Joint St. Joseph's Health & St. Peter's Health Partners

Human Research Protection Program / Institutional Review Board

Standard Operating Procedures

Effective: July 1, 2023

(Standard Operating Procedures will be applied to all
Joint St. Joseph's Health & St. Peter's Health Partners ongoing and future research)

Table of Contents

1. Human Research Protection Program (HRPP)

Joint St. Joseph's Health & St. Peter's Health Partners ("SJH/SPHP") fosters a research environment that promotes respect for the rights and welfare of individuals recruited for, or participating in, research conducted by or under the auspices of the organization. In support of this, SJH/SPHP has established a Human Research Protection Program (HRPP). The SJH/SPHP HRPP, in partnership with its research community, is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted under the auspices of Joint St. Joseph's Health & St. Peter's Health Partners.

1.1. Mission

The mission of the HRPP is to:

- Safeguard and promote the health and welfare of human research subjects by ensuring that their rights, safety, and well-being are protected.
- Provide guidance and support to the research community in the conduct of research with human subjects.
- Assist the research community in ensuring compliance with relevant regulations.
- To provide timely and high-quality education, review, and oversight of human research projects; and
- To facilitate excellence in the conduct of human subjects research.

The HRPP includes mechanisms to:

- Monitor, evaluate and continually improve the protection of human research participants
- Exercise responsible oversight of human subjects research
- Educate IRB members, investigators, and staff about their ethical responsibility to protect research participants
- When appropriate, intervene in research and respond directly to concerns of research participants.

1.2. Organizational Authority

The Human Research Protection Program (HRPP) of SJH/SPHP operates under the policies "Human Subject Research and Institutional Review Board (IRB) Requirements" and "Human Subject Research – Human Subjects Participation". As stated in the policy "Human Subject Research and Institutional Review Board (IRB) Requirements", the operating procedures in this document "…serve as the governing procedures for the conduct and review of all human research conducted under the auspices of Joint St. Joseph's Health & St. Peter's Health Partners." The HRPP Policy and these operating procedures are made available to all SJH/SPHP investigators and research staff and are posted in the IRB Electronic System (IRBManager) and on the SJH/SPHP IRB website (https://irb.sjhsyr.org/).

1.3. Definitions

Human Subject Research. Human Subject Research means any activity that meets the definition of "research" and involves "human subjects" as defined by either the Common Rule or FDA regulations.

Note: The terms "subject" and "participant" are used interchangeably in this document and have the same definition.

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 encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Common Rule. The Common Rule refers to the "Federal Policy for the Protection of Human Subjects" adopted by a number of federal agencies. Although the Common Rule is codified by each agency separately, the text is identical to DHHS regulations in 45 CFR 46 Subpart A. For the purposes of this document, references to the Common Rule will cite the DHHS regulations.

Common Rule Definitions:

Clinical Trial. Per the 2018 Common Rule and NIH Policy, clinical trial means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes. FDA regulations refer to "clinical investigations" (see definition of "research" below).

Research. The Common Rule defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge. Activities which meet this definition constitute research whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

For purposes of this part [the Common Rule], the following activities are deemed not to be research: (1) Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected. (2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters). (3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes. (4) Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions. [45 CFR 46.102(l)]

For the purposes of this policy, a **"systematic investigation"** is an activity that involves a prospective study plan that incorporates data collection, either quantitative or qualitative, and data analysis to answer a study question. Investigations designed to develop or contribute to **generalizable knowledge** are those designed to draw general conclusions (i.e., knowledge

gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings.

Human Subject. A human subject as defined by the Common Rule is a living individual about whom an investigator conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. [45 CFR 46.102(e)(1)]

Intervention means both physical procedures by which information or biospecimens are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. [45 CFR 46.102(e)(2)]

Interaction means communication or interpersonal contact between investigator and subject. [45 CFR 46.102(e)(3)]

Private information means information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). [45 CFR 46.102(e)(4)]

Identifiable private information means private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information. [45 CFR 46.102(e)(5)]. Note: This definition is within the Common Rule.
For a discussion of identifiability under HIPAA, please see Section 25.

Identifiable biospecimen means a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen [45 CFR 46.102(e)(6)]

Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research. *See section 13.3.*

Public health authority means an agency or authority of the United States, a state, a territory, a political subdivision of a state or territory, an Indian tribe, or a foreign government, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate.

Note: The Food and Drug Administration (FDA) research terms differ from the Common Rule definitions. For researchers conducting FDA related research, please refer to those definitions in section 15 of this SOP.

1.4. Ethical Principles

SJH/SPHP is committed to conducting research with the highest regard for the welfare of human subjects. With the exception of international research, where consideration of alternative ethical principles may apply (see Section 26).

1.4.1. SJH/SPHP upholds and adheres to the principles of The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research. These principles are:

1. **Respect for Persons**, which involves the acknowledgment and support of autonomy, and protection of those with diminished autonomy
2. **Beneficence**, which involves ensuring that possible benefits of research are maximized, and possible harms are minimized
3. **Justice**, which involves the fair distribution of the benefits and burdens of research through the equitable selection of subjects

1.4.2. Ethical and Religious Directive for Catholic Health Care Services. Consideration for Catholic ethical and religious directives must be given in the implementation of human subject research and IRB policies regarding the protection of human subjects. Areas from the Ethical and Religious Directives to be considered include:

1) The Social Responsibility of Catholic Health Care Services
2) The Pastoral and Spiritual Responsibility of Catholic Health Care
3) The Professional-Patient Relationship
4) Issues in Care for the Beginning of Life
5) Issues in Care for the Seriously Ill and Dying

The SJH/SPHP HRPP, in partnership with its research community, is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted under its auspices

1.5. Regulatory Compliance

The HRPP facilitates compliance with federal regulations, state and local law and organizational policies (including tribal laws passed by the official governing body of an American Indian or Alaska Native tribe). Human subjects research at SJH/SPHP is conducted in accordance with applicable regulations and requirements including, but not limited to, the following:

Research conducted, supported, or otherwise subject to regulation by any federal department or agency which adopts the Common Rule is reviewed and conducted in accordance with the Common Rule. Although the Common Rule is codified by each agency separately, the text is identical to U.S. Department of Health and Human Services (DHHS) regulations in 45 CFR 46 Subpart A. For the

purposes of this document, references to the Common Rule will cite the DHHS regulations (45 CFR 46).

SJH/SPHP has opted to apply the Common Rule to all its human subject research regardless of the source of support, as addressed below.

Research subject to **FDA regulations** is reviewed and conducted in accordance with applicable regulations including, but not limited to, 21 CFR 50, 21 CFR 56, 21 CFR 312 and 21 CFR 812.

Research involving the use of Protected Health Information is reviewed and conducted in accordance with the **Health Insurance Portability and Accountability Act** (HIPAA), 45 CFR Part 160, 162, and 164.

Additional requirements for International Research are described in section 26.12.

1.5.1. Management of pre-existing studies once the revised Common Rule goes into effect

Studies approved prior to January 21, 2019, where enrollment is permanently closed and only follow-up or collection of standard care data continues, and studies reviewed under expedited procedures may be transitioned to the new common rule on a case-by-case basis at the time of continuing review. All other studies approved prior to January 21, 2019, will continue to follow the pre 2018 common rule.

1.6. International Conference on Harmonization-Good Clinical Practice (ICH-GCP)

SJH/SPHP voluntarily applies the International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines (sometimes referred to as ICH-GCP or E6) to clinical trials of drugs when required by a sponsor or funding agency. SJH/SPHP applies the ICH-GCP guidelines only to the extent that they are compatible with FDA, DHHS, and other applicable regulations. *See the Special Topics section of this manual for more information.*

1.7. Federal Wide Assurance (FWA) and IRB Registration

The federal regulations require that federally funded human subject research only be conducted at facilities covered by an FWA approved by the DHHS Office for Human Research Protections (OHRP). An FWA is an organization's assurance to the federal government that human subject research conducted at that site complies with federal regulations pertaining to the protection of human subjects.

Likewise, federal regulations require IRBs to register with DHHS if they will review human subjects research conducted or supported by DHHS or research subject to FDA regulations.

The HHS registration system database can be used to verify the status of SJH/SPHPs FWA, IORG, and IRB registration.

St. Joseph's Hospital/St. Peter's Health Partners Federal Registration Numbers	
SJH FWA # **00004277**	SPHP FWA # **00004388**
SJH IORG # **0000678**	SPHP IORG # **0002685**

IRB Registration # **00001024**	SPHP IRB # **00003258**

1.8. Research under the Auspices of SJH/SPHP

Research under the auspices of SJH/SPHP includes research conducted at or using any property or facility of SJH/SPHP conducted by or under the direction of any employee or agent of SJH/SPHP (including students) in connection with his or her position or responsibilities, or involving the use of SJH/SPHP's non-public information (e.g., medical records) to identify, contact, or study human subjects.

The research may be externally funded, funded from internal sources, or conducted without direct funding.

All human subjects research under the auspices of SJH/SPHP is under the jurisdiction of the SJH/SPHP HRPP. Human subjects research that is engaged in (per OHRP or FDA guidelines) is under the jurisdiction of the SJH/SPHP IRB, unless SJH/SPHP chooses to rely upon another IRB for review and ongoing IRB oversight of the research (the IRB of record for the research).

Employee or Agent. For the purposes of this document, *employees or agents* refers to individuals who: (1) act on behalf of the organization; (2) exercise organizational authority or responsibility; or (3) perform organizationally designated activities. "Employees and agents" can include staff, students, contractors, credentialed physicians, and volunteers, among others, regardless of whether the individual is receiving compensation.

Engagement. DHHS regulations [45 CFR 46.103[a]] require that an institution "engaged" in human subject research conducted or supported by a Federal Department or Agency provide the Office for Human Research Protection (OHRP) with a satisfactory assurance of compliance with the DHHS regulations, unless the research is exempt under 45 CFR 46.104. *"In general, an institution is considered engaged in a particular non-exempt human subjects research project when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research."* Institutions that receive an award through a grant, contract, or cooperative agreement directly from DHHS for the non-exempt human subjects research (i.e. awardee institutions), are also considered engaged in research even where all activities involving human subjects are carried out by employees or agents of another institution.

FDA regulations are oriented to the responsibilities of IRBs, investigators, and sponsors as opposed to institutions. In general, FDA-regulated research conducted in SJH/SPHP facilities or by SJH/SPHP Principal or Sub-Investigators (as defined on the FDA 1572 or equivalent, or the delegation of responsibilities log) requires review by an SJH/SPHP designated IRB. Exceptions to this requirement may be granted on a case-by-case basis (e.g., when the involvement of SJH/SPHP in the research is limited to the provision of a common diagnostic procedure and associated reading or analysis)

Jurisdiction of the SJH/SPHP IRB

The SJH/SPHP HRPP and its IRB has jurisdiction over human subject research projects that meet the following criteria:

- Conducted by SJH/SPHP employees and/or agents acting on behalf of SJH/SPHP as the performance-site institution regardless of funding source and/or the location at which the research will be conducted;
- Conducted within the facilities and on the properties of SJH/SPHP by outside investigators. **Note** that SJH/SPHP does not permit an external investigator (non- SJH/SPHP employee or agent, outside of its institution) to be the sole principal investigator (PI) of a study (there must be an SJH/SPHP employee acting as a site-co-investigator and supervising liaison for the external PI);
- Conducted utilizing the private records of SJH/SPHP and SJH/SPHP patients (EPIC);
- Conducted in any SJH/SPHP owned, operated, or controlled domestic facility or program and / or by any SJH/SPHP Physician member acting as an employee or agent of SJH/SPHP.

The IRB Chair, or designee, with the assistance of the HRPP Administrator and legal counsel as needed, are authorized to determine whether SJH/SPHP is engaged in a particular research study. Investigators and other institutions **may not** independently determine whether SJH/SPHP is engaged in a particular research study.

When SJH/SPHP is engaged in research, the Institutional Official (IO) may choose to enter into an agreement to cede review to an external IRB (see section 6).

For additional information on engagement please refer to OHRP's Guidance on Engagement on Institutions in Human Subjects Research.

1.9. Written Procedures

These Standard Operating Procedures (SOPs) for Human Research Protection detail the procedures, standards, and requirements for research with human subjects under the auspices of SJH/SPHP and the requirements of the SJH/SPHP IRB. This is not a static document. The SOPs are reviewed at a minimum of every 2 years and revised, as needed, by the HRPP Administrator. The HRPP Administrator, in consultation with the Research Integrity Compliance Oversight (RICO) Committee will revise the SOPs.

The HRPP Administrator will keep the research community apprised of new information that may affect the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues on its website, through email, and other forums. These SOPs will be available on the SJH/SPHP IRB website and within the IRB's electronic system. Changes to the SOPs will be communicated through the HRPP Administrator to investigators and research staff, and IRB members by way of e-mail announcements, and announcements during convened meetings of the IRB and Clinical Coordinators.

1.10. SJH/SPHP HRPP Structure

The HRPP consists of individuals, departments, and committees with responsibilities for human research protections such as the Institutional Official, the HRPP Administrator, the IRB, the Radiation Safety Committee (RSC), Pharmacy, Legal Counsel, Privacy Officer, Finance, investigators, research staff, and others. The objective of this system is to assist SJH/SPHP in meeting ethical principles and regulatory requirements for the protection of human subjects in research.

The following officials, administrative units and individuals have primary responsibilities for human

subject protections:

1.10.1. Institutional Official

The ultimate responsibility of the HRPP resides with the **Institutional Official (IO)** of the program. The IO is legally authorized to represent SJH/SPHP. The IO is the signatory of the FWA and assumes the obligations of the FWA. At SJH/SPHP, the Chief Medical and Clinical Officer is the IO. The IO is responsible for ensuring that the SJH/SPHP HRPP and IRB have the resources and support necessary to fulfill their responsibilities and to comply with the regulations and requirements that govern human subject research. Such resources include, but are not limited to:

- Staffing commensurate with the size and complexity of the research program;
- Appropriate office space, meeting space, equipment, materials, and technology;
- Resources for the production, maintenance, and secure storage of HRPP and IRB records;
- Resources for auditing and other compliance activities and investigation of noncompliance;
- Access to legal counsel; and
- Ensuring that the IRB, investigators, and staff receive training related to human research protections.

The IO is also responsible for:

- Fostering, supporting and maintaining a culture that supports the ethical conduct of research involving human subjects and compliance with applicable regulatory and other requirements;
- Ensuring that the IRB functions independently by, among other mechanisms, being directly accessible to the IRB Chair and members if they experience undue influence or if they have concerns about the function of the IRB;
- Oversight of the IRB;
- Oversight over the conduct of human subjects research under the auspices of SJH/SPHP;
- Ensuring training and educational opportunities for IRB members and staff to support their ability to review research in accordance with ethical standards and applicable regulations;
- Ensuring training and educational opportunities for investigators and research staff to support their ability to conduct research in accordance with ethical standards and applicable regulations; and
- Taking action as necessary to ensure the protection of human subjects and compliance with regulatory and other requirements.

The IO is made known to employees of the organization and is accessible by phone, email, in person or other methods of communication. The HRPP Administrator and IRB Chair have access to the IO for any concerns or issues related to the HRPP or IRB.

