIRB [[CFR 46.116\(b\)\(5\)](#)].

7.3 Identification and Reporting of Adverse Events, Unanticipated Problems, and Other Safety Information

During the course of a research study it is the Principal Investigator's responsibility to keep the IRB informed of any adverse events or problems that may affect the risk/benefit ratio (i.e. an increase in anticipated risk or a decrease in anticipated benefit). This includes any local adverse events as well as non-local serious adverse events that are unexpected, possibly or probably related to the research interventions, procedures or assessments, and place the subjects or others at increased risk of harm. The following provides guidance on which types of adverse events are required to be reported to the IRB and indicates the timeline for reporting.

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, that occurs during the subject's participation in the research, whether or not it is considered related to the subject's participation in the research. Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

In the context of multi-center research projects, adverse events are characterized as either local or non-local adverse events. When investigators are participating in a multi-center studies, local adverse events

are those experienced by subjects enrolled by the investigator(s) under the Seton IRB jurisdiction; whereas non-local adverse events are those experienced by subjects enrolled by investigators at another institution(s) engaged in the same research study or using the same investigational drug/device. In the context of a single center research study conducted by an investigator under the Seton IRB, all adverse events would be considered local.

For the purposes of this guidance, IND/IDE Safety Report refers to reports from sponsors informing researchers using the same drug or device in a different trial, about adverse events or reactions occurring in trials not conducted by an investigator under the Seton IRB jurisdiction, or adverse experiences reported in the context of usual clinical use of the study drug/device.

A serious adverse event is any event that:

1. Results in death;
2. Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. Results in inpatient hospitalization or prolongation of existing hospitalization;
4. Results in a persistent or significant disability/incapacity;
5. Results in a congenital anomaly/birth defect; or
6. 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.

Note: A 'serious adverse event' is by definition an event that meets any of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself.

The term 'unanticipated problem' is found, but not defined in the regulations for the Protection of Human Subjects at 45 CFR 46, and the FDA regulations at 21 CFR 56. Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets all of the following criteria:

1. Unexpected or unforeseen; and
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.

An unanticipated problem may be any of the following:

1. An actual unforeseen harmful or unfavorable occurrence to participants or others that relates to the research protocol (injuries, side effects, deaths);
2. An unforeseen development that potentially increases the likelihood of harm to participants or others in the future;
3. A problem involving data collection, data storage, privacy, or confidentiality;
4. A participant complaint about IRB approved research procedures;
5. New information about a research study (e.g., a publication in the literature, interim findings, safety information released by the sponsor or regulatory agency, or safety monitoring report) that indicates a possible increase in the risks of the research;
6. Changes in approved research initiated without IRB review and approval to eliminate

- apparent immediate hazards to the participant; or
 7. Incarceration of a subject.

Please use the chart and diagrams below to determine which adverse events and other research-related information requires reporting to the IRB and the local IRB reporting timeframes.

Type of Event	When to Report*	What Form to Use**
Adverse Events		
Local Adverse Event – Not Serious that is also: (occurring to a subject enrolled on a protocol under the Seton IRB jurisdiction) <ul style="list-style-type: none"> • Unexpected (in terms of nature, severity or frequency); and • Definitely, probably or possibly related 	Within 10 working days of PI awareness	Local Adverse Event and Unanticipated Problem Report Form
Local Serious Adverse Event (occurring to a subject enrolled on a protocol under the Seton IRB jurisdiction) <ul style="list-style-type: none"> • All local Serious Adverse Events are reportable to the IRB regardless of whether they are expected or related to research participation 	With 5 working days of PI awareness	Local Adverse Event and Unanticipated Problem Report Form
Non-Local Serious Adverse Event that meets all of the following criteria for an Unanticipated Problem: (occurring in the same multi-site study as is conducted by the PI at Seton but at a different site) <ul style="list-style-type: none"> • Unexpected (in terms of nature, severity or frequency); • Definitely, probably or possibly related; and • Serious or otherwise places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized. 	Within 10 working days of PI awareness	External Adverse Event and Unanticipated Problem Report Form
Other Types of Events or Safety Information		
External audit or monitoring report with findings	Within 10 working days of PI awareness	Miscellaneous Requests Form
DSMB/DMC Report		Miscellaneous Requests Form
Other safety information or publication that suggest a change to the risk/benefit ratio of the research		Miscellaneous Requests Form
Safety hold on study activities due to new or unexpected risk(s)		Miscellaneous Requests Form
Protocol Deviations and Other Research-Related Incidents		
Protocol Violation/Deviation – any intentional or accidental change to the IRB approved protocol	Within 10 working days of	Protocol Deviation Report Form

that increases the risk or decreases benefit, and/or affects the subject's rights, safety or welfare, and/or the integrity of the data. Including, but not limited to: incorrect intervention given, enrollment of ineligible participant, or key safety procedure/lab not done.	PI awareness	
Protocol Change Without Prior IRB Approval – necessary to avoid immediate and apparent harm to participants	With 5 working days of PI awareness	Protocol Deviation Report Form
Complaint – a complaint made by a subject, subject's family or others that is unresolved by the research team, or that indicates increased or unexpected risks.	Within 10 working days of PI awareness	Protocol Deviation Report Form
Other – including, but not limited to: breach of confidentiality; laboratory or pharmacy errors, problems with the consenting or recruitment process.	Within 10 working days of PI awareness	Protocol Deviation Report Form

*Initial notifications by the research team can be done via email to the ORA/IRB until a full report is available or able to be submitted (i.e., if a submission is already pending in the online IRB submission system).