In the performance of these duties, the IO has the authority to delegate such activities as may be necessary in order to effectively administer the program. However, the IO is ultimately responsible and is expected to be knowledgeable about human subject protections and research at the organization.

1.10.2. HRPP Administrator

The HRPP Administrator serves as the HRPP Administrator and reports to the IO and is responsible for:

- Developing, managing and evaluating policies and procedures that ensure compliance with state and federal regulations and SJH/SPHP policies. This includes monitoring changes in regulations and policies that relate to human research protection and overseeing the administration of the IRB;
- Advising the IO on key matters regarding human subjects research;
- Implementing the organization's HRPP SOPs;
- Overseeing the administration of the HRPP and IRB;
- Overseeing the administration of IRB Reliance Agreements and Independent Investigator Agreements;
- Submitting, implementing and maintaining an approved FWA through the IO and the OHRP;
- Assisting the IRB in its efforts to review research and ensure the protection of human subjects;
- Assisting investigators in their efforts to carry out the organization's research mission;
- Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program;
- Developing training requirements as required and as appropriate for IRB members, investigators, and staff, and ensuring that training is completed on a timely basis;
- Serving as the primary contact at SJH/SPHP for the OHRP, the FDA, and other regulatory agencies on matters of human research protections; and
- Serving as an internal expert resource for questions and other matters regarding the protection of human subjects.

1.10.3. HRPP Staff

The staffing for the HRPP and IRB includes the HRPP Administrator. The HRPP Administrator for SJH/SPHP complies with all ethical standards and practices.

1.10.4. Institutional Review Board (IRB)

SJH/SPHP has one internal IRB, appointed by the IO. The IRB prospectively reviews and makes decisions concerning all non-exempt human subjects research under the auspices SJH/SPHP unless it has been determined that SJH/SPHP is not engaged in the research or SJH/SPHP has entered into agreement with an external IRB to serve as the IRB of record. The IRB is responsible for the protection of the rights and welfare of human research subjects, through review and oversight of safe and ethical research. It discharges this duty by complying with the requirements of federal and state regulations, the FWA, and organizational policies.

The IRB functions independently of, but in coordination with, other organizational committees and officials. The IRB, however, makes independent determinations whether to approve, require modification in, or disapprove research based upon whether human subjects are adequately protected.

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of the organization. However, those officials may not approve human research that has not been approved or has been disapproved by the IRB.

1.10.5. SJH/SPHP Counsel

The SJH/SPHP HRPP relies on the SJH/SPHP Legal Counsel for the interpretations of New York State law and the laws of other jurisdictions where research is conducted as they apply to human subjects research.

Counsel is available to provide guidance on other relevant topics as needed.

1.10.6. Principal Investigators (PI)

The PI is ultimately responsible for the protection of the human subjects participating in research they conduct or oversee. The PI is expected to abide by the highest ethical standards when developing a research plan and to incorporate the principles of the Belmont Report. The PI is expected to conduct research in accordance with the IRB approved research plan and to personally conduct or oversee all aspects of the research. In addition to complying with all applicable regulatory policies and standards, PIs must comply with organizational and administrative requirements for conducting research. The PI is responsible for ensuring that all investigators and research staff complete all organization required trainings as well as training for their specific responsibilities in any given research study. When investigational drugs or devices are used, the PI is responsible for ensuring an appropriate plan for their storage, security, dispensing, accounting, and disposal.

The IRB reviews investigator expertise when reviewing research and may determine that an investigator may not serve as PI or may require the addition of other investigators to supplement the expertise available on the research team or to conduct or oversee certain aspects of the research.

If the PI will have an extended absence (e.g., sabbatical) a replacement PI is required.

The PI or secondary (Co-investigator) must be affiliated with SJH/SPHP.

For SJH/SPHP -College of Nursing (CON) student projects, Medical Education resident projects, and Doctor of Pharmacy resident projects, an SJH/SPHP faculty/preceptor (resident director for pharmacy, or designee) must be listed as the secondary (Co-) investigator / advisor. An unaffiliated person may not be listed as the secondary investigator/advisor. For unaffiliated corporate or student projects conducted on SJH/SPHP -properties, an SJH/SPHP-affiliate must be listed as a secondary investigator/ advisor. If the SJH/SPHP-colleague is unfamiliar with the SJH/SPHP-research and IRB processes, an SJH/SPHP employee-colleague, research liaison must be listed as advisor.

Individuals who are debarred, disqualified, or otherwise restricted from participation in research or as a recipient of grant funds for research by a federal, state, or other agency **may not** serve as PI.

Individuals with a history of compliance issues related to the conduct of research (e.g., recipients of an FDA Warning Letter) will be considered on a case-by-case basis. Factors to consider include whether corrective actions have been accepted as adequate, whether information from an audit or quality review indicates that the issues have been resolved, and similar considerations.

1.10.7. Other Related Units

1.10.7.1. Pharmacy

A representative from SJH/SPHP Pharmacy serves on the IRB, providing expertise on pharmacologic matters and operational concerns related to study drug handling. Additionally, the Pharmacy representative is provided access to study materials in advance of the IRB meeting, allowing the Pharmacy to have complete information about all IRB approved research that takes place at SJH/SPHP under its jurisdiction.

The SJH/SPHP Pharmacy is responsible for storing, accounting for, dispensing, and compounding of most investigational drugs used in research, whether conducted in outpatient or inpatient settings. Waivers from use of the SJH/SPHP pharmacy for handling investigational/study drugs will be considered on a case by case basis by both the IRB and the SJH/SPHP pharmacy, with required information regarding storage, accounting, dispensing etc.

1.10.7.2. Radiation Safety Committee

Review by the Radiation Safety Committee (RSC) - is required for studies in which research participants may be exposed to extra ionizing radiation for research purposes (e.g., extra x-rays or CT scans).

RSC review is not generally required when the use of ionizing radiation involves routine therapeutic or diagnostic procedures and exposure levels on people for whom these procedures would be considered part of their standard of care for an existing or suspected medical condition. Additional scans or exposures for research, however, require review. MRI or ultrasound procedures do not require Radiation Safety Review.

This process provides the IRB with expert opinions of the appropriateness, safety, dosimetry and relative risks concerning the use of ionizing radiation in research protocols involving human subjects.

1.10.7.3. Clinical Information Systems

Access to SJH/SPHP Clinical information systems may be provided to SJH/SPHP staff and/or affiliates per Policy Scope of Care & Services Health Information Management. Health Information Management is responsible for the approval of all clinical information systems access in accordance with the policy.

1.10.8. Study-Specific Coordination

In addition to IRB approval, PIs must obtain the approval, support, or permission of other individuals and departments or entities impacted by the research as well as approval by other oversight committees, including, but not limited to:

- Pharmacy
- Pathology/laboratory
- Radiology
- Hospital Billing
- Hospital Research Committee (Financial review)
- Nursing
- Radiation Safety Committee
- Facilities where research activities will occur
- Records access permissions (e.g., EPIC)

- Research Conflict of Interest (COI)
- Others, as deemed necessary

When applicable, a letter of support, collaboration, permission, or approval from the designated authority, should be included in the Initial Study Submission to the IRB. The IRB may request review by or consultation with any of the above listed or other organizational committees or components even when such review or consultation is not required by policy.

If the research sites, or research personnel, are also under the jurisdiction of another IRB, documentation of the external IRB's approval or agreement to cede or waive review may be required.

Other committees and officials may not approve research involving human subjects to commence that has not been approved or has been disapproved by the IRB.

2. Quality Assurance

SJH/SPHP performs Quality Assessment and Improvement activities for the purposes of monitoring the safety of ongoing studies and improving human research protection effectiveness, quality, and compliance with organizational policies and procedures, ethical and regulatory requirements, and applicable federal, state, and local laws.

2.1. External Monitoring, Audit, and Inspection Reports

The HRPP Administrator should be notified in advance, whenever possible, of upcoming audits or inspections of research whether the study is reviewed by an external agency or an external IRB on behalf of SJH/SPHP. IRB representatives may participate in entrance and exit interviews and otherwise observe or support the audit or inspection. Likewise, SJH/SPHP representatives may assist in the development of any responses to audits or inspections.

When research is under the oversight of the SJH/SPHP IRB, all reports from external monitors, auditors, or inspectors must be submitted to the IRB for review. The IRB Chair or designee will review such reports to monitor for issues that could impact the rights or welfare of human subjects and for issues indicative of possible serious or continuing noncompliance. If such issues are identified, the report will be forwarded to the convened IRB to determine what additional actions are necessary, if any.

When SJH/SPHP is engaged in research reviewed by an external IRB, all reports from audits or inspections must be submitted to the HRPP Administrator for review. The HRPP Administrator may require submission to the external IRB, corrective and preventative actions (CAPA), a follow up review, or other actions as needed to ensure the protection of human subjects and to support compliance.

2.2. Internal Compliance Reviews

Compliance reviews are conducted to assess investigator compliance with federal, state, and local law, SJH/SPHP policies, and the IRB approved study plan, and to identify areas for improvement and to provide recommendations based on existing policies and procedures. The Quality Assessment & Improvement Program (QAIP) conducts three types of reviews. They include:

Not-For-Cause Reviews: These are scheduled reviews that are part of the annual routine quality monitoring process and are employed to ensure federal regulations and SJH/SPHP-IRB policies and

procedures are being met. Two approved studies are randomly selected (one exempt study and one expedited or full board review study).

For-Cause Reviews: These are directed reviews that are performed when concerns regarding research compliance, protocol adherence, or subject safety are brought to the attention of the IRB. Reviews may be focused on a specific researcher, protocol, or type of research.

Study Start-Up Review/Study Initiation Visit: These are scheduled reviews for new studies that have received IRB approval, but have not started enrollment activities. A study initiation visit may be requested by the study team or required by the IRB, as a condition of approval. Study Start-Up Review/Study Initiation Visits may include:

- Assistance with set-up/organization of study records and required documents;
- Instruction concerning IRB reporting requirements for:
    - Unanticipated Problems & Other Incidents
    - Amendments
    - Continuing review
    - Data safety and monitoring reports/audits or inspection reports
    - Protocol deviations
    - Education about the informed consent process and documentation; confidentiality and HIPAA issues.

The IRB may appoint a subcommittee for the purpose of conducting a for-cause or not for-cause compliance review of one or more research plans under its jurisdiction. The subcommittee may be composed of IRB members and staff from within, or individuals from outside of the organization. The results of compliance reviews will be reported to the HRPP Administrator, the SJH/SPHP IRB, the IRB of record (if not the SJH/SPHP IRB), the principal investigator, and other SJH/SPHP leadership, as appropriate. Any IRB reporting and evaluation of noncompliance will be handled according to the procedures of the IRB of record.

If it is identified that subjects in a research project may have been exposed to unexpected serious harm or risk of harm, the reviewer will promptly report such findings to the HRPP Administrator and the IRB of record.

If issues are identified that indicate possible misconduct in research, compliance reviews may include:

- Requesting progress reports from investigators
- Examining investigator-held research records and records held by pharmacy or other ancillary services, if applicable
- Reviewing source documentation
- Reviewing the recruitment process and materials
- Reviewing consent materials and the documentation of consent and HIPAA authorization
- Observing the consent process and other research activities
- Interviewing investigators and research staff
- Interviewing research subjects
- Reviewing projects to verify from sources other than the investigator that no unapproved changes have occurred since previous review

- Conducting other monitoring or auditing activities as deemed appropriate by the HRPP or IRB.

2.3. IRB Compliance Reviews and Assessment

The QAIP will periodically review the activities of the IRB to assess compliance with regulatory requirements and to identify areas for improvement; this will include a review of IRB records at least annually.

Review activities may include:

- Review of the IRB minutes to evaluate whether adequate documentation of the meeting discussion and any required determinations has occurred, and that quorum was met and maintained and to evaluate whether adequate documentation of exemptions, expedited review, and other committee reviews has occurred
- Reviewing consent forms to evaluate whether all required elements are included
- Other review activities as appropriate

If substantive deficiencies are identified in the review, a corrective action plan will be developed by the HRPP Administrator and approved by the IRB Chair and IO. The HRPP Administrator will have responsibility for implementing and reporting progress on the corrective action plan, the results of which will be evaluated by the IO.

Additionally, the SJH/SPHP-IRB members will periodically evaluate the IRB's functioning and effectiveness, as well as their own performance, in the form of a self-assessment. Results of the self-assessment will be collated and reviewed at an IRB meeting by the chairperson to foster continuous improvement. The IO will review the self-assessment results prior to implementing any program changes.

2.4. HRPP Quality Improvement

The QAIP provides assistance and ongoing education to the institution and investigators and their staff with regard to human subject research and compliance issues.

During the review of compliance reports, the HRPP Administrator, the SJH/SPHP IRB, and the IO will determine whether improvement activities at an institutional level are required, such as additional education, clarification of policies and procedures, etc. The QAIP Coordinator is available to provide the necessary institutional training.

The QAIP Coordinator is also available to provide investigators and/or study team members with on-site education pertaining to the conduct of human subject research. An On-Site Education Visit is an informal education meeting that can be tailored to individual or departmental needs. *Topics typically covered include:*

- Study set-up and documentation
- Informed consent process
- Proper documentation of informed consent
- Compliance with HIPAA regulations as they pertain to clinical research
- IRB forms and correspondence
- Reporting requirements

The IRB website under the QAIP Section includes useful information to support study quality and compliance such as a list of reference materials, an Investigator Self-Assessment checklist, Informed consent compliance checklist, compliance tips and sample subject enrollment log, eligibility checklist, signature and delegation of responsibility log.

3. Education & Training

3.1. Training / Ongoing Education of IRB Chair, Members, and Staff

Recognizing that a vital component of a comprehensive HRPP is an education program, SJH/SPHP is committed to providing training and on-going education for IRB members and the staff of the HRPP and IRB, related to ethical concerns and regulatory and organizational requirements for the protection of human subjects.

Orientation: New IRB members, including alternate members, will meet with the HRPP Administrator for an orientation session. At the session, IRB processes, regulations, and resources will be reviewed, and the location of the following documents will be provided.

- Belmont Report
- SJH/SPHP Policies and Procedures for the Protection of Human Subjects
- Federal regulations relevant to the IRB
- Tools used by IRB reviewers (checklists etc.)
- IRB Meeting Schedule
- Contact Information for HRPP Administrator and IRB Office

New members will also be offered an in-person training for the IRB Electronic System (IRBManager).

Initial Education: IRB members and HRPP Administrator must complete the required modules in the Collaborative Institutional Training Initiative (CITI) Program Courses in the Protection of Human Research Subjects (HSR), Responsible Conduct of Research (RCR), Conflict of Interest (COI), and Good Clinical Practice (GCP) and other training determined to be equivalent by the HRPP Administrator.

New members are required to complete orientation and the Initial Education requirement before they may serve as Primary Reviewer.

Continuing Education: To ensure that oversight of human research is ethically grounded, and the decisions made by the IRB are consistent with current regulatory and policy requirements, training is continuous for IRB members throughout their service on the IRB.

In addition to CITI training, SJH/SPHP also uses the following activities as a means for offering continuing education to IRB members and HRPP and HRPP Administrator:

- Educational sessions at IRB meetings
- Email or printed distribution of articles, announcements, presentations, and other materials relevant to human subject protections

IRB members and HRPP Administrator are also required to complete CITI training. Training is considered current for a period of 4 years for HSR, RCR, and COI, and 3 years for GCP per the FDA. After those time periods, IRB members must maintain CITI training. There is no exception to this

requirement.

IRB members with previous training may provide documentation of that training to the HRPP Administrator to determine if it is equivalent.

The activities for continuing education vary on a yearly basis depending on areas of need, as determined by the HRPP Administrator. Whenever possible, the HRPP provides support for staff and IRB members to attend relevant conferences.

Continuing failure to complete training may result in a member's service being discontinued.

3.2. Training / Ongoing Education of Investigators and Research Team

As stated previously, a vital component of a comprehensive HRPP is an education program for all individuals with human subject responsibilities. SJH/SPHP is committed to providing training and on-going education for investigators and research staff members on human subject protections and other relevant topics. Education may be requested by investigators and/or research teams or required by the IRB.

3.2.1. Initial Education

Investigators and research staff who interact or intervene with subjects, or who use identifiable information of subjects for the purposes of research, must complete the CITI Courses relevant to the type of research being conducted and the investigator or staff members' responsibilities.

Current training for each member of the research study team is verified by the HRPP Administrator for all submissions to the IRB (including: new studies, exemption submissions, amendments, continuing reviews, etc.). Submissions will not receive final IRB approval, acknowledgement or exemption determination until CITI is completed.

At the discretion of the HRPP Administrator, the SJH/SPHP-*IRB will consider the acceptance of external program training (other than CITI) from other institutions when research personnel include external investigators or subcontract recipients who have been trained elsewhere and are under the legal jurisdiction of that institution with respect to compliance with Federal regulations. A copy of any external site program training with an active coverage date must be provided with the IRB application.*

3.2.2. Continuing Education

SJH/SPHP Provides researchers and staff training through the CITI program (www.citiprogram.org). Training is considered current for a period of 4 years for HSR, RCR, and COI, and 3 years for GCP per the FDA. There is no exception to this requirement.

Training will be verified at the time of continuing review or other submission. If training has not been completed, expiring, or lapsed and is not completed in a timely manner, the investigator or staff member may be removed from the study or otherwise restricted from participating in the research.

In addition to the basic requirements described above, SJH/SPHP will periodically provide training on topics relevant to human subject protections, regulations, policies and standards, and IRB

submission processes and requirements. Training may be provided during workshops, webinars, e-Learning, or through the distribution of articles, presentations, and other materials. Investigators, departments, colleges, and staff may request training or offer training suggestions by contacting the HRPP Administrator

3.2.3. Documentation of CITI Education

The SJH/SPHP-IRB accepts CITI training certificates or completion reports (with the module scores) as proof of completion. CITI Completion Reports may be uploaded into *IRBManager* for every investigator and key personnel. The SJH/SPHP HRPP Administrator also has CITI administrative rights to view CITI training for any training completed and affiliated with Trinity Health New York.

4. "Human Subjects" and "Research" Determinations

The responsibility for initial determination whether an activity constitutes "research" rests with the individual with primary responsibility for the activity. This individual should make this determination based on the definitions of "research" and "clinical investigation" as provided by the Common Rule and FDA regulations, respectively. Consultation with the HRPP Administrator is encouraged.

Under the Common Rule, information is considered identifiable, and thus involving human subjects, when the identity of the subject is or may readily be ascertained by the investigator or associated with the information. It should be noted that this definition differs significantly from de-identified in accordance with HIPAA standards. **FDA regulations do not incorporate the concept of "identifiability" in the evaluation of whether an activity is a clinical investigation (or research) subject to FDA regulations. For example, the use of de-identified human specimens to evaluate the safety or effectiveness of a diagnostic device is considered human subjects research subject to FDA regulations.**

Investigators **may not** self-determine that research involving the use of **coded** private information or specimens does not involve "human subjects". Such determinations may only be made by the IRB. The only exception to this policy is when the research is not subject to FDA regulations and the coded private information or specimens are to be obtained from an SJH/SPHP IRB-approved registry and the rules of that registry forbid the release of**: a.** identifiable information, **b**. the key or code that would enable re-identification, or **c.** the release of sufficient information that investigators could readily ascertain the identity of subjects.

Human Subjects Research Determinations must be submitted, and determined, prospectively (i.e., before the proposed activity or research begins). Conducting human subjects research without IRB approval or exemption is noncompliance and will be managed as described in Section 17.

Determinations whether an activity constitutes human subject research will be made by the HRPP Administrator or IRB Chair or designee according to the definitions in Section 1.3, applicable federal regulations, and federal guidance. A submission requesting determination should be created in IRBManager and then after IRB review a determination letter will be posted in the IRB Electronic System (IRBManager), by the HRPP Administrator to document the determination. Investigators conducting research under the auspices of SJH/SPHP **may not** rely upon determinations made by other organizations or through the use of electronic (or other) determination tools.

5. Exempt Determinations

Although certain categories of human subject research are exempt from regulatory requirements, at SJH/SPHP the determination of exempt status must be made by the IRB Chair, IRB Vice Chair or HRPP Administrator. The SJH/SPHP-IRB may also choose to accept an exempt determination made by an external IRB. Such requests will be considered on a case by case basis.

Exempt studies with waivers or alterations of HIPAA: The SJH/SPHP IRB is responsible for reviewing waivers or alterations of HIPAA authorization; this review must be made by the IRB using expedited or convened review even when the research is otherwise exempt.

If the exempt research requires limited IRB review (as noted in the categories listed below), the IRB Chair or HRPP Administrator may conduct the review using expedited review procedures to determine that there are adequate protections to protect the privacy of subjects and to maintain the confidentiality of the data.

As with all other research subject to IRB review requirements, when conducting limited IRB review the IRB has the authority to approve, require modifications in (to secure approval), or disapprove all research activities; and to suspend or terminate IRB approval. Actions of disapproval may only be made by the convened IRB. [45 CFR 46.109(a), 45 CFR 46.110]

Proposed modifications to the aspects of research subject to limited IRB review must be submitted to and approved by the IRB prior to implementation, except when necessary to eliminate apparent immediate hazards to the subject(s), in which case the change must be promptly reported to the IRB (i.e. within 10 business days). [45 CFR 46.108(a)(3)(iii)]

Continuing review is generally not required for research determined to be exempt, even when that research is subject to limited IRB review. However, the IRB may determine that continuing review is required for a particular study subject to limited IRB review, in which case it shall document the reasons for its determination in the IRB record and communicate the requirement to the investigator in the IRB determination letter. [45 CFR 46.109(f)(ii), 45 CFR 46.115(a)(3)]

Individuals involved in making the determination of an IRB exempt status of a proposed research project cannot be involved in the proposed research. Reviewers must not have any apparent COI.

Unless otherwise required by law or by Federal department or agency heads, exempt studies are exempt from the requirements of the Common Rule (i.e., IRB approval and full research consent are not required) other than as specified within the regulations (e.g., the conditions that permit exemption, and when limited IRB review is required). Exempt research is not exempt from ethical considerations, such as honoring the principles described in the Belmont Report. The individual/s making the determination of exemption will determine whether to require additional protections for subjects in keeping with ethical principles (e.g., requiring disclosure/consent, etc.).

5.1. Limitations on Exemptions

Children: Most of the exemptions apply for research involving children with some exceptions, as noted below.

Prisoners: Exemptions do not apply except for research aimed at involving a broader subject population that only incidentally includes prisoners. [45 CFR 46.104(b)(2)].

5.2. Categories of Exempt Research

With the above-referenced limitations and any other limitations or restrictions due to applicable law, regulation, or agency policy, **research activities not regulated by the FDA** (see Section 5.3 for FDA Exemptions) in which the only involvement of human subjects are determined to be in one or more of the following categories may be determined exempt:

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

2. Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met: ***(Applies to research involving children with only: 1. the use of educational tests and 2. observation of public behavior when the investigator(s) do not participate in the activities being observed and conditions i or ii are met).***
   - **i.** The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
   - **ii.** Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
   - **iii.** The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by .111(a)(7): *When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.* ***This option is NOT applicable to research involving children.***

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

   A. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

B. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
C. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by .111(a)(7): *When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data*.

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

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

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

i. The identifiable private information or identifiable biospecimens are publicly available;

ii. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re- identify subjects;

iii. The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or

iv. The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for non-research activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable

private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44
U.S.C. 3501 et seq.

5. Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.

   i. Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal website or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

6. Taste and food quality evaluation and consumer acceptance studies:

   i. If wholesome foods without additives are consumed, or

   ii. If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or
   agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Regulations include additional categories for exempt research which SJH/SPHP has determined not to use due to additional regulatory requirements.

5.3. FDA Exemptions

The following categories of clinical investigations are exempt from the requirements for prior IRB review and approval:

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article is subject to IRB review. [21 CFR

56.104(c)]

See Section 15.9.3 for detailed discussion of this exemption.

2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or 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 FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [21 CFR 56.104(d)]

5.4. Procedures for Exemption Determination

To request an exempt determination, investigators should fill out and submit a Claim of Exemption Form and submit the following materials via IRBManager:

1. Complete the **Claim of Exemption Form**
    a. Include a brief description of the project, the applicable category of research (section 5.2) which may be exempt from IRB Review and how the project meets the requirements of the designated category.
    b. List all individuals assisting the PI on the project in the Co-Investigators and Other Personnel section.
2. Submit supporting materials, as applicable, such as:
    - Data collection tool or form, if data is to be collected (in any format-which includes a complete list of the specific information you will record-for example, from the medical record or that will be associated with the specimens- i.e., age, dx, etc.)
    - Mechanism to comply with HIPAA (De-identification , Limited Data set, waiver of HIPAA authorization)
    - Subject materials, such as recruitment materials, information sheets, consents, scripts, questionnaires, diaries, or surveys
    - If the research requires limited IRB review (as noted in the categories listed above), a plan to protect the privacy of subjects and to maintain confidentiality of data in the proposed research must be included. Share the project with all study team members and ensure that each person has reviewed and signed the COI statement in the package.
3. Submit the package to the IRB.

If the request does not appear to meet the definition of human subject research, or if information is missing, the investigator will be asked to revise and re-submit the request as described in Section 4. The HRPP Administrator, IRB Chair/Vice Chair reviews all requests for exemptions and determines whether the request meets the criteria for exempt research. The HRPP Administrator, IRB Chair/Vice Chair will determine whether to require additional protections for subjects in keeping with the guidelines of the Belmont Report.

An exemption letter will be posted in the IRB Manager by the HRPP Administrator to document the exempt determination. The exempt materials, review documentation, and determination letter are maintained in the same manner and for the same length of time as other IRB review documentation.

Exempt determinations will include a termination date, with the maximum time allotted being 3 years. If the investigator wants the research to extend beyond the termination date, the investigator must request another exemption determination. This process will allow the investigator and the organization the opportunity to review and update the research activity and determine whether it still qualifies for exemption.

Investigators must report any proposed additions to study personnel so that CITI training can be verified and COI evaluated prior to their involvement with the research. Proposed modifications to the research itself must be submitted for a determination of whether the research still qualifies for exemption. Finally, investigators should submit a letter of closure when an exempt research project is complete so that the organization can maintain an accurate database of research activities.

6. IRB Reliance

When engaged in multi-site research, research involving external collaborators, or research that is otherwise under the jurisdiction of more than one IRB, SJH/SPHP acknowledges that each organization is responsible for safeguarding the rights and welfare of human subjects and for complying with applicable federal regulations. SJH/SPHP may choose to review the research in its entirety, only those components of the research SJH/SPHP is engaged in, rely on the review of another qualified IRB, or make other arrangements for avoiding duplication of effort. When SJH/SPHP is the prime awardee on an HHS grant, it will ensure that at least one IRB reviews the research in its entirety.

When relying upon another IRB, a formal relationship must be established between SJH/SPHP and the outside organization through a Reliance Agreement, IRB Authorization Agreement, a Memorandum of Understanding, or other such written agreement. The written agreement must be executed before SJH/SPHP will rely on the review of an external IRB.

IRB reliance agreements establish the authorities, roles, and responsibilities of the reviewing IRB and the relying organization. The procedures for reliance, including for communication, information-sharing, and reports, may be outlined in the reliance agreement, in SOPs, or other written materials.

Requests for SJH/SPHP to rely upon an external IRB should be submitted as early as possible in the grant/contract process by submitting a reliance request to the HRPP Administrator.

St. Joseph's Hospital and St. Peter's Health Partners will not serve as the IRB of Record for clinical trials.

6.1. External IRB Review of SJH/SPHP Research

All non-exempt human subject research (or exempt research for which limited IRB review takes place pursuant to § .104(d)(2)(iii), (d)(3)(i)(C), that SJH/SPHP is engaged in must be reviewed and approved by the SJH/SPHP IRB or an external IRB that SJH/SPHP has agreed to rely upon prior to the initiation of the research. See Section 1.8 for information regarding engagement.

Research that requires External IRB Review must be submitted to the SJH/SPHP IRB prior to

submission to the external IRB following the procedures outlined in Section 6.1.1. Post-approval requirements are summarized in Section 6.1.2.

The HRPP Administrator in consultation with the IO and/or IRB Chair evaluates the following factors, and others as appropriate, when considering a request to rely upon an external IRB:

1. The FWA and IRB Registration status of the organization;
2. The research activities that will be conducted at or by SJH/SPHP;
3. The proposed reliance terms and procedures including the procedures for the management of matters such as conflicts of interest (COI), noncompliance, unanticipated problems, and federal reports;
4. The plan for review and allowance of the incorporation of site-specific consent language; and
5. The plan for incorporation of other relevant local requirements or context information in the review process.

The external IRBs that serve as the IRB of record for SJH/SPHP research have the same authority as the SJH/SPHP IRB and all determinations and requirements of the external IRBs are equally binding.

Investigators must be familiar with and comply with the policies and procedures of the external IRB and any additional requirements or procedures outlined in the IRB reliance agreement or companion materials (e.g., reliance SOPs). SJH/SPHP will support compliance with the terms of reliance agreements by providing investigators with information relevant to their responsibilities, such as a copy or summary of the agreement, an information sheet, or reliance SOPs.

Regardless of which IRB is designated to review a research project, SJH/SPHP is responsible for the conduct of the research in which it engages. Research reviewed by external IRBs remains subject to review, approval, and oversight by SJH/SPHP and appropriate SJH/SPHP leadership and must adhere to all applicable policies, procedures, and requirements, including those of the SJH/SPHP HRPP. An expedited review procedure may be used for studies that have been reviewed by an external IRB.

6.1.1. Submission of Studies to be Reviewed by External IRBs

Investigators must submit studies (via IRBManager) to the SJH/SPHP IRB office that will be reviewed by an external IRB by submitting basic information about the research. The HRPP Administrator will review the information and verify that CITI training, COI review, and any other applicable approvals or requirements have been completed and determine the need for relaying local context information to the reviewing IRB in accordance with the reliance agreement.