**All forms are to be completed in the online IRB submission system. The IRB will review the report/form submitted in the system.

The researcher is obligated to keep the Seton Institutional Review Board informed of local adverse events that also meet the criteria that would qualify them to be unanticipated problems involving increased risks to others, and to report any occurrence of serious harm to subjects [CFR46.103(b)(5)]. The IRB requires PIs to promptly report a summary of each unanticipated problem to the IRB.

7.3.1 Reviewing and Reporting Responsibilities of the IRB and ORA

1. Adverse events not meeting the definition above (unexpected and definitely, probably, or possibly related) involving risks to participants or others – the event was foreseen, not related to the research procedures, and did not cause harm to participants or others, or place them at increased risk of harm:
 - a. The IRB Chair and IRB Project Coordinator(s) will confer to determine if the reported adverse event meets the criteria of the definition of an unanticipated problem: (1) unforeseen, (2) more likely than not related to the research, (3) caused harm to participants or other, or placed them at an increased risk of harm.
 - b. For those adverse events failing to meet the above criteria, the ORA will work with the PI towards a satisfactory and reasonable resolution for all parties. If the event is determined to be an unanticipated problem, it will be referred to the full IRB for review. The IRB Coordinator will formally report back to the PI all submitted unanticipated problem reports determined to be not unanticipated problems.
2. Unanticipated problems found to meet the criteria above (unexpected, definitely, probably, or possibly related, and serious or otherwise places subjects or others at a greater risk of harm) are placed on the agenda for the next full IRB review.
 - a. The report is distributed to all IRB members in advance of the meeting. The IRB

members will be provided with a copy of the report, the protocol with all approved modifications, and currently approved consent documents.

- b. If after reviewing the information, the IRB determines that the event was not an unanticipated problem; the IRB will decide if the report and PIs plan of action is sufficient and the IRB will make this determination by voting.
 - c. The IRB votes to take one or more of the following actions:
 - i. Accept the actions taken by the PI to report and resolve the incident;
 - ii. Notify current participants when information about the unanticipated problem might affect their willingness to continue to take part in the research;
 - iii. Alter the continuing review schedule;
 - iv. Approve with explicit changes:
 1. notification of previous subjects;
 2. modification of consent and/or protocol;
 - v. Suspension of some or all research activities; if necessary,
 - vii. Termination of the study for cause, if necessary.
3. The IRB follows the Reporting Policy, [45 CFR 46.103\(a\)](#) and [45 CFR 103 \(b\)\(5\)](#) for procedures taken when reporting unanticipated problems that involve risk to participants or others.
 4. Deliberations and determinations of the IRB will be fully documented in the minutes.

7.3.2 Additional Reporting Requirements

1. If a sponsor funds or supports the study, then the PI is responsible for notifying the sponsor. For any studies under FDA jurisdiction, it is the PI and/or sponsor's responsibility to notify the FDA within 24 hours.
2. Similarly, if the study is a multi-site project, and the unanticipated problem (and only the unanticipated problem) occurs at a site other than a Seton site, then the Sponsor is required to inform investigators of unanticipated problems that occur at other sites. When PIs are informed of unanticipated problem(s) in Sponsor safety memos or other correspondence, then the PI must notify the IRB. Reports to the IRB should be submitted as promptly as possible after receipt of the report from the Sponsor.

All deaths of any Seton Family of Hospitals research participant, whether expected or unexpected, must be reported with the following exceptions:

1. **Exception 1:** Deaths occurring in a registry study do not need to be reported.
2. **Exception 2:** Deaths occurring at an external site (e.g. multi-site study) in a study that includes a Data Safety Monitoring Board or Data Safety Monitoring Plan can be reported in aggregate at the time of continuing review.

7.3.3 What Not to Report to the IRB

1. Individual non-local adverse events that do not meet the criteria for reporting to the IRB should not be reported to the IRB. For example, non-local adverse events that are expected, are not serious, or are not related to the research do not need to be reported. If the study sponsor requires submission of these events to the IRB, the events should be summarized and submitted in a DSMB report or similarly reported at continuing review.
2. Individual study sponsor IND/IDE safety reports that do not meet the non-local reporting criteria. These are generally reports from sponsors informing researchers using the same drug or device in a different trial, about adverse events or reactions occurring in trials not conducted by an

investigator under the Seton IRB jurisdiction, or adverse experiences reported in the context of usual clinical use of the study drug/device.