The HRPP Administrator will notify the investigators once the proposed research has been approved for submission to the external IRB (via *Utilization of an External IRB)* by a letter posted in IRBManager. Once approved by the external IRB, investigators must e-mail a copy of the approval notice to the HRPP/IRB office unless the HRPP Administrator is copied on the approval notice. If the consent/assent form(s) or protocol were modified during the external IRB review process, the approved version of the protocol and/or consent/assent form(s) should be submitted via IRBManager to the SJH/SPHP IRB.

6.1.2. Post-Approval Requirements

Investigators approved through external IRB review must still report local unanticipated problems, unresolved subject complaints, and any serious or continuing noncompliance to the SJH/SPHP IRB office via IRBManager, in addition to reporting to the external IRB. Copies of the report submitted to the external IRB are generally acceptable, but additional information may be requested on an as-needed basis.

Amendments will be reviewed by the external IRB. For external IRBs, Investigators must also submit copies of updated protocols, IBs, updated consent forms, changes in study status, and the corresponding external IRB approval or action letter to the IRB office (via IRBManager), so that the SJH/SPHP IRB has current study information. Minor changes that do not revise the protocol or IB and do not increase the level of risk or change the research design or methods, do not need to be submitted to the SJH/SPHP IRB. An acknowledgment letter will be posted in IRBManager.

Changes in PI and the addition of other research team members must be submitted to the HRPP/IRB office via IRBManager prior to the new PI or research team member assuming any study responsibilities. The HRPP Administrator must verify CITI training, COI review, and any other applicable requirements. Once the review is completed, an acknowledgment letter will be posted and submission to the external IRB (as appropriate) may be completed.

Continuing review will be conducted by the External IRB. Once a study has been approved by the External IRB for continuation, submit the following items to the HRPP/IRB office via IRBManager:

- External IRB approval letter
- SJH/SPHP Progress Report for studies using an External via the Annual Status Report Form.
- The PI is required to sign the submission
- An acknowledgement letter will be posted in IRBManager.

Study Termination: will be reviewed by the External IRB. Once a study has been terminated by the External IRB submit the following items to the HRPP/IRB office via IRBManager:

- External IRB approval/acknowledgement of closure letter
- SJH/SPHP Closure X-Form
- An acknowledgement letter will be posted on IRBManager

Notices about and reports from external monitors, auditors, or inspectors must be provided to the HRPP/IRB Office as described in Section 2.1 of this manual.

6.2. NIH Single IRB (sIRB) for Multi-Site Research

In June 2016, the National Institutes of Health (NIH) released a final policy requiring domestic awardees and domestic sites of NIH-funded multi-site research to use a single IRB (sIRB) for review of non-exempt human subject research unless there is justification for an exception. This policy is intended to streamline the IRB review process and reduce inefficiencies and redundancies while maintaining and enhancing subject protections. The policy **does not** apply to career development, research training, or fellowship awards, nor to sites that are not conducting the same protocol as the other sites (e.g., sites providing statistical support or laboratory analysis only) or to foreign sites.

Exceptions to the policy are automatic when local IRB review is required by federal, tribal, or state

law/regulation/policy and when the proposed research is the "child" of a grant that predates the requirement for sIRB review. Such exceptions and the basis (and information regarding the "parent" study, when applicable) should be cited in the proposed sIRB plan and, when the exception is based on law/regulation/policy, apply only to the site(s) to which the law/regulation/policy applies. Other exceptions will be considered when there is compelling justification. The site(s) and justification for why the site(s) cannot rely on the single IRB of record should be included in the proposed sIRB plan. The NIH will consider the exception request and inform the applicant of the outcome.

6.2.1. Selection and Designation of a sIRB

SJH/SPHP investigators submitting applications for NIH-funded multi-site research must describe the sIRB plan in the funding proposal (grant application or contract proposal). Requests for an alternative IRB option when SJH/SPHP would be the prime awardee should be directed to the HRPP Administrator. The HRPP Administrator will consult with others within the organization as needed and make a recommendation to the IO for consideration. When SJH/SPHP will not be the prime awardee, investigators should, as early in the process as possible, submit a request for SJH/SPHP to rely upon an external IRB as the sIRB by submitting a reliance request to the HRPP Administrator.

6.2.2. Reliance Agreements for sIRB Studies

A Reliance Agreement (or "Authorization Agreement") between the sIRB and the participating sites is required. The Reliance Agreement documents the respective authorities, roles, responsibilities, and communication between an organization providing the ethical review and a participating organization relying on a reviewing IRB.

Reliance Agreements should describe the responsibilities of all parties and how communication between parties will occur, for example, notifications of the outcome of regulatory review and management of federally-mandated reports such as reports of unanticipated problems, serious or continuing noncompliance, and suspensions or terminations of IRB approval. When IRB certification requirements apply (e.g., for NIH Genomic Data Sharing), the agreement or written procedures should indicate who is responsible for meeting the certification requirements.

The agreement or written procedures should also specify points of contact and contact information for the sIRB and relying institution(s).

The institution that is awarded the funding for the research is responsible for maintaining all agreements and for ensuring that adequate and appropriate communication channels between the sIRB and participating sites are in place. Participating sites are responsible for maintaining copies of the site agreement in accordance with the terms of their FWA.

6.2.3. Responsibilities

The sIRB will be responsible for compliance with the regulatory requirements for IRBs specified in the federal regulations (i.e., 45 CFR 46 and other applicable regulations) and for any other responsibilities outlined in the reliance agreement and/or procedures. Participating sites (Relying institutions) are responsible for providing relevant local context information to the sIRB, ensuring that the research is conducted in accordance with applicable regulations and the determinations and requirements of the

sIRB, and for other responsibilities, as outlined in the reliance agreement and/or procedures.

When an external IRB serves as the sIRB for a study SJH/SPHP is engaged in, investigators must submit the study to the SJH/SPHP IRB (via IRBManager) prior to submission to the external IRB following the procedures outlined in Section 6.1.1. Post-approval requirements are summarized in Section 6.1.2.

Research reviewed by external IRBs remains subject to review, approval, and oversight by SJH/SPHP IRB and appropriate SJH/SPHP leadership and must adhere to all applicable policies, procedures, and requirements, including those of the SJH/SPHP HRPP. An expedited review procedure may be used for studies that have been reviewed by an external IRB.

6.2.4. Trinity Health, System Level, Multi-site Research

Trinity Health maintains its own, sIRB of Record as designated by the Trinity Health System Home Office of Academic Affairs (*Trinity Health Policy: Clinical Effectiveness, Policy #1*). St. Joseph Mercy Ann Arbor's IRB has been designated to serve as a system-wide IRB of Record for authorized system level research. The IRB of Record reviews and monitors research projects that have been authorized by Trinity Health leadership and the Trinity Health Research Program. Information about the IRB of Record can be found by contacting aasjirbsubmissions@stjoeshealth.org.

System level research is defined as any investigation, study or research directly involving Trinity Health patients, associates or business operations, or using Trinity Health data that is (1) led or sponsored by a System Office colleague or (2) **involves at least three (3) System Ministries** (Trinity Health Ministry-sites). System Level Research may be requested, conducted, or led by Trinity Health colleagues, affiliated physicians including residents, consultants or contractors, or external researchers (including students).

7. Research Previously Approved by Another IRB

When an investigator transfers human subjects research to SJH/SPHP that was previously approved by another IRB, the investigator must:

- Submit the research for review by the internal IRB or determination of exemption; or
- Submit a request for SJH/SPHP IRB to rely upon the existing IRB of record (such requests must be approved by both organizations)

Research determined to be exempt at the previous institution will be reviewed according to the procedures in Section 5. All other research must be submitted as if it were undergoing initial review and will be reviewed under expedited review or by the convened IRB. Research activities under the auspices of SJH/SPHP cannot commence until all necessary approvals are in place including approval by the internal IRB or an IRB reliance agreement is executed (and the transferred activities are approved by the IRB of record).

For research transfers where stopping research interventions or procedures might harm subjects, the investigator can request permission from both organizations to continue the research under the oversight of the prior organization's IRB until final SJH/SPHP IRB approval is obtained.

8. SJH/SPHP Institutional Review Board

SJH/SPHP has established an Institutional Review Board (IRB) to ensure the protection of human

subjects in research conducted under its auspices.

8.1. IRB Authority

The IRB operations under the policy "Human Subjects Research and IRB Requirements". The authority of the IRB under the federal regulations is outlined in the IRB Charter.

The IRB functions independently. Attempts to coerce or otherwise unduly influence the actions of the IRB are forbidden and are to be reported as described in Section 8.6. Likewise, the IRB must remain free from the influence of financial and other organizational interests.

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of St. Joseph's Hospital and St. Peter's Health Partners, if hospital facilities and/or staff are to be utilized or other units. However, those officials may NOT approve research if it has not been approved or has been disapproved by the IRB. Reviewing officials may strengthen requirements and/or conditions, or add other modifications before approval, or may require approval by an additional committee, office, or person. Previously approved research proposals and/or consent forms must be re-approved by the IRB before initiating any changes or modifications that result from such additional organizational reviews.

8.2. Roles and Responsibilities

8.2.1. Chair of the IRB

The IO, in consultation with the HRPP Administrator, appoints a Chair and as needed, a Vice Chair of the IRB. Any change in appointment, including removal, requires written notification. The IRB Chair works closely with the IO and the IRB Chair term od service is at the discretion of the IO.

The IRB Chair will be served by a physician college of SJH/SPHP and should be a highly-respected individual, fully capable of managing the IRB and the matters brought before it with fairness and impartiality. The task of making the IRB a respected part of the research community falls primarily on the shoulders of the Chair. The IRB must be perceived to be fair, impartial, and immune to pressure by administration, the investigators whose research plans are brought before it, and other committees and departments.

The IRB Chair is responsible for conducting IRB meetings, reviewing protocols as needed, reviewing adverse events and serious problems, conducting expedited reviews, and changes in protocols. The IRB Chair may serve as signatory for correspondence generated by the IRB.

The IRB Chair is authorized to take immediate action to suspend a study or studies if subjects may be at risk of harm, when serious noncompliance may have occurred, or for any other reason where such action would be deemed appropriate. Such action requires subsequent notice to and review by the convened IRB.

The IRB Chair may designate other experienced IRB members to perform duties such as expedited reviews and other IRB functions.

8.2.2. Vice Chair of the IRB

The Vice Chair works closely with the IRB Chair and serves as the Chair of the IRB in his/her absence

with the same authority, and duties as the Chair. The IRB Vice Chair may also designate to conduct expedited reviews. This individual is appointed by the IO with recommendations from the Chairperson and HRPP Administrator. The length of appointment is at the discretion of the IO. The IRB Vice Chairperson has a direct line to the IRB Chairperson and IO as necessary.

8.2.3. IRB Members

The role of an IRB member is to ensure that human research activities comply with federal regulations, state and local laws, and organizational policies and procedures, by:

- Completing member education and training, both initial and on-going *(See Section 3.1)*
- Maintaining the confidentiality of IRB deliberations and research reviewed by the IRB
- Conducting and documenting reviews in a timely fashion when:
    - Serving as a reviewer for new protocols.
    - Serving as appointed reviewer(s) for applications for expedited, limited or continuing review.
    - Serving as a primary reviewer for internal or external adverse events or serious problems, incidents of noncompliance, and/or protocol deviations.
    - Serving as appointed reviewer(s) for changes in protocol and / or consent documents.
- Attending IRB meetings as scheduled
- Recusing self from reviewing or voting on research when s/he has a COI (See Section 23.2)
- Participating in subcommittees of the IRB if requested and available
- Conducting themselves in a professional and collegial manner.

Members should attend all meetings for which they are scheduled. If a member is unable to attend a scheduled meeting, they should inform the HRPP Administrator. If a member's availability changes and they are no longer able to regularly attend IRB meetings or will be absent for an extended period of time, they should inform the HRPP Administrator. The HRPP Administrator will assess the situation, including the availability of the alternate when applicable, and make recommendations to the IRB Chair to ensure the IRB is able to meet quorum requirements and has the necessary expertise to review the research which regularly comes before it.

Experienced IRB members (with at least one-year experience) may be designated by the Chair/HRPP Administrator to conduct expedited reviews.

8.2.4. Alternate Members

The appointment and function of alternate members is the same as that for primary IRB members. An alternate's expertise and perspective should be comparable to those of the primary member. The role of the alternate member is to serve as a voting member of the IRB, on either a scheduled basis or when the regular member is unavailable to attend a convened meeting, in part or in full, or when the regular member has a COI in regards to a protocol under review. When an alternate member substitutes for a primary member, the alternate member will receive and review the same materials prior to the IRB meeting that the primary member would have received.

The IRB roster identifies the primary member(s) or class of members (e.g., physician scientist) for whom

each alternate member may substitute. When both the regular member and the alternate is in attendance at an IRB meeting, only one may be counted towards quorum and vote. The IRB minutes will document the members present at each meeting.

Experienced alternate members may be designated by the Chair to conduct expedited reviews.

8.2.5. Subcommittees of the IRB

The IRB Chair, in consultation with the HRPP Administrator, may appoint one or more other IRB members to a subcommittee of the IRB to review study/protocol specific related issues and to make recommendations to the IRB (e.g., to supplement the IRB's review of research proposals or to review reports of potential unanticipated problems or noncompliance). The size and composition of the subcommittee shall depend on the scope of duties delegated by the IRB Chair. Any such subcommittee cannot approve research or issue determinations that require review by the convened IRB.

8.2.6. Research Integrity Compliance and Operations (RICO) Council

The RICO is responsible for providing administrative support to SJH/SPHPs HRPP by working parallel with the IRB in its oversight of research activities. This support includes but is not limited to research-related policies, procedures, and finances to SJH/SPHP, St. Joseph's Physicians (SJP) and individuals and organizations conducting research under the SJH/SPHPs FWA. Protection of human subject research is within the oversight of the IO and the SJH/SPHP IRB who report to the SJH/SPHP Board of Trustees through the Corporate Compliance and Organizational Integrity Committee (CCOIC).

8.3. Composition of the IRB Membership

The IRB must promote respect for its advice and counsel in safeguarding the rights and welfare of the research that comes before it and possess the professional competence necessary to review specific research activities. The structure and composition of the SJH/SPHP IRB is based upon regulatory requirements and the characteristics of the research it reviews. A member of the IRB may fill multiple membership position requirements (e.g., nonscientific and unaffiliated).

- The IRB will have at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the organization. The IRB shall not consist entirely of members of one profession
- The IRB will include members who are knowledgeable about and experienced working with subjects vulnerable to coercion or undue influence (e.g., children, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons) that are regularly included in the research under its review
- Every nondiscriminatory effort will be made to ensure that the IRB does not consist entirely of men or entirely of women, including the organization's consideration of qualified persons of both sexes, so long as no selection is made to the IRB solely on the basis of gender
- The IRB includes at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas
- The IRB includes at least one member who is not otherwise affiliated with the organization and who is not part of the immediate family of a person who is affiliated with the organization

- The IRB will include at least one nurse representative

At the discretion of the IO and IRB Chair, the HRPP Administrator may be appointed as an IRB member or alternate.

On an annual basis, the IRB Chair and the HRPP Administrator review the membership and composition of the IRB to determine if it continues to meet regulatory and organizational requirements.

8.3.1. Appointment of Members to the IRB

When the need for a new IRB member or alternate is identified, the HRPP Administrator informs the IO and seeks out qualified candidates. Others institutional officials may forward recommendations to the IO, HRPP Administrator, IRB Chair or to the IRB Office.

The final decision in selecting a new member is made by the IRB Chair, in consultation with the HRPP Administrator.

Appointments are made by the IRB Chair. Any change in appointment, including removal, requires written notification. Members may resign by written notification to the HRPP Administrator or the, IRB Chair.

The HRPP Administrator will ensure that changes in IRB membership are reported via the federal IRB registration in accordance with the instructions provided on OHRP's website.

8.4. Use of Consultants

When necessary, the IRB Chair or the HRPP Administrator may solicit individuals from within or outside the organization with the expertise to assist in the review of research or issues which require expertise beyond or in addition to that available on the IRB. The IRB Office will ensure that all relevant materials are provided to the consulting reviewer prior to the convened meeting or expedited review.

The HRPP Administrator reviews the COI policy for IRB members with consultants and consultants must confirm that they do not have a COI prior to review. Individuals who have a conflicting interest or whose spouse or immediate family members have a conflicting interest will not be invited to provide consultation.

The findings of the consultants will be presented to the IRB for consideration either in person or in writing. If in attendance at an IRB meeting, consultants may provide information and assist in the deliberations of the IRB but may not participate in the vote. Consultants may be excused upon conclusion of discussion of the protocol in question.

Written statements from consultants will be kept in the IRB records. Information provided by consultants at IRB meetings will be documented in the minutes.

Ad hoc or informal consultations requested by individual members (rather than the convened board) will be managed in a manner that protects the confidentiality of the investigator.

8.5. Reporting and Investigation of Allegations of Undue Influence

If the IRB Chair, member, or staff person feels that the IRB has been unduly influenced by any party, they shall make a confidential report to the HRPP Administrator or IO. The IO will ensure that a thorough investigation is conducted and, if the allegation is determined valid, that corrective action is

taken to prevent additional occurrences. In the event that the allegation is regarding the IO, the matter will be referred to the Integrity and Compliance Office for investigation and any necessary action.

Undue influence means attempting to interfere with the normal functioning and decision-making of the IRB, or to attempt to influence an IRB member or staff member or any other member of the research team, outside of the established processes or normal and accepted methods in order to obtain a particular result, decision, or action by the IRB or one of its members or staff.

9. IRB Actions, Failure to Respond, Appeals

9.1. Possible IRB Actions for initial, continuing review or modifications

Approval (Full Review or Expedited Review): The study, proposed modification to previously approved research, or another item is approved as submitted.

Modifications Required (Full Review or Expedited Review): The requested revisions are prescriptive, e.g., the submission requires minor revisions, such as wording changes, with replacement language provided or confirmation by the PI of the IRB's understanding of a particular issue.

For studies undergoing full review, the needed revisions are agreed upon at the meeting; for those undergoing expedited review, they are designated by the reviewer(s).

In order to receive approval for a protocol requiring modifications:

- For full review studies, the response of the investigator and all other materials will be reviewed by either the HRPP Administrator, IRB Chair, Vice Chair or a particular IRB member. The reviewer may approve the study upon receipt and approval of the revisions without further action by the IRB.
- For expedited studies, the response of the investigator and all other materials will either be reviewed by the HRPP Administrator, the original reviewer, or handled by the IRB Chair or Vice Chair.

Approval of the study will not be granted, and approval letters will not be issued until all deficiencies, if any, are corrected to the satisfaction of the final reviewer(s).

The outcome of the IRB's or expedited reviewer's deliberations is once again communicated to the investigator in writing.

Referred to Full Board (Expedited Review): If an expedited reviewer defers a study, the HRPP Administrator will place it on the agenda for the next IRB meeting.

Deferred (Full Review)*:* This action is taken by the IRB when modifications are required of the nature or amount that the full IRB cannot make or specify exact changes or parameters, or additional information or clarification is needed in order to determine that one or more criteria for approval are satisfied (e.g., the risks and benefits cannot be assessed until additional information is provided.).

The deferral is documented in the IRB minutes and is communicated to the investigator in writing.

When the convened IRB defers approval, the responsive materials from the investigator will be provided to the convened IRB for review at a subsequent meeting.

Not Approved (Full Review): This action is taken when the convened IRB determines that the proposed research activity does not satisfy the criteria for approval and that it cannot be modified to render it approvable (or the sponsor or investigator will not make necessary modifications that would render the research approvable).

9.2. Failure to Respond

Upon review of a research study, the IRB may require changes or request certain information from an investigator. Failure to respond to IRB required changes or requests for information may result in suspension or termination of IRB approval for the study. For studies that have not yet been approved, the study submission may be administratively withdrawn.

9.3. Reporting IRB Actions

All IRB actions are communicated to the principal investigator (PI) in writing via the IRB Electronic System (IRBManager) within ten (10) working days, whenever possible, of the review.

9.4. Appeal of IRB Decisions

When the IRB suspends, terminates, or disapproves research, the IRB letter to the PI, which communicates the decision and the action taken by the IRB will include the basis for the action and will offer the investigator the opportunity to respond or address the concerns of the IRB. Additionally, whenever an investigator disagrees with an IRB requirement or decision, or believes that providing the IRB with additional information may result in a different outcome, they may request that the IRB reconsider its decision by submitting a memo and other supporting materials via the IRB Electronic System (IRBManager). Such a request for reconsideration or appeal must be submitted to the IRB no later than one month after the decision of the IRB unless the IRB Chair/Vice Chair agrees to a later deadline. The investigator may be invited to attend an upcoming IRB meeting to discuss their request for reconsideration and elaborate on the additional information that they provide. If the investigator is invited to attend such meeting, the investigator will be asked to leave the meeting prior to the final deliberations and vote of the IRB on the request for reconsideration by the investigator.

10. IRB Review Process

The SJH/SPHP IRB will review and ensure that research under its oversight meets all required ethical and regulatory criteria for initial and continuing review and any modifications of approved research. The IRB may conduct their review using the following review methods:

- Expedited Review
- Review by Convened IRB

10.1. Expedited Review

The IRB may use the expedited review procedure to review the following:

- Some or all of the research appearing on the list of categories of research eligible for expedited review unless the Chair or Vice Chair determines that the research involves more than minimal

risk.
- Minor changes in research previously approved by the convened IRB.
- Research for which limited IRB review is a condition of exemption under 45 CFR 46.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7) and (8).

The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--used by the IRB.

10.1.1. Definitions

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 daily life or during the performance of routine physical or psychological examinations or tests.

Minor Change. A minor change is one which, in the judgment of the IRB reviewer, makes no substantial alteration in:

1. The acceptability of the risk-to-benefit analysis (i.e., the change does not increase the level of risk);
2. The research design or methods (adding procedures that are not eligible for expedited review (See Section 10.1.2) would be considered more than a minor change);
3. The qualifications of the research team (i.e., the change does not negatively impact the expertise available to conduct the research);
4. The facilities available to support safe conduct of the research; or
5. Any other factor which would warrant review of the proposed changes by the convened IRB.

Minor changes also include the addition of sites to a protocol approved by the convened IRB so long as the investigator(s)/site(s) do not have a COI, potential compliance concerns (e.g., a 483 that has not been adequately resolved), or any other investigator or site-specific concerns (e.g., qualifications, facilities, or resources to safely conduct the research).

10.1.2. Categories of Research Eligible for Expedited Review

SJH/SPHP applies the categories of research eligible for expedited review, which were published in the Federal Register notice 63 FR 60364-60367, November 9, 1998.

The categories in this list apply regardless of the age of subjects, except as noted in category 2.

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

The expedited review procedure may not be used for classified research.

Expedited Categories one (1) through six (6) may be used for both initial and continuing 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/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:

   a. From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week; or

   b. 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. (Note: Children are defined as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.)

3. Prospective collection of biological specimens for research purposes by noninvasive means.

   Examples: (a) hair and nail clippings in a nondisfiguring 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 gum base or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization; (k) vaginal swabs that do not go beyond the cervical os; rectal swabs that do not go beyond the rectum; and nasal swabs that do not go beyond the nares.

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. (Note: Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

   Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the

subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, 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 DHHS regulations for the protection of human subjects. See Exempt Categories and 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. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior); or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46.101(b)(2). This listing refers only to research that is not exempt.)

Categories 7 and 8 apply only to continuing review.

7. Continuing review of research previously approved by the convened IRB as follows:
    a. Where (i) the research at SJH/SPHP 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 (Note: "Long-term follow-up" includes research *interactions* that involve no more than minimal risk to subjects (e.g., quality of life surveys); and collection *of follow-up* data from procedures or interventions that would have been done as part of routine clinical practice to monitor a subject for disease progression or recurrence, regardless of whether the procedures or interventions are described in the research study, but not *interventions* that would not have been performed for clinical purposes, even if the research interventions involve no more than minimal risk.); ***or***
    b. Where no subjects have ever been enrolled at SJH/SPHP and no additional risks have been identified (Note: "no additional risks have been identified" means that neither the investigator nor the IRB has identified any additional risks from any institution engaged in the research project or from any other relevant source since the IRB's most recent prior review.); ***or***
    c. Where the remaining research activities at SJH/SPHP are limited to data analysis. (Note: Simply maintaining individually identifiable private information without using,

studying, or analyzing such information is not human subject research and thus does not require continuing review).

8. Continuing review of research previously approved by the IRB at a convened meeting that meets the following conditions:

    a. The research is not conducted under an investigational new drug application (IND) or an investigational device exemption (IDE); ***and***
    b. Expedited review categories (2) through (8) do not apply to the research; ***and***
    c. The IRB has determined and documented at a convened meeting that the research, or the remaining research activity involving human subjects, involves no greater than minimal risk to the subjects; ***and***
    d. No additional risks of the research have been identified. (Note: "no additional risks have been identified" means that neither the investigator nor the IRB has identified any additional risks from any institution engaged in the research project or from any other relevant source since the most recent prior review by the IRB).

10.1.3. Expedited Review Procedures

Under an expedited review procedure, IRB review is carried out by the IRB Chair, IRB Vice Chair, HRPP Administrator or by one or more reviewers designated by the Chair or Vice Chair from among experienced members of the IRB. Designated reviewers must be professionally competent (i.e., experienced with and having demonstrated knowledge of and the ability to apply IRB review requirements) to conduct expedited reviews.

IRB members do not participate in the review of research in which they have with a COI (see Section 23.2) but may answer questions about the research if requested.

When reviewing research under an expedited review procedure, the IRB Chair, IRB Vice Chair, HRPP Administrator or designated reviewer, will receive and review the same materials that would be reviewed if the research were to be reviewed by the convened IRB, and for previously approved research, will have access to the study history. The reviewer evaluates and documents whether the research qualifies for expedited review on a checklist or in the reviewer comments section of IRB electronic management system (IRBManager).

When a reviewer determines that research that does fall within the expedited categories involves more than minimal risk, the reviewer will document the rationale for that determination and refer the research for review by the convened IRB. If the research does not meet the criteria for expedited review, then the reviewer will indicate that the research requires review by the convened IRB and the submission is placed on the next available IRB meeting agenda.

In reviewing the research, expedited reviewers will apply the same criteria for review and approval of research described throughout this manual and may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may only be disapproved by the convened IRB.

Reviewers may use an appropriate checklist to assess the criteria for approval and may document their review on the reviewer comments section of IRBManager. For initial and continuing reviews, the

category under which the research qualifies for expedited review will be documented in IRBManager. The checklist, if used, is maintained in IRBManager. When expedited review is carried out by more than one IRB member and the reviewers disagree, the IRB Chair or Vice Chair may make a final determination or refer the submission to the convened IRB for review.

Documentation of the outcome of the review will be prepared by the HRPP Administrator and provided to the investigator.

10.1.4. Informing the IRB

Members of the IRB will be apprised of expedited review approvals, including limited IRB reviews conducted using expedited review procedures, by means of a list in the agenda for the next scheduled meeting. Any IRB member can request to review the materials for any study by contacting the IRB Office.

10.2. Convened IRB Meetings

Except when an expedited review procedure is used or the research is deemed exempt (including exempt research subject to limited IRB review), the IRB will conduct initial and continuing reviews of research at convened meetings at which a quorum of the members is present.

10.2.1. IRB Meeting Schedule

The IRB meets on the first Tuesday of every month (except if otherwise noted). The schedule for the IRB may vary due to holidays, lack of quorum, or other reasons. The IRB meeting dates and deadlines are available on the IRB Web site at: https://irb.sjhsyr.org/ and in IRBManager. Special meetings may be called as needed by the Chair or Vice Chair.

10.2.2. Preliminary Review

The HRPP Administrator will perform a preliminary review of all submissions for determination of completeness and accuracy. The investigator will be informed via IRBManager of missing materials or signatures. If an investigator is submitting for the first time or is not be well-versed in submission procedures, consultations can be arranged with the HRPP Administrator.

10.2.3. Materials received by the IRB

All required materials need to be submitted to the IRB office by the published deadline for inclusion on the IRB agenda. On occasion, when a review is time-sensitive, the IRB office may make an exception to this rule provided that there is still sufficient time for all members to review the submission materials. The meeting agenda will be prepared by HRPP Administrator in consultation as needed with the IRB Chair or Vice Chair. All IRB members receive the IRB agenda, prior meeting minutes, applicable business items, and research submission materials at least 7 business days before the scheduled meeting to allow sufficient time for review. On occasion, a time-sensitive item may be added to the agenda less than 7 business days in advance if circumstances warrant and IRB members have sufficient time for review.

All IRB members have access in the IRBManager to all materials submitted for studies which will be reviewed by the committee on the agenda, which include the following, as applicable:

- The complete protocol
- The application or submission form (e.g., initial, continuing review, modification request)
- The proposed and/or previously approved Consent/Parental Permission/Assent Form(s)
- Proposed recruitment materials, including advertisements intended to be seen or heard by potential study participants
- Any other subject materials, such as questionnaires or diaries
- The Investigator Brochure(s)
- Sample consent/parental permission/assent form(s)

All IRB members are expected to perform an in-depth review of the submission materials for each study on the agenda, to be reviewed by the committee at the meeting.

If an IRB member requires additional information to complete the review, they may contact the IRB office. Any additional requested information will be provided to the other members in the IRBManager.

10.2.4. Quorum

A quorum of the IRB consists of a majority (more than half) of the voting membership, including at least one member whose primary concern is in a non-scientific area. When research involving an investigational new drug is on the agenda for review, a physician should be included in the quorum. When nursing research is on the agenda, a nurse should be included in the quorum. At meetings of the IRB, a quorum must be established and maintained for the deliberation and vote on all matters requiring a vote.

The IRB Chair, with the assistance of the HRPP Administrator, will confirm that quorum is present before calling the meeting to order. The IRB Chair, with the assistance of the HRPP Administrator, will be responsible to ensure that the IRB meeting remains appropriately convened. If a quorum is not maintained, either by losing a majority of the members, or losing all non-scientific members or another required member, the IRB may not take votes until quorum is restored. An attendance sheet and agenda notes are used by the HRPP Administrator and/or IRB Chair to monitor quorum and to temporarily document attendance and quorum until the minutes are prepared and finalized.

It is generally expected that at least one unaffiliated member will be present at all IRB meetings. The IRB may, on occasion, meet without this representation; however, this should be the exception.