7.3.4 Assessing Whether an Adverse Event is an Unanticipated Problem

Assessing Whether an Adverse Event is Expected

An unexpected adverse event is defined as any 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 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.

The vast majority of adverse events occurring in the context of research are expected in light of:

1. The known toxicities and side effects of the research interventions/procedures;
2. The expected natural progression of subjects' underlying diseases, disorders, and conditions; and
3. The subjects' predisposing risk factor profiles for the adverse events.

Thus, most individual adverse events do not meet the first criterion and do not need to be reported.

Assessing Whether an Adverse Event is Related

Adverse events may be caused by one or more of the following:

1. The interventions/procedures involved in the research;
2. An underlying disease, disorder, or condition of the subject, or
3. Other circumstances unrelated to the research or any underlying disease, disorder or condition of the subject.

'Possibly related' means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures or interventions involved in the research. In general, adverse events that are determined to have at least a reasonable relationship to the research procedures or interventions would be considered related to participation in the research.

'Probably related' means that it is likely, but uncertain, that the incident, experience or outcome was caused by the procedures or interventions involved in the research.

Adverse events determined to be solely caused by the underlying disease, disorder or condition, or events occurring that are clearly unrelated to the research project or condition under study would be considered 'unrelated' to participation in the research.

Assessing Whether an Adverse Event Places Subjects or Others at Increased Risk

Adverse events that are unexpected, related (definitely, probably, or possibly) to participation in research and serious suggest that the research places subjects or others at increased risk than was previously known or recognized. These adverse events would warrant consideration of substantive changes in the protocol, consent document or other corrective actions in order to protect the safety of subjects, with consideration including but not limited to sponsor and data safety monitoring committee oversight, IRB review, and investigator determinations. In rare occasions, it may be advisable to temporarily suspend research in order to adequately assess the event(s) and make any necessary changes.

However, adverse events that do not meet the definition of 'serious' may still suggest the possibility of increased risk or harm to subjects or others (i.e., adverse events, although expected, occurred at a greater frequency or severity than previously known or anticipated). It is important to recognize that greater risk of harm is not limited to adverse events that are 'serious.'

7.3.5 Investigator Responsibilities

Investigators are responsible for:

1. Timely, accurate and complete adverse event reporting as described in this guidance.
2. Safety monitoring according to the IRB approved data safety monitoring plan. This includes monitoring for, and maintaining documentation of, adverse events whether or not they meet the criteria for reporting to the IRB.
3. Ensuring that adverse events are reported to the monitoring entity (e.g., the research sponsor, a coordinating or statistical center, an independent medical monitor, or a DSMB/DMC), as required under the monitoring provisions described in the IRB-approved protocol.
4. Evaluating whether adverse events or other safety-related information may affect subject's willingness to continue participation in the study, and/or whether changes to the protocol or consent document are indicated to protect the safety and welfare of subjects
5. The causality assessment and follow-up of all local study related adverse events and other safety-related information (such as sponsor or DSMB updates, or holds on study activities due to safety concerns).
6. Providing the IRB with a progress report at continuing review. The progress report should include a summarization of the investigator's overall assessment of any adverse events and any other new information that has become available in order for the IRB to determine if the risk/benefit ratio has changed. The investigator's assessment may be a statement that expected adverse events have not occurred at a greater frequency or severity than previously anticipated; and/or a report from a monitoring entity such as a Data Safety Monitoring Board (DSMB), Data Safety Committee (DSC), the research sponsor, or coordinating center.

Adherence to the IRB reporting requirements will be monitored as part of the IRB's routine administrative monitoring activities. Findings of non-compliance will be handed in accordance with the Seton IRB policy on regulatory non-compliance (see Section 6.14).