When the IRB regularly reviews research that involves subjects vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, one or more individuals (e.g., IRB members, alternate members, or consultants) who are knowledgeable about and experienced with such subjects should be present during the review of the research.

IRB members are considered present and participating at a duly convened IRB meeting when either physically present or participating through electronic means (e.g., teleconferencing or video conferencing) that permits them to listen to and speak during IRB deliberations and voting. When not physically present, the IRB member must have received all pertinent materials prior to the meeting and must be able to participate actively and equally in all discussions.

Opinions of absent members may be considered by the attending IRB members but may not be counted

as votes or to satisfy quorum requirements for convened meetings.

10.2.5. Meeting Procedures

The IRB Chair, Vice Chair or HRPP Administrator will call the meeting to order, once it has been determined that a quorum is in place. The Chair, Vice Chair or Specialist will ask IRB members if they have any unknown conflicts with agenda items, in order to ensure they recuse themselves from discussion and voting, when they have a conflict. IRB members, who have a conflict, will absent themselves from the room during the discussion and voting on such studies.

The IRB will review and discuss the minutes from the prior meeting and determine if there are any revisions/corrections to be made. If there are no changes to be made, the minutes will be accepted as presented and considered final. If major revisions/corrections are necessary, the minutes will be amended and presented at the following IRB meeting. Minor revisions/corrections may be verified by the HRPP Administrator, IRB Chair or Vice Chair outside of the meeting. The IRB reviews submissions for initial and continuing review, requests for modifications to previously approved research, and other business items, as applicable (e.g., potentially serious noncompliance).

The PI or Sub-PI (for new Studies) and/or the Research Coordinator (for approved studies) presents an overview of the submission and leads the IRB through the evaluation of the regulatory criteria for approval or other required determinations. Applicable checklist(s) may be used as a guide. For the research to be approved, or any motion on a business item of the agenda to pass, it must receive the approval of a majority of those voting members present at the meeting.

The HRPP Administrator is responsible for taking minutes at each IRB meeting.

10.2.6. Guests

Other guests may be permitted to attend IRB meetings at the discretion of the IRB Chair and the HRPP Administrator. Such guests do not participate in discussion unless requested by the IRB; under no circumstances may they vote, and they will be reminded that all discussions and deliberations are confidential. PI and Guest may sign a Confidentiality Agreement prior to the start of the IRB Meeting.

10.3. Criteria for IRB Approval of Research

For the IRB to approve human subjects research, either through expedited review or by the convened IRB, it must determine that the following requirements are, or remain, satisfied.

1. Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of

applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

3. Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving subjects vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by the Federal Regulations [45 CFR 46.116/21 CFR 50].
5. Informed consent will be appropriately documented, in accordance with, and to the extent required by the Federal Regulations [45 CFR 46.117/21 CFR 50].
6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

When some or all of the subjects are likely to be vulnerable to coercion or undue influence such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

10.3.1. Risk/Benefit Assessment

The goal of the assessment is to ensure that the risks to research subjects posed by participation in the research are justified by the anticipated benefits to the subjects or society. Toward that end, the IRB must:

- Judge whether the anticipated benefit, either of new knowledge or of improved health or other direct benefit for the research subjects, justifies asking any person to undertake the risks; and
- Disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits.

The assessment of the risks and benefits of proposed research involves a series of steps:

1. **Identify the risks** associated with the research, as distinguished from the risks of activities, diagnostic tests, treatments, or therapies the subjects would receive or undergo even if not participating in the research;
2. **Determine whether the risks will be minimized** to the extent possible by evaluating the necessity of procedures that impart risk and whether the data could be gained by procedures that are already being performed for other purposes or by alternative procedures that impart less risk;
3. **Identify the anticipated benefits** to be derived from the research, both direct benefits to

subjects and possible benefits to society, science and others;

4. **Determine whether the risks are reasonable in relation to the benefits**, if any, and assess the importance of the knowledge that can reasonably be expected to result from the research.

In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research - as distinguished from risks and benefits subjects would receive even if not participating in the research.

The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks and benefits that fall within the purview of its responsibility.

The IRB should not consider any compensation that subjects may receive to be a benefit of the research.

When research subjects are assigned to different arms or otherwise undergo differing interventions, procedures, or exposures, the evaluation of risk and benefit should be made for each subject group (i.e., a "component analysis'). This is especially important when a subset of subjects will have no possibility of direct benefit but will be exposed to greater than minimal risks.

10.3.2. Equitable Selection of Subjects

The IRB evaluates whether the selection of subjects is equitable with respect to gender, age, class, etc. by reviewing the IRB application, protocol, and other materials and information. The IRB will not approve a study that does not provide adequately for the equitable selection of subjects or has not provided an appropriate scientific and ethical justification for excluding classes of persons who might benefit from the research. In making this determination, the IRB evaluates:

- The purposes of the research;
- The setting in which the research occurs;
- Scientific and ethical justification for including subjects vulnerable to coercion or undue influence such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons;
- The scientific and ethical justification for excluding classes of persons who might benefit from the research; and
- The inclusion/exclusion criteria, and the procedures/materials intended for use for the identification and recruitment of potential subjects.

10.3.2.1. Recruitment of Subjects

The investigator will provide the IRB with a plan for recruitment of potential subjects. All recruiting materials will be submitted to the IRB, including advertisements, flyers, scripts, information sheets and brochures. The IRB should ensure that the recruitment plan and materials appropriately protect the rights and welfare of the prospective subjects (e.g., do not present undue influence). See Section 10.4.9 for a discussion of IRB review of advertisements and Section 10.4.10 for a discussion of IRB review of payments.

10.3.3. Informed Consent

The IRB will ensure that informed consent will be sought from each prospective subject or their Legally Authorized Representative (LAR), in accordance with, and to the extent required by 45 CFR 46.116 and 21 CFR 50.20. In addition, the IRB will ensure that informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117 and 21 CFR 50.27. The IRB will ensure, as part of its review, that the information in the consent document and process is consistent with the research plan. See Section 13 for a detailed discussion on informed consent.

10.3.4. Data and Safety Monitoring Requirements

For research that is more than minimal risk, the investigator should submit a data and safety monitoring (DSM) plan. The initial plan submitted to the IRB should describe the procedures for safety monitoring, reporting of unanticipated problems involving risks to subjects or others, descriptions of interim safety reviews and the procedures planned for providing DSM findings to the IRB. DSM may be performed by a researcher, medical monitor, safety monitoring committee, or other means.

The IRB reviews the safety monitoring plan and determines if it makes adequate provision for monitoring data to ensure the safety of subjects and for addressing problems that may arise over the course of the study. If a plan was not submitted, the IRB determines whether a plan is required, and, depending on the circumstances, what the plan should include. The overall elements of the monitoring plan depend on the potential risks, complexity, and nature of the research study.

The principles the IRB applies in evaluating the adequacy of a proposed DSM plan include:

- Monitoring should be commensurate with the nature, complexity, size, and risks of the research
- Monitoring should be timely. Frequency should be commensurate with risk. Conclusions are reported to the IRB
- For low risk studies, continuous, close monitoring by the study investigator or an independent party may be an adequate and appropriate format for monitoring, with prompt reporting of problems to the IRB, sponsor, and regulatory bodies, as applicable
- For greater than minimal risk studies that do not include a plan for monitoring by a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), and that are blinded, multi-site, involve vulnerable populations, or involve high-risk interventions or procedures, the IRB will carefully evaluate the proposed DSM plan and may require establishment of a DSMB, DMC, or other methods to enhance the monitoring and management of safety

DSM plans should specify:

- The entity or person(s) who will perform the monitoring, and the independence or affiliation that the entity or person(s) has with the sponsor or investigator
- The safety information that will be collected and monitored, including serious adverse events and unanticipated problems
- The frequency or periodicity of review of safety data
- The procedures for analysis and interpretation of the data
- The procedures for review of scientific literature and data from other sources that may inform the safety or conduct of the study
- The conditions that trigger a suspension or termination of the research (i.e., stopping rules),

when appropriate
- The procedures for reporting findings to the IRB, including a summary description of what information, or the types of information, that will be provided

For a DSMB or DMC, the plan should also describe the composition of the board or committee. Generally, a DSMB or DMC should be composed of experts in all scientific disciplines needed to interpret the data and ensure subject safety. Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease/condition and treatment under study should be part of the monitoring group or be available if warranted.

The NIH requires the establishment of DSMBs for multi-site clinical trials involving interventions that entail potential risk to the participants.

10.3.5. Privacy and Confidentiality

The IRB will determine whether adequate procedures are in place to **protect the privacy** of subjects and to **maintain the confidentiality of the data**.

10.3.5.1. Definitions

Privacy. Having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others. It is the state or condition of being free from unauthorized intrusion, being observed or disturbed by other people.

Confidentiality. Methods used to ensure that information obtained by investigators about subjects is not improperly divulged.

Private information. Information that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).

Sensitive Information. Data or information, on any storage media or in any form or format, which requires protection due to the risk of harm that could result from inadvertent or deliberate disclosure, unauthorized access, misuse, alteration, or loss or destruction of the information (e.g., could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation).

Identifiable information. Information where the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

10.3.5.2. Privacy

The IRB determines whether the activities in the research appropriately protect the privacy of potential and enrolled subjects. In order to make that determination, the IRB must obtain information regarding how the investigators plan to access subjects or subjects' private, identifiable information, and the subjects' expectations of privacy in the situation.

In developing strategies for the protection of privacy, consideration is given to the:

- Methods used to identify and contact potential participants
- Settings where recruitment and research activities will occur

10.3.5.3. Confidentiality

The IRB must determine if appropriate protections are in place to minimize the likelihood that information about subjects or their participation in research will be inappropriately accessed or divulged. Safeguards designed to protect confidentiality should be commensurate with the potential of harm from unauthorized, inappropriate or unintentional disclosure.

The IRB assesses whether there are adequate provisions to protect data confidentiality by evaluating the methods used to obtain, record, share, and store information about individuals who may be recruited to participate in studies and about subjects. The investigator will provide the IRB with a plan regarding the procedures to be taken to protect the confidentiality of research data and sensitive information. The investigator will provide plans to address the protection of paper documents, other physical media (e.g., audio or videotapes), and electronic data, and information regarding the use, maintenance, storage, and transmission of information. The IRB will review the information received from the investigator and determine whether the confidentiality of research data is sufficiently protected. In some cases, the IRB may also require that a Certificate of Confidentiality is obtained to protect data from compelled disclosure (See Section 26.3).

Research regulated by the FDA that involves the use of electronic data collection/storage systems must comply with the requirements of 21 CFR Part 11.

10.3.6. Vulnerable Populations

Certain individuals, by nature of their age or mental, physical, economic, educational, or other circumstances, may be more vulnerable to coercion or undue influence than others. At the time of initial review, and when a proposed modification includes the involvement of vulnerable subject populations, the IRB will consider the scientific and ethical reasons for including vulnerable subjects in research. When appropriate, the IRB may determine and require that additional safeguards be put into place for vulnerable subjects, such as those without decision-making capacity.

For an extensive discussion about the IRB review process for specific populations of vulnerable subjects, please refer to Section 14.

10.4. Additional Considerations

10.4.1. Determination of Risk Level

At the time of initial review, the IRB will make a determination regarding the risks associated with the research. Risks associated with the research will generally be classified as either "minimal" or "greater than minimal" with additional classifications as required by the various subparts or FDA regulations. Risk determinations may vary over the life of a research study depending on the procedures and risks that subjects will be exposed to as the research progresses. Because of this, the IRB may reevaluate the risk determination with modifications to the research, at continuing review, and when new information becomes available. The level of risk associated with the research influences eligibility for expedited

review. The meeting minutes will reflect the determination of the convened IRB regarding risk levels; expedited reviewers will confirm the determination of risk level on the reviewer checklist or in the reviewer comments section (IRBManager).

10.4.2. Approval Period

Determination of the approval period is made by the IRB on a protocol-by-protocol basis.

For each initial or continuing approval, the IRB will indicate an approval period with an expiration date specified. The IRB approval is considered to have lapsed at midnight on the expiration date of the approval. For a study reviewed by the convened IRB, the approval commences on the date that the IRB conducts its final review of the study; that is, the date that the convened IRB approves the research or the date that a final reviewer approves the study following a 'modifications required' determination, for non-substantive issues by the full committee. The expiration date is no later than one year from the date that the full committee last reviewed the study. For a study approved under expedited review, the approval period begins on the date the IRB Chair or Vice Chair gives final approval to the protocol, and the expiration date, if continuing review is required, is no later than one year from date of final approval.

The approval date and expiration date (if continuing review is required) are clearly noted on all the IRB letters sent to the PI and must be strictly adhered to. Investigators should allow sufficient time for development and review of continuing review submissions. Electronic courtesy reminder notices are sent 60 and 45 days prior to expiration, but it remains the PI's responsibility to maintain continued approval for their studies.

IRB review of a proposed modification to research does not alter the date by which continuing review (if required) must occur.

The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of the IRB approval. Therefore, continuing review and re-approval of research must occur by midnight of the date when the IRB approval expires.

10.4.3. Review More Often Than Annually

The following factors will be considered when determining which studies require review more frequently than on an annual basis:

1. The probability and magnitude of anticipated risks to subjects;
2. The novelty of the research making unanticipated adverse events/unanticipated problems more likely;
3. The involvement of especially vulnerable populations likely to be subject to undue influence or coercion;
4. A history of serious or continuing noncompliance on the part of the investigator; and
5. Any other factors that the IRB deems relevant.

In specifying an approval period of less than one year, the IRB may define the period with either a time interval or a maximum number of enrolled subjects. If a maximum number of subjects is used to define the approval period, it is understood that the approval period in no case can exceed one year unless the study does not require continuing review. If an approval period of less than one year is specified by the

IRB for research that is subject to continuing review, the reason for more frequent review will be documented in the minutes, or in the IRB management system. When the IRB determines the need for increased monitoring, this oversight may be accomplished by either: 1) submission of interim reports by the PI, or 2) auditing of investigator records by HRPP / Compliance Staff.

10.4.4. Independent Verification That No Material Changes Have Occurred

The IRB recognizes that protecting the rights and welfare of subjects sometimes requires that the IRB use sources other than the investigator to independently verify that no material changes have occurred since previous IRB review.

In support of this requirement, the SJH/SPHP IRB requires the submission of Other Reportable Information (See Section 19) including reports from external monitors, auditors, or inspectors (See Section 2.1).

The IRB will also determine the need for verification from outside sources on a case-by-case basis. The following factors may be considered when determining which studies require independent verification:

1. The probability and magnitude of anticipated risks to subjects;
2. The likely medical/psychological/social/legal/educational condition of the proposed subjects; The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed;
3. Concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources;
4. Investigators who have previously failed to comply with federal regulations and/or the requirements or determinations of the organization or the IRB;
5. Research without routine independent monitoring;
6. Any other factors the IRB deems verification from outside sources is relevant.

If any material changes have occurred without IRB review and approval, the IRB will decide the corrective action to be taken (see Section 17 on Noncompliance).

When the IRB determines that verification from sources other than the investigator is necessary, the HRPP staff and / or IRB member(s) will perform the necessary verification by conducting an audit.