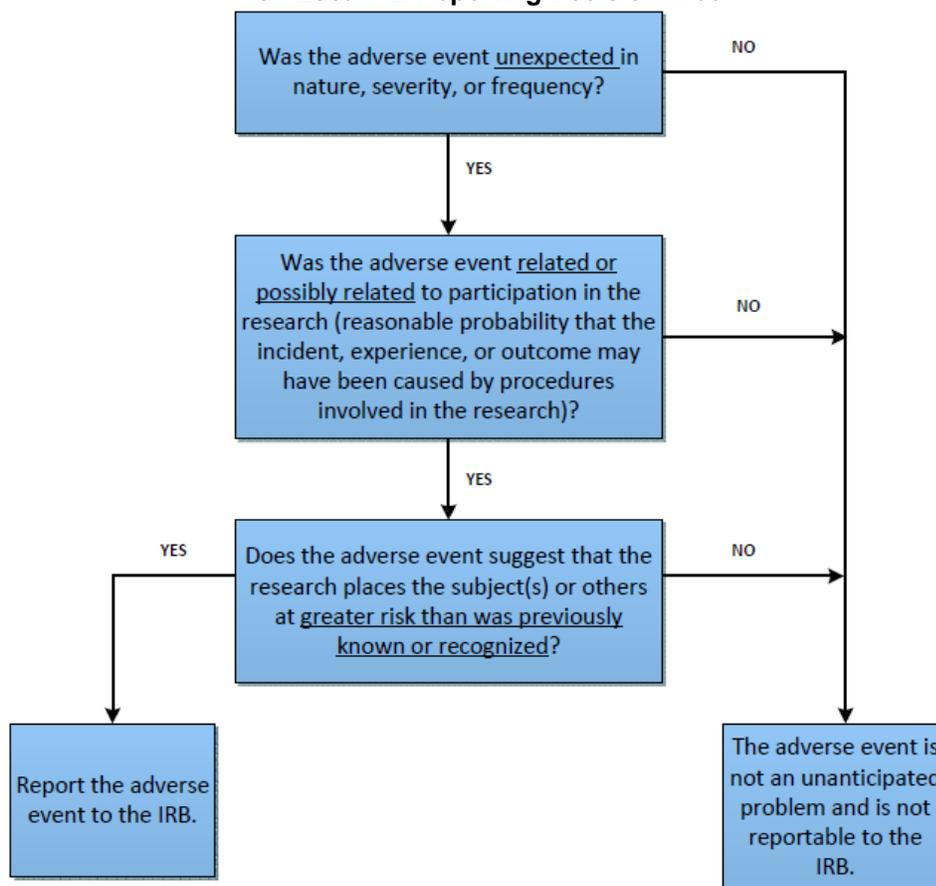
7.3.6 Other Reportable Events and Safety Information

1. External Audits and Monitoring Reports: Any time an audit of Seton Family of Hospitals study records is conducted by an external regulatory entity such as the US Food and Drug Administration (FDA), it is the responsibility of the Principal Investigator to inform the IRB promptly. If the Principal Investigator is given advance notice of an audit by an external entity, the

IRB staff can help the study team to gather essential documents and can be available to help answer the auditor's questions about human subject protections at Seton. The IRB may also wish to send a representative to observe proceedings of any 'exit interview' which may occur. The written report of any audit findings by FDA or other regulatory agencies must be forwarded to the IRB for their records. Other audit activities, such as sponsor-initiated study monitor reports, should be reported to the IRB if there are significant findings that could potentially affect the safety, rights or welfare of subjects, and/or as required by the study sponsor.

2. **Data Safety Monitoring Reports:** For ongoing trials, the IRB is responsible for considering new information arising from interim data safety monitoring by the PI, Data Safety Monitoring Board (DSMB) or Data Safety Committee (DSC). Investigators are responsible for assuring that the IRB is made aware of significant new information that arises about a clinical trial. Such information may include DMC recommendations to the sponsor. Data Safety Monitoring Reports should be reported to the IRB, even when no problems have been identified and the DSMB has recommended continuation of the trial as designed.
3. **Protocol Deviations/Violations:** Federal regulations require that no changes be made to research protocols without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects. A protocol violation is an intentional or accidental change to the IRB approved protocol that has the potential to increase risk or decrease benefit, and/or affect the subject's rights, safety or welfare, and/or the integrity of the data. Protocol violations are to be reported to the IRB even if no actual harm to the subject results. It is the responsibility of the principal investigator to ensure that all individuals involved in the conduct of the research follow the IRB-approved research protocol. When changes to the protocol are necessary, a modification request must be submitted to the IRB for review and approval prior to implementation of the changes.

Non Local AE Reporting Decision Tree



7.4 Quality Improvement/Monitoring Program

The purpose of the IRB Quality Improvement/Monitoring Program is twofold:

1. We are committed to the process of quality assurance. This process includes (a) the initial and ongoing review of research protocols by the IRB, (b) the organized dialogue between researchers and the IRB for the purposes of education of both parties, and (c) the peer review, or monitoring, of ongoing research (45 CFR 46).

The circumstances that lead to peer review are detailed below and include such criteria as:

- a. The pursuit of additional information to expand the content knowledge of the IRB collectively;
 - b. Research that is subject to high levels of institutional exposure;
 - c. Research involving high-risk populations or procedures;
 - d. Unanticipated events that pose risk to study participants; or
 - e. Significant non-compliance.
2. We are committed to efforts to improve all processes surrounding the implementation of research involving human subjects, and the review of such research. By this plan, the goal is to enhance the quality of the dialogue between researchers and research oversight committees

and relevant offices (e.g., Institutional Review Board (IRB), the Office of Research Support (ORA), and Clinical Research Steering Committee (CSRC)). This is an education plan whereby researchers, IRB members, and ORA representatives are invited to participate in a discussion of a program of research, research methodology, and administrative processes involved in the submission, review, and approval of research studies.

This process may be initiated by either the researcher or the IRB. The process may focus on a specific research protocol, or a series of research projects characteristic of the researcher's laboratory or office. These organized field observations and interactions are instigated by invitation and are not to be interpreted as an investigation of a 'for-cause' action.

It is a Federal mandate that the IRB be composed of members who possess expertise with regard to the protocols under review. Adjunct members may be appointed to the IRB when such expertise does not exist on the Board. It is a useful process, however, that proficiency be developed among current board members and relevant ORA staff members. Likewise, it will correspond with the IRB's mission to ensure the wellbeing of human participants that individual investigators be aware of the federal policies for research involving human subjects. To serve these purposes, selected departments, investigators, and research laboratories may be invited to participate in a process of discussion and review. Following this review, recommendations may be made to improve the integrity of human subject's protection in research

7.5 Policy & Procedures for Data and Safety Monitoring Plans (DSMP)

Concerns within Congress and Federal agencies responsible for assuring the safety and welfare of subjects participating in clinical research studies have prompted the issuance of new guidance and policies on oversight of clinical trials. More specifically, many investigators are now required by either the Federal government or private sponsors to establish plans for ongoing, real time data and safety monitoring in studies involving human subjects. Specific responsibility for and methods of data and safety monitoring depend in part on the sponsor of the study (e.g., industry sponsored-FDA regulated, NIH supported, or investigator initiated).

The methods and amount of monitoring required are somewhat dictated by the degree of risk involved to the individual subjects and the complexity of the research. Some research activities may require the establishment of a Data and Safety Monitoring Plan (DSMP) to review interim analyses of data and cumulative unanticipated problem data to determine if the research activities should continue as originally designed, be changed, or be terminated.

Both OHRP and NIH have written statements on the definition of a DSMP, the types of information that it may review, and when it should be reported to and used by an IRB in its continuing review process.

At the time of submission of a new protocol to the SIRB, researchers are asked to complete an IRB application form for their research study. The IRB application form asks the researcher to "list the potential risk(s), describe the likelihood of the risk(s), and summarize how they plan to minimize and control the risk(s)". In addition to the application, the researcher is asked to submit a research protocol. The protocol should list the potential risks involved with the study, describe their process for protecting against (or minimizing) any potential risks, and include an assessment of their effectiveness. This includes the review of unanticipated problems, along with a DSMP when necessary. If the researcher does not utilize the research proposal template as provided by the ORA, this information is still required to be outlined in their proposal. The SIRB may require a Data and

Safety Monitoring Board (DSMB) to be put in place when deemed necessary.

In order to receive renewal of IRB approval for a research study, the researcher must complete a **Study Status Report Form**. This form requests information from the researcher regarding whether any data and safety monitoring reports have been prepared and received by the IRB. This information may include a current statement from the DSMB or Study Sponsor indicating that the DSMB has reviewed study-wide adverse events, unanticipated problems, interim findings, and any recent literature that may be relevant to the research, along with the DSMB's determination on the continuance of the study.

In studies that are greater than minimal risk, the IRB requires the inclusion of a DSMB. The following elements of the DSMB will be reviewed by the IRB to determine whether the DSMB has adequate potential for qualified, timely review of useful information regarding participant information:

1. Reporting mechanisms;
2. Frequency of monitoring and reporting; such as subject accrual number, or length of time after study has begun;
3. Qualifications and number of people serving on the DSMB and whether they have any perceived conflict of interest with the investigator or sponsor;
4. A specific list of the data to be reviewed;
5. Procedures for reviewing, analyzing and interpreting the participant data. If specific end-points are anticipated in a study under scrutiny of a DSMB, a list of the actions the DSMB might take when such end-points are reached;
6. Methods of communication between the DSMB and the IRB, and if the study is a multi-site study, methods of communication between the sites, DSMB, and the IRB

The responsibilities of a DSMB include:

1. Become familiar with the research protocol and the procedures for data safety and monitoring;
2. Review interim analyses of outcome data and unanticipated problem reports to determine if the study can continue as originally designed or if the study should be changed or terminated;
3. Review and approve major proposed modifications to the study prior to submission of the proposed modifications to the IRB; and
4. Provide the "study personnel" and SIRB with written information relating to the trial, e.g., a summary of unanticipated problems reported (from all sites), and recommendations with regards to continuance of the study at the completion of each meeting.

Section 8: Procedures for Research with Vulnerable Populations

8.0 Inclusion of Pregnant Women, Human Fetuses, and Neonates in Research

In addition to the responsibilities prescribed for the Institutional Review Board (IRB), the IRB shall follow special procedures with respect to vulnerable populations. In this case, the procedures provide additional safeguards in research activities involving, pregnant women, human fetuses, and neonates. This section is intended to follow the guidelines set forth in [Subpart B of 45 CFR 46](#).

Principal Investigators (PI) should include with their submission for initial review: the research proposal with a rationale and details for the inclusion of pregnant women, fetuses, or neonates in research activities and all applicable online forms. PIs should also ensure that the informed consent process adequately addresses the risk to the fetus or neonate and pregnant women. The IRB reviews all guidelines as set forth in Subpart B of 45 CFR 46 by utilizing the **Primary Reviewer Checklist**. The IRB approves only those studies in which the IRB has determined to fulfill all necessary regulatory requirements. The IRB, when reviewing research, ensures that there is adequate scientific and scholarly expertise to review the research. The IRB reserves the right to request expert consultation, as necessary for adequate review.