10.4.5. Consent Monitoring

In reviewing the adequacy of informed consent procedures for proposed research, the IRB may on occasion determine that monitoring of the consent process by an impartial observer (e.g., consent monitor) is required in order to reduce the possibility of coercion and undue influence, ensure that the approved consent process is being followed, or ensure that subjects are truly giving informed consent.

Such monitoring may be particularly warranted for:

1. High risk studies;
2. Studies that involve particularly complicated procedures or interventions;
3. Studies involving highly vulnerable populations (e.g., ICU patients, children who are wards);
4. Other situations when the IRB has concerns that consent process may not be/is not being conducted appropriately (e.g., prior investigator noncompliance, etc.).

Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

If the IRB determines that consent monitoring is required, the IRB may consult with the QAIP Coordinator, and others to develop an appropriate plan. The consent monitoring may be conducted by HRPP Administrator, IRB members, QAIP Coordinator, or another appropriate designee. The investigator will be notified of the IRB determination and the reasons for the determination. Arrangements will be made with the investigator for the monitoring of the consent process, typically for a specified number of subjects. When warranted, the investigator may not be notified until after the observation has occurred. When observing the consent process, the monitor will evaluate whether:

1. The informed consent process was appropriately conducted and documented;
2. The participant had sufficient time to consider study participation, and to ask questions and have them answered;
3. The consent process involved coercion or undue influence;
4. The information was accurate and conveyed in understandable language; and
5. The subject appeared to understand the information and provided their voluntary consent.

Following the monitoring, a report of the findings will be submitted to the IRB, which will determine the appropriate action to be taken, if any.

The IRB will ensure that consent forms are consistent with applicable state and local laws. The age of majority is 18 years of age in NY State.

Under the following conditions, a minor may consent for themselves (or their child): 1. If the minor is a parent of a child, that minor parent may consent for research for themselves (or their child); 2. If the minor is pregnant, she may give consent for research if it pertains to prenatal care. If the research does not pertain to prenatal care, she does not have the capacity to give consent; 3. A minor who is married may give consent for research.

The following persons may act as authorized representatives for adults who have been determined to lack capacity (listed in descending order of priority):

- A health care agent properly designated on a health care proxy form
- A court-appointed guardian or committee under the New York Surrogates Court Procedure Act Article 17-A;
- The spouse;
- An adult son or daughter;
- A parent;
- An adult brother or sister; **or**
- A close friend, who is an adult (18 years or older) who has a close personal relationship with the subject and provides a signed written statement, to the PI or his/her designee that he/she is a close friend of the subject, and that he/she has maintained such regular contact with the patient as to be familiar with the patient's activities, health, religious or moral beliefs and stating the facts and circumstances that demonstrate such familiarity.

10.4.6. Investigator Qualifications

The IRB relies upon the Principal Investigator, and other SJH/SPHP processes (e.g., credentialing, physician's appointment, curriculum vitae/resume) to determine whether investigators and members of the research team are appropriately qualified to conduct the research.

10.4.7. Significant New Findings

During the course of research, significant new knowledge or findings about the research, the test article, and/or the condition under study may develop. The investigator must report any significant new findings to the IRB and the IRB will review them and evaluate the impact on the rights and welfare of subjects. When the new knowledge or findings may affect the risks or benefits to subjects or subjects' willingness to continue in the research, the IRB may require that the investigator contact subjects to inform them of the new information. The IRB will communicate this requirement to the investigator. If the study is still enrolling subjects, the consent document should be updated. The IRB may require that the currently enrolled subjects be re-consented or otherwise provided with the new information. When appropriate, the IRB may also require that former subjects be provided with the new information (e.g., late emerging safety information).

10.4.8. Conflicts of Interest

The IRB Application solicits information about investigator and research staff COI. If any potential conflict is noted, the study is referred to the SJH/SPHP Research Integrity and Compliance (RICO) Committee for review and recommendations. The IRB will make a final determination as to whether any COI is adequately addressed and protects the human subjects in the research.

Likewise, when there is an institutional COI, the IRB has final authority to determine whether the conflict and the management plan, if any, allow the study to be approved. (See Section 23 for a more detailed discussion of COI).

10.4.9. Advertisements and Recruitment Materials

The IRB must review and approve all advertisements and recruitment materials prior to posting, use, or distribution. The IRB will review:

- The information contained in the advertisement/recruitment material
- The mode/method of its communication.
- The format of printed advertisement/recruitment material
- The proposed script of any audio/video advertisements/recruitment materials

This information must be submitted to the IRB with the initial application, or, if proposed after study approval, as a modification request.

The IRB reviews the material to assure that the material is accurate and is not coercive or unduly optimistic, creating undue influence to the subject to participate.

Recruitment materials should be limited to the information prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included:

1. The name and address of the investigator and/or research facility;

2. The condition being studied and/or the purpose of the research;
3. In summary form, the criteria that will be used to determine eligibility for the study;
4. The time or other commitment required of the subjects;
5. The location of the research and the person or office to contact for further information;
6. A clear statement that the activity is research and not treatment;
7. A brief list of potential benefits (e.g., no-cost health exam).

Once approved by the IRB, advertisements and recruitment materials cannot be altered or manipulated in any way without prior IRB approval.

Directory listings of research such as ClinicalTrials.Gov are not considered advertisements and therefore do not require IRB review and approval if the listing is limited to the following basic trial information: title, purpose of the study, summary description of the research, basic eligibility criteria, study site location(s), and how to contact the study site for further information.

The first contact prospective study subjects make is often with a person who follows a script to determine basic eligibility for the specific study. The IRB should review the script and procedures to ensure that the screening procedures adequately protect the rights and welfare of the prospective subjects.

10.4.10. Payments to Research Subjects

Payments to research subjects are commonly proposed as an incentive for participation in recognition of the time, effort, inconveniences, and discomforts that participation in the proposed research may entail. In contrast to payments, reimbursement is provided to cover actual costs incurred by subjects as a result of participation (e.g., travel, parking, lodging, etc.). Payment arrangements should be managed separately from reimbursement whenever possible because the ethical considerations differ (as well as the potential tax implications).

Reimbursement offsets costs and may decrease financial risks associated with participation and in doing so may facilitate equitable selection of subjects. In contrast, the amount, timing, and nature of payments may unduly influence potential subjects' decision-making, influencing them to accept discomforts or risks that they otherwise would find unacceptable and interfering with truly voluntary informed consent. Payment arrangements may also create issues with equitable selection of subjects, including the societal distribution of research risks and benefits and the generalizability of the research results.

The IRB must consider the proposed amount of payment, the method and timing of disbursement, the subject population, the recruitment methods and materials, and the information provided within the proposed consent form in order to evaluate the acceptability of a proposed payment plan. The IRB does not consider payment as a benefit when weighing the risks and benefits of the research, payment is an incentive not a benefit of the research.

Investigators who wish to pay research subjects must include in their application to the IRB the amount and schedule of all payments. Proposed payments should be reasonable and commensurate with the time and inconveniences associated with study participation and do not constitute (or appear to constitute) undue pressure on the potential subject to volunteer for the research study.

When research involves multiple visits or interactions, payment should be prorated and not be contingent

upon the participant completing the entire study. Further, any amount paid as a bonus for completion of the entire study should not be so great that it could unduly induce subjects to remain in the study when they otherwise would have withdrawn.

The consent form must describe the terms of payment including the amount and schedule of payments and any conditions under which subjects would receive partial payment (e.g., if they withdraw from the study before their participation is completed) or no payment.

Plans to reimburse subjects for incurred expenses must also be outlined in the application to the IRB and described within the consent.

10.4.11. Non-Monetary Gifts and Incentives

Similar to financial incentives, non-monetary gifts or incentives can also present problems of undue influence or coercion that impact a potential subject's ability to fully and freely consider participation in research.

If subjects will be provided with non-monetary gifts, entry into a prize drawing, or tokens of appreciation, such as course credit, totes, books, toys, or other non-monetary gifts or incentives, the IRB will be provided with a description of the product/prize to review and the approximate retail value (if applicable).

As appropriate, the IRB will consider:

- The odds of "winning": The odds of winning as stated to the participant must remain at least as good as what the researcher promised. *For example, the researcher plans to recruit 25 participants and tells the participants that the odds of winning are 1 in 25. Thirty participants are recruited. The researcher now must offer two incentives so that the odds remain at least 1 in 25.* The odds can improve, but they cannot become worse.
- A description of who is conducting the drawing and when the participants will be notified if they will receive the incentive.
- The following must be included in an IRB protocol submitted when students of a professor or instructor are the subjects of a study and extra credit is used as an incentive.
    - Description of the proposed research along with the points allowed for extra credit must be submitted with the IRB protocol. It is recommended that the extra credit for research be worth no more than 2% of the class grade.
    - Alternative non-research activities for extra credit should be available.
    - Receiving extra credit is not contingent upon completing the study.

10.4.12. State and Local Laws

The IRB considers and adheres to all applicable state and local laws in the jurisdictions where the research is taking place. The HRPP and IRB rely on SJH/SPHP Counsel for the interpretation and application of New York State law and the laws of any other jurisdiction where research is conducted as they apply to human subject research.

New York State Public Health Law at section 574 states "No person shall own or operate a clinical laboratory located in or accepting specimens from New York State or own or operate a blood bank which

collects, processes, stores and/or distributes, human blood, blood derivatives or blood components, in New York state unless a valid permit has been issued as provided in section five hundred seventy-five of this title. A permit shall be issued authorizing the performance of one or more procedures or services within one or more categories. A separate permit shall be required for each facility at which clinical laboratory tests are to be performed or at which a blood bank is to be operated…".

> ***Interpretation for Research*** (from the Director of the Clinical Laboratory Evaluation Program Wadsworth Center, NYS Dept. of Health): "Regarding clinical trial testing, if laboratories performing tests on specimens from trial participants for participant management under IRB-approved research or clinical trials protocols, where the results are reported and are used for clinical decision making, are required to obtain a NYS clinical laboratory permit (https://www.wadsworth.org/regulatory/clep/clinical-labs/obtain-permit) and test- specific approval prior to initiating testing on specimens originating from NYS. Examples of testing performed for participant management include those that influence enrollment (exclusion or inclusion), safety, or dosing."

Laboratory Developed Test (NYS DOH): LDTs used in Clinical Trials: Laboratories performing tests on specimens from trial participants for participant management under IRB-approved research or clinical trials protocols, where the results are reported and are used for clinical decision making, are required to obtain a NYS clinical laboratory permit and test-specific approval prior to initiating testing on specimens originating from NYS.

Genetic Test results see section 26.6.2.

10.5. Continuing Review

The IRB will conduct continuing review of ongoing research requiring review by the convened IRB at intervals that are appropriate to the level of risk of the research, but not less than once per year, except as described below.

Unless the IRB determines otherwise, continuing review of research is not required in the following circumstances:

- Research eligible for expedited review in accordance with 45 CFR 46.110;
- Research reviewed by the IRB in accordance with the limited IRB review described in Section 5;
- Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
    - Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
    - Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

The SJH/SPHP IRB may determine that continuing review is required for any research protocol that falls within the above criteria. For example, the IRB may determine that continuing review is required when:

1. Required by other applicable regulations (e.g., FDA);
2. The research involves topics, procedures, or data that may be considered sensitive or controversial;

3. The research involves particularly vulnerable subjects or circumstances that increase subject vulnerability;
4. An investigator has minimal experience in research or the research type, topic, or procedures; and/or
5. An investigator has a history of noncompliance

When the SJH/SPHP IRB determines that continuing review is required for such research, it will document the rationale in the IRB record and communicate the requirement to the investigator in the IRB determination letter.

Even when continuing review is not required for a project, the study team must still:

- Submit amendments for project changes, including changes to the study team,
- Report unanticipated problems, complaints, or other reportable events,
- Maintain required human subjects training,
- Terminate the project once it ends, or when personal identifiers are removed from the data/biospecimens and all codes and keys are destroyed.

The SJH/SPHP IRB may re-evaluate its decision that continuing review is not required for a project depending on the type of change(s) proposed in an amendment (e.g., protocol change that increase subject risk), or as an outcome of the IRB's review of unanticipated problems, complaints, or other reportable events.

There is no exception to the requirement for continuing review in FDA regulations. The IRB will conduct continuing review of ongoing FDA-regulated research, and any research where it is required as a condition of funding or contractually, at intervals that are appropriate to the level of risk of the research, but not less than once per year, as long as the research remains active. The date by which continuing review must occur (the expiration date) will be recorded in the IRBManager and on initial and continuing review approval letters.

10.5.1. Continuing Review Process

As a courtesy to investigators, IRBManager, will send out reminder notices to investigators 60 and 45 days in advance of the expiration date; however, it is the responsibility of the investigator to ensure that the continuing review of ongoing research is approved prior to the expiration date.

The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of the IRB approval.

Investigators should submit continuing review materials 21 Days Prior to the IRB meeting date in which it must be reviewed (i.e., the meeting prior to the expiration date) or 14 Days Prior to the expiration date, for studies eligible for expedited review. This allows sufficient time for IRB review before the expiration date.

Investigators must submit the following for continuing review, as applicable to the research:

1. The Continuing Review Renewal Form (this serves as the progress report).
2. The current consent document(s) in Microsoft word with no tracked changes.
3. The most recent signed consent document (with the subject name and any other

identifiers blacked-out).
4. The most recent report from the DSMB or DMC.
5. The most recent annual report or progress report to the FDA and/or funding agency.
6. Any previously un-submitted reports identified while completing the Continuing Review Renewal Form.

IRB members/expedited reviewers have access to study materials via the IRBManager and can request any additional materials required for their review from the HRPP Administrator.

10.5.2. Convened Board Review

In conducting continuing review of research not eligible for expedited review, IRB members will be directed to conduct a substantive review of the materials submitted for continuing review along with all study history residing in IRBManager. The IRB Chair, Vice Chair, HRPP Administrator or other IRB Member designated by the Chair will lead the discussion at the convened meeting regarding the study, including its aims, progress, history, and assessment of whether or not the approval criteria continue to be met.

10.5.3. Expedited Review

Generally, research approved by expedited review will not require continuing review under the Common Rule (See Section 10.5) unless the reviewer determines that continuing review is required, and the rationale is documented.

When continuing review is required, the reviewers have access to all materials submitted for continuing review as well as all study history residing in IRBManager.

The reviewer may use a checklist to determine whether the research meets the criteria allowing continuing review using the expedited procedure, and if so, whether the research continues to meet the regulatory criteria for approval.

Generally, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, unless it has progressed to the point that it involves only one or both of the following:

- Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
- Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

and in limited circumstances described by expedited review categories (7) and (8) (see Expedited Review Categories in Section 10.1.2). It is also possible that research activities that previously qualified for expedited review, have changed or will change, such that expedited continuing review would no longer be permitted.

If the study does not require continuing review, the PI will receive a courtesy automated email (via IRBManager) at about 6 and 11 months after approval, with the following information:

Even though the SJH/SPHP IRB has determined this study does not require formal continuing review, you are still required to:

- Submit amendments for project changes, including changes to the study team prior to implementing any changes (unless necessary to eliminate an immediate hazard to the subject, in which case the IRB should be promptly notified).
- Report any unanticipated problems, complaints or other reportable events.
- Maintain required human subjects training.
- Terminate the project (by submitting a termination form) once it ends, or when personal identifiers are removed from the data/biospecimens and all codes and keys are destroyed.