Definitions:

1. Embryo – The embryonic period commences at the beginning of the third week after ovulation and fertilization, which coincides in time with the expected day that the next menstruation would have started. The embryonic period lasts 8 weeks and is when organogenesis takes place (Source: Williams Obstetrics: 23rd Edition).
2. Fetus – The end of the embryonic period and the beginning of the fetal period is arbitrarily designated by most embryologists to begin 8 weeks after fertilization – or 10 weeks after onset of last menses. The fetal period continues until delivery of the fetus (Source: Williams Obstetrics: 23rd Edition).
3. Neonate – A subset of infants, referring to an infant from birth to the first 28 days of life (<29 days). Also referred to as “newborn”. For the purposes of adverse event/statistical reporting:
 - a. ‘Early’ Neonatal Death – From birth to the first 7 days of life.
 - b. ‘Late’ Neonatal Death – From day 8 to day 28 of life.
4. Pregnancy – Encompasses the time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus.
5. Viable – As it pertains to the fetus, means being able, after either spontaneous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respiration. Once a fetus is viable it is a premature infant.

Pregnant women or fetuses may be involved in research if all of the following conditions are met ([45 CFR 46.204](#)):

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
2. The risk to 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;

3. Any risk is the least possible for achieving the objectives of the research;
4. If the research holds out:
 - a. the prospect of direct benefit to the pregnant woman,
 - b. the prospect of a direct benefit both to the pregnant woman and the fetus, or
 - c. 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 and the woman's consent is obtained;
5. If the research holds out the prospect of direct benefit solely to the fetus, then the consent of the pregnant woman and the father is obtained, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest;
6. Each individual providing consent under (4) or (5) above is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children who are pregnant, assent and permission are obtained in accord with Subpart D for studies involving children;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy;
10. Individuals engaged in the research will have no part in determining the viability of a neonate, and
11. A data safety monitoring plan has been established to monitor participants.

Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met [\[45 CFR 46.205\(a\)\]](#):

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; and if the neonate is of uncertain viability [\[45 CFR 46.205\(b\)\]](#) until it has been ascertained whether or not a neonate is viable, the following additional conditions are met:
 - a. The IRB determines that 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 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
 - b. 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, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

According to [45 CFR 46.205\(c\)](#) if the neonate is nonviable after delivery, 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, except that the waiver and alteration provisions of Subpart A 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 requirement of this paragraph.

According to [45 CFR 46.207\(b\)](#), 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 will be sent to the Secretary of DHHS for review. The Secretary will determine the approvability of the research based on the conditions stated in [45 CFR 46.207\(b\)](#).

In addition to the responsibilities of the PI for obtaining sufficient, ongoing consent/assent for any pregnant or potentially pregnant participants in research, the PI should also ensure that the consent/assent forms appropriately address the reproductive risks involved with participating in the research, if there are any. The language addressing these risks in the consent/assent forms should be written in accordance to the [Model Language for IRB Consent Clauses Regarding the Use of Contraception](#), as has been prescribed by Seton's institutional values and mission. The Seton Institutional Review Board (SIRB) will review the language to determine whether or not it is appropriate.

8.1 Inclusion of Prisoners in Research

Special procedures are in place in the Federal Regulations that provide additional safeguards for the protection of prisoners involved in research activities. Investigators engaging in research including prisoners as participants should provide with their initial submission a specific detail and rationale in the research proposal and the appropriate online form. Investigators are also required to take extra measures to ensure appropriate informed consent. Since prisoners may be influenced by their incarceration to participate in research, and, in order to assure that their decision to participate is not coerced, the IRB will adhere to [Subpart C of 45 CFR 46](#).

Prior to IRB approval, investigators are required to obtain and submit written confirmation from the prison that the parole boards will not take into account a prisoner's participation in the research when making decisions regarding parole. In the review of research involving prisoners, SIRB will apply the prisoner specific definition of minimal risk as stated in [45 CFR 46.303\(d\)](#). In reviewing prisoner research, the SIRB will follow the requirements for IRB membership outlined in [45 CFR 46.107](#). Reviewers will document their findings in the **Primary Reviewer Checklist** and the SIRB will document all committee findings in the minutes.

If, at some point, while participating in a research project a participant becomes incarcerated, it is the responsibility of the PI to notify the Office of Research Administration (ORA). The protocol will then be re-

reviewed according to Subpart C or the participant-prisoner is withdrawn from research. [Subpart C of 45 CFR 46](#) provides four research categories that the IRB may approve for prisoner research. Using the Primary Reviewer Checklist, the IRB will review the proposed research to ensure one of the following four categories is applicable:

1. Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects [\[45 CFR 46.306\(a\)\(1\)\(A\)\]](#);
2. Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects [\[45 CFR 46.306\(a\)\(1\)\(B\)\]](#);
3. Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of his intent to approve such research [\[45 CFR 46.306\(a\)\(1\)\(C\)\]](#); or
4. Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of the intent to approve such research [\[45 CFR 46.306\(a\)\(1\)\(D\)\]](#).

The IRB will then proceed to confirm that the following items are applicable per [45 CFR 46.305\(a\)](#):

1. Any possible advantages accruing to the prisoner through his/her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his/her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
2. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;
3. Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
4. The information is presented in language which is understandable to the subject population;
5. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole;
6. Where the IRB finds there may be a need for follow-up examinations or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact; and

7. A data-safety monitoring plan has been established to monitor participants.

8.2 Inclusion of Children in Research

Special procedures are in place in the Federal Regulations that provide additional safeguards for the protection of children involved in research activities. The IRB will adhere to [45 CFR Part 46, Subpart D](#) or [21 CFR Part 50, Subpart D](#). The exemptions listed in 45 CFR 46.101(b)(1) through b(6) are applicable for research involving children except for 45 CFR 46.101(b)(2) for research involving surveys, interview procedures, or interventions with children. PIs should include with their initial submission, if involving children, the research proposal with a rationale and details for the inclusion and the appropriate online form.

Studies involving children require parental, guardian, or legally authorized representative (LAR) consent and participant assent; however, if there is any person other than the biological or adoptive parent who claims to be the child's guardian (grandparents, foster parents, etc.), the PI must contact the ORA and legal counsel will be consulted to determine whether the individual has the legal authority to make health care decisions on behalf of the child and therefore is the guardian as defined in federal regulations.

Definitions:

1. Child/Adolescent – Persons who have not attained the legal age for consent to treatment or procedures involved in the research/clinical investigations under the applicable laws of the jurisdiction in which the research will be conducted.
2. Assent – A child's affirmative agreement to participate in the research/clinical investigation. Mere failure to object or absent affirmative agreement should not be construed as assent. The assent form (including the assent script) is also the document used to inform and verify the child's agreement to participate in research.
3. Permission – A person/parent's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate/give permission for their child to participate in research or to undergo a diagnostic therapeutic or preventative procedure.
4. Parent – A child's biological or adoptive parent.
5. Guardian – An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care when general medical care includes research/clinical investigations.

If research takes place outside the state of Texas, the IRB will consult with legal counsel and the legal counsel will provide guidance and interpretation to the IRB.

For studies involving children where the risk is greater than minimal, the IRB may approve only the categories of research listed below, provided all applicable criteria are met:

1. Research not involving greater than minimal risk [[45 CFR 46.404](#)]: if the IRB finds that no greater than minimal risk to children is presented, approval may be given only if adequate provisions are made for soliciting the assent of the children and the permission of at least one (1) parent/guardian. Minimal risk means that the probability and magnitude of the harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological exams or tests.
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects [[45 CFR 46.405](#)]: if 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, approval may be given 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;
 - c. adequate provisions are made for soliciting the assent of the children and permission of at least one (1) parent/guardian; and
 - d. a data safety monitoring plan has been established to monitor participants.
3. 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 [[45 CFR 46.406](#)]: if the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, approval may be given only if IRB finds that:
- a. the risk represents a minor increase over minimal risk;
 - b. the intervention/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/procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the subject's disorder or condition;
 - d. adequate provisions are made for soliciting assent of the child and permission of both parents/guardians; and
 - e. a data safety monitoring plan has been established to monitor participants.
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children [[45 CFR 46.407](#)]: if the IRB does not believe the research meets the requirement of 404, 405, or 406, approval may be given 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;
 - b. The Secretary of DHHS, after consultation with a panel of experts in pertinent disciplines and following opportunity for public review and comment, has determined either (1) that the research in fact satisfies the conditions of 404, 405, or 406, or (2) 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 the research will be conducted in accordance with sound ethical principles and adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians; and
 - c. A data safety monitoring plan has been established to monitor participants.

8.3 Requirements for Consent and Assent Involving Children

In accordance with [45 CFR 46.408\(a\)](#), the SIRB must determine that adequate provisions have been made for soliciting the assent of children when, in the judgment of the SIRB, the children are capable of providing assent. In making the determination as to whether an assent process will be required, and how assent will be obtained, the SIRB considers the age of the subjects, their maturity, and their ability to read

and comprehend a written document given their mental and physical capacities and psychological state. The assent to participate in a research protocol should be obtained in accordance with instructions found with the sample assent form found at <http://www.seton.net/research>. The SIRB recommends that assent be sought for children ages 7 through 17, but may be appropriate for younger children depending on their aptitude. The SIRB may determine that assent is not a necessary condition for proceeding with the research if:

1. The aptitude of some or all of the children is so limited that they cannot reasonably be assented (determinations of capacity to assent will be assessed by age, maturity, and psychological state; and may be made for one, some, or all children in the research as the SIRB deems appropriate);
2. The intervention or procedure involved 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 research;
3. The assent process is not appropriate for the particular study; or
4. The research meets the required criteria for waiver of consent stated in [45 CFR 46.116\(d\)](#).