10.5.4. Lapses in Continuing Review

The regulations permit no grace period or approval extension after approval expiration. Research that continues after the approval period has expired is research conducted without IRB approval. If the continuing review does not occur before the study expires, all research activities must stop, including recruitment (media advertisements must be withdrawn), enrollment, consent, interventions, interactions, and data collection, unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. **This will occur even if the investigator has submitted the continuing information before the expiration date. Therefore, investigators must allow sufficient time for IRB review and approval before the expiration date.**

The electronic management system notifies the investigator of the expiration of approval with notice that research activities must stop. With this notice, the PI is advised to immediately submit to the IRB a list of any currently enrolled research subjects (identified by Study #) for whom suspension of the research would cause harm. Enrollment of new subjects cannot occur, and continuation of research interventions or interactions for already enrolled subjects should only continue, when the IRB or the IRB Chair finds that it is in the best interest of the individual subjects to do so.

Once approval has expired, the IRB review and re-approval must occur prior to re-initiation of the research. If the study approval has lapsed more than 90 days and the PI has not provided the required continuing review information, the PI may be required to submit a new application to the IRB for review and approval. If the study approval has lapsed 90 days or less and the PI provides the required continuing review information, the existing protocol may be reviewed for consideration of continued IRB approval.

If the IRB requires modifications at the time of continuing review, and the approval expires before the IRB has reviewed and approved the response, all activities involving human subjects, or their tissue/data must be stopped as described above.

The lapse of IRB approval due to a failure to complete continuing review and obtain re-approval prior to expiration of the prior approval does not ordinarily constitute a suspension or termination of IRB approval, for federal reporting purposes; however, the failure to meet continuing review obligations may be grounds for suspension or termination of the research. If the IRB notes a pattern of noncompliance with the requirements for continuing review (e.g., an investigator repeatedly or deliberately neglects to submit materials for continuing review in a timely fashion or the IRB itself is not meeting the continuing review dates), the IRB should determine the reasons for the non-compliance and take appropriate corrective actions. When research is subject to federal reporting mandates, the IRB must report to FDA/OHRP any instance of serious or continuing noncompliance with FDA regulations or IRB requirements or determinations.

10.6. Modification of an Approved Protocol

Investigators may wish to modify or amend approved research. **Investigators must obtain IRB approval before making any changes, no matter how minor, in approved research** unless the change is necessary to eliminate apparent immediate hazards to the subject (in which case the IRB must then be notified at once).

Investigators should consider whether the proposed changes to the research alter the original scope, purpose, or intent of the research. When the research itself is fundamentally changed, the IRB may require a new study submission rather than allow such changes to be made through a modification to the existing research plan.

10.6.1. Procedures

Investigators must submit to the IRB a Modification Form and any and all revised documents that are impacted by the modification, as well as a justification and summary of changes, and track-changed materials whenever possible.

The modifications may not be implemented until the IRB has reviewed and approved the proposed changes. When the modification involves the addition of investigators or study personnel, the investigators/personnel may not assume any study responsibilities involving human subjects or their identifiable data until the IRB has approved their participation.

The HRPP Administrator will review the submission and make an initial determination whether the proposed changes may be approved through an expedited review process (if the changes are minor and not increasing risk), or whether the modification warrants full board review. If expedited, the IRB reviewer(s) has the ultimate responsibility to determine that the proposed changes may be approved through the expedited review procedure and, if not, must defer the study to full board review.

10.6.2. Convened Board Review of Modifications

When a proposed change in a convened board research study is not minor, or when a proposed change to an expedited study renders it no longer eligible for expedited review, the IRB must review and approve the proposed change at a convened meeting before the change can be implemented. The only exception is implementation of a change necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB must be promptly informed of the change following its implementation and will review the change to determine whether it was consistent with ensuring the continued welfare of subjects.

All documents provided by the investigator are accessible to all IRB members.

At the meeting, the IRB Chair (or other IRB member) presents an overview of the proposed modifications to lead the IRB through the criteria for approval and evaluating whether the modification alters any previous determinations (e.g., the risk determination), or necessitates any additional determinations (e.g., for vulnerable populations).

When the IRB reviews modifications to previously approved research, the IRB considers whether information about those modifications might relate to subjects' welfare or willingness to continue to take

part in the research, and, if so, whether to provide that information to subjects.

10.6.3. Expedited review of Modifications

An IRB may use expedited review procedures to review changes to expedited research (as long as the proposed changes would not make the research no longer eligible for expedited review) and for minor changes to studies normally subject to full board review. Expedited reviews are carried out by the IRB Chair, Vice Chair, HRPP Administrator or designee(s) among the IRB members.

Expedited reviewer(s) determine whether the modifications meet the criteria allowing review using the expedited procedure (i.e., changes to expedited research that do not alter the eligibility of the research for expedited review or minor changes to full board studies), and, if so, whether the research with the proposed modifications continues to meet the regulatory criteria for approval.

The reviewer will also consider whether information about the modifications might relate to subjects' welfare or willingness to continue to take part in the research, and, if so, whether to provide that information to subjects.

10.6.4. Protocol Exceptions

Protocol exceptions are circumstances in which the investigator wishes to deviate from eligibility criteria or one or more of the specific procedures called for in a research plan. Unlike modifications that apply to all subsequent subjects in the research, a protocol/research plan exception only applies to a specific subject or group of subjects.

Exceptions are planned, and the investigator gets approval from the IRB ahead of time. For sponsored research, prior approval from the sponsor is generally required. Depending on the nature of the exception, an expedited review may be possible. For an exception to be approved under expedited review, the research as a whole must be eligible for expedited review, or, for convened board research, the proposed exceptions must not increase risk or decrease benefit, negatively impact the risk/benefit analysis, negatively affect the participant's rights, safety, or welfare, or negatively affect the integrity of the resultant data.

Procedures for exceptions are the same as for a Protocol Modification. The investigator must submit an "Modification Form" along with any new or revised materials, and documentation of sponsor approval, if applicable.

The only time a Protocol/Research Plan exception would not require prior sponsor or IRB approval is when the exception is necessary to avoid an apparent immediate hazard to the subject(s). In such cases, the exception must be submitted to the IRB as soon as possible.

10.7. Closure of Research Studies

The completion or early termination of a study, is a change in research activity and must be reported to the IRB. Although subjects will no longer be "at risk" under the study, a final report to the IRB allows it to close its files as well as providing information that may be used by the IRB in the evaluation and approval of related studies.

Studies may be closed when the involvement of human subjects ceases (interventions, interactions,

observations, and the gathering, use, study, and analysis of identifiable private information, including specimens, are all complete).

For multi-center research, the study may be closed once all research activities (as above) are complete at SJH/SPHP and any sites for which the IRB is serving as the "IRB of record". If the investigator is serving as the lead investigator or the site is the coordinating center, the study must remain open as long as the lead investigator or coordinating center is still receiving, studying, using, or analyzing identifiable private information from other sites (even if local interventions, interactions, observations, and data gathering is complete).

Investigators may submit study closures to the IRB on a Closure Form. With closure submissions, the investigator must provide a summary of the research activity and any findings available at that time.

Investigators may maintain the data that they collected, including identifiable private data, if this is consistent with the IRB-approved research plan. However, investigators may not conduct any additional analysis of identified data without applying for IRB approval or exemption.

Investigators must continue to protect the confidentiality of the data as described to the IRB and honor any other commitments that were agreed to as part of the approved research including, for example, future use of data or specimens, provision of research results to subjects, and provision of any outstanding payments or compensation.

The HRPP Administrator will review study closure reports, typically by administrative review, and either acknowledge the closure of the study or request additional information or confirmation of facts from the investigator.

11. Study Suspension, Termination & Holds

11.1. Suspension/Termination/Holds

IRB approval may be suspended or terminated if research is not being conducted in accordance with IRB or regulatory requirements or if the research has been associated with unexpected problems or serious harm to subjects. (See Section 16 for a discussion of unanticipated problems and Section 17 for a discussion of noncompliance.) The IRB has the authority to suspend or terminate research. This authority applies to all research subject to IRB approval, including exempt research with limited IRB review and research for which IRB continuing review is no longer required.

Suspension of IRB approval is a directive of the convened IRB, IRB Chair, IRB Vice Chair, or the IO to temporarily stop some or all previously approved research activities. Suspended protocols remain open and require continuing review. Termination of IRB approval is a directive of the convened IRB to stop all activities in a previously approved research protocol. Terminated protocols are considered closed and no longer require continuing review.

The IRB shall notify the PI in writing of such suspensions or terminations and shall include a statement of the reasons for the action of the IRB. The investigator shall be provided with an opportunity to respond in person/writing in 30 days.

The IRB Chair, IRB Vice Chair, or IO may suspend research to ensure protection of the rights and welfare of subjects. Suspension directives made by these individuals must be reviewed by the convened IRB for

further deliberation and actions, including but not limited to continuing the suspension, requiring changes to the research, or study termination.

Research may only be terminated by the convened IRB. Termination of studies approved under expedited review must be made by the convened IRB.

If the sponsor/PI requests that a study be put on HOLD, the IRB Chair or Vice Chair will review the rationale for the Hold and determine what, if any, actions are needed to protect the rights and welfare of currently and/or formerly enrolled subjects. The study may remain open during the Hold; however, before study activities resume, the Convened Board, IRB Chair or Vice Chair must approve study continuation. All reporting requirements must continue during the study Hold (e.g. reporting complaints or unanticipated problems & submission of continuing review materials).

When study approval is suspended or terminated by the convened IRB or an authorized individual, consideration will also be made of actions needed to protect the rights and welfare of currently and/or formerly enrolled subjects, e.g., informing them of the suspension/termination, procedures that are needed to withdraw them safely such as transferring currently enrolled subjects to another investigator; making arrangements for care or follow-up outside the research; allowing continuation of some research activities; or requiring or permitting follow-up of subjects for safety reasons.

If follow-up of subjects for safety reasons is permitted/required by the convened IRB or individual ordering the suspension or termination, the convened IRB or individual ordering the suspension or termination will require that any adverse events/outcomes be reported to the IRB and the sponsor.

The investigator MUST continue to provide reports on adverse events and unanticipated problems to both the IRB and sponsor just as if there had never been a suspension (i.e. all events that need to be reported during a study need to continue to be reported during the suspension period). *Refer to Section 20 for a detailed discussion of reporting requirements*

12. Documentation and Records

SJH/SPHP prepares and maintains adequate documentation of the IRB's activities. All records are accessible for inspection and copying by authorized representatives of the FDA, OHRP, sponsors, and other authorized entities at reasonable times and in a reasonable manner.

12.1. IRB Records

IRB records include, but are not limited to:

1. Written policies and operating procedures;
2. IRB membership rosters;
3. IRB correspondence including reports to regulatory agencies;
4. IRB study Files (See Section 12.2);
5. Documentation of exemptions including exemptions related to emergency uses; and when limited IRB review is a condition of exemption;
6. Convened IRB meeting minutes;
7. Documentation of review by an external IRB, when appropriate;
8. Documentation of IRB reliance and cooperative review agreements (see section 6);

9. Documentation of independent or external investigator agreements;
10. Federal Wide Assurances.

12.2. IRB Study Files

SJH/SPHP will maintain an electronic study file, under a unique identification number assigned by the system, for each IRB study submission that is submitted via the electronic management system for review.

As applicable, protocol files include, but are not limited to the following:

1. Protocol and all other documents submitted as part of a new study submission;
2. Modification requests and all associated documents and materials;
3. Continuing review/progress reports and all associated documents and materials, including the rationale for conducting continuing review of research that otherwise would not require continuing review as described in Section 10.5;
4. Closure reports and all associated documents and materials;
5. Reports submitted after study or HUD approval including reports of significant new findings, DSM reports, protocol violation reports, complaints, noncompliance, and reports of injuries to subjects including reports of potential unanticipated adverse device events and unanticipated problems involving risks to subjects or others;
6. IRB-approved consent, parental permission, and assent forms;
7. Documentation of scientific or scholarly review (if available);
8. Documentation of the type of IRB review. For exempt determinations and expedited review, this will include the category under which the review is allowed;
9. For expedited review, documentation of any findings and determinations required by the regulations and study-specific findings supporting those determinations, including, but not limited to, waiver or alteration of consent, waiver of documentation of consent, research involving pregnant women, fetuses, and neonates, research involving prisoners, and research involving children. For research reviewed by the convened board these findings and determinations are recorded in the minutes;
10. For expedited review, documentation of the risk determination and period of approval (when continuing review is required). For research reviewed by the convened board these determinations are recorded in the minutes;
11. For expedited review, the rationale for an expedited reviewer's determination under 45 CFR 46.110(b)(1)(i) that research appearing on the expedited review list described in 45 CFR 46.110(a) is more than minimal risk.
12. Documentation of all IRB review actions;
13. Notification of expiration of IRB approval to the investigator;
14. Notification of suspension or termination of research;
15. Letters to investigator informing them of IRB review outcomes;
16. IRB correspondence to and from investigators related to the protocol;
17. For studies evaluating the safety or effectiveness of medical devices, documentation of the device determination (exempt, non-significant risk, significant risk);
18. Reports of unanticipated problems involving risk to subjects or others; and
19. Any statements of significant new findings provided to subjects.

12.3. IRB Minutes

1. Proceedings must be written and available for review by the next regularly scheduled IRB meeting date. A copy of the minutes are provided to the IO. The IRB minutes, once approved, may not be altered by any persons of authority except with the concurrence and approval of the convened IRB.

Minutes of the IRB meetings must contain sufficient detail to show:

2. Attendance
    a. Names of members or alternates present;
    b. Names of any consultants present;
    c. Names of any investigators present; and
    d. Names of guests/visitors present.

The vote on each action will reflect those members present for the vote on that item. Members who recuse themselves because of COI are listed by name.

3. The presence of a quorum throughout the meeting, including the presence of one member whose primary concern is in a non-scientific area.
4. Business Items discussed.
5. Continuing Education.
6. Actions taken, including separate deliberations, actions, and votes for each protocol undergoing initial review, continuing review, or review of modifications by the convened the IRB.
7. Votes on these actions (total number voting; number voting for; number voting against; number abstaining; number of those recused).
8. Basis or justification for these actions including required changes in research.
9. Summary of controverted issues and their resolution.
10. Approval period for initial and continuing reviews, when applicable, including identification of research that warrants review more often than annually and the basis for that determination.
11. The rationale for requiring continuing review of research that otherwise would not require continuing review as described in Section 10.5;
12. Risk level for initial and continuing approved protocols.
13. Justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document.
14. Protocol-specific documentation that the research meets the required criteria [45 CFR 46.116(d)] when approving a consent procedure that does not include or that alters some or all of the required elements of informed consent, or when waiving the requirement to obtain informed consent altogether. Alternatively, the IRB may cite concurrence with the justifications as presented by the investigator on submission materials (or as modified per the IRB). This documentation may also be available in a supporting meeting document or checklist.
15. Protocol-specific documentation that the research meets the required criteria [45 CFR 46.117(c)] when the requirements for documentation of consent are waived. Alternatively, the IRB