When assent is required, the PI and the child will sign the assent form to document that the participant has been given an explanation of the proposed research, in language appropriate to the children's age and intellectual capacity. For research conducted under [45 CFR 46.406](#) ([21 CFR 50.53](#)) and [45 CFR 46.407](#) ([21 CFR 50.54](#)) consent is required from both parents unless: 1) one parent is deceased, unknown, incompetent, or not reasonably available; or 2) when only one parent has legal responsibility for the care and custody of the child. Parental consent must be documented according to [45 CFR 46.117](#).

The Seton IRB may waive the requirement for obtaining consent from a parent or legal guardian if the research meets the provisions for waiver set forth in [45 CFR 46.116\(d\)\(1-4\)](#), if the Seton IRB determines that the research is designed for conditions or a population for which parental, guardian, or LAR is not a reasonable requirement to protect the participants (examples: homeless, neglected, abused children), the waiver is consistent with Federal, State, or local law, and the research is not subject to FDA regulations. However, in such cases the SIRB will substitute an appropriate mechanism for protecting the children who will participate. The determination for an appropriate mechanism would depend upon the nature and purpose of the research, risks, benefits, age, maturity, and psychological condition of the participants.

Children who are wards of the State or any other agency, institution, or entity can be included in research approved under [45 CFR 46.406](#) and [45 CFR 46.407](#) only if such research is: 1) related to their status as wards; or 2) conducted in school, camps, hospitals, institutions, or similar setting in which the majority of children involved as participants are not ward. If the research meets the criteria above, the Seton IRB requires the appointment of a participant advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or LAR. One individual may serve as an advocate for more than one child. The advocate must have necessary expertise, and agree to act in the best interest of the child. The SIRB requires the advocate to disclose any conflicts of interest. Only those advocates without any conflicts of interest can be appointed as advocates.

8.4 Inclusion of Subjects Without Sufficient Capacity to Consent in Research

Special procedures for IRB review and approval apply to research activities involving potential research subjects who, for a wide variety of reasons, are incapacitated to the extent that their decision-making capabilities are diminished or absent. Impaired capacity is not limited to individuals with neurologic, psychiatric, or substance abuse problems. Conversely, individuals with these problems should not be presumed to be cognitively impaired. Generally, subjects without sufficient capacity to consent may not understand the difference between research and treatment or the dual role of the researcher. Therefore;

when appropriate, it is essential that the consent/assent process clearly indicate the differences between individualized treatment and research.

The PI should also consider implementing a DSMB to review the consent / assent process. PIs may want to also consider using an independent expert to assess the participant's capacity to consent or assent. PIs should include with their submission for initial review (if the study involves persons without sufficient capacity to consent) the rationale and details for the inclusion of this vulnerable population as well as the appropriate online form. For those participants who are unable to consent, the PI must have consent obtained from that participant's LAR. The SIRB will evaluate whether participants, who are unable to consent, should be required to assent to participation. In some circumstances, consent may need to be reviewed with participants at appropriate intervals. The SIRB will only approve research involving adults without sufficient capacity to consent provided the following criteria are met:

1. The research question cannot be answered by using adults able to consent;
2. The research is of minimal risk or more than minimal risk with the prospect of direct benefit to each individual participant;
3. The assent of the adult will be a requirement for participation unless the adult is incapable of providing assent; and
4. When assent is obtained, the PI will document the assent by noting on the consent or assent form that the participant assented to participate in research.

8.5 Inclusion of Seton Family of Hospitals Students, Residents, Interns, Volunteers, and Staff in Research

In addition to pregnant women, children, incapacitated adults, and incarcerated individuals, the Seton IRB considers medical students, medical residents, Seton Family of Hospitals interns, Seton Family of Hospitals volunteers, and Seton Family of Hospitals staff as a vulnerable population; therefore, the IRB follows special procedures designed to safeguard these subjects.

Medical students, medical residents, Seton Family of Hospitals interns, Seton Family of Hospitals volunteers, and Seton Family of Hospitals staff have the same rights as any other potential subject to participate in a research project, irrespective of the degree of risk, provided all of the following conditions exist:

1. The research must not bestow upon participating Seton Family of Hospitals subjects any competitive academic or occupational advantage over other Seton students, residents, or staff who do not volunteer; and the researchers must not impose any academic or occupational penalty on those Seton students, residents, or staff who do not volunteer;
2. Seton Family of Hospitals students, residents, and staff must not be systematically treated differently from non- Seton Family of Hospitals subjects as part of the project; and
3. Due to the potential for perceived or real coercion to participate, Seton students, residents, and staff who desire to participate in the research must not be under the direct supervision of the PI or listed research collaborators except as necessitated by scientific merit or overwhelming benefit to subject(s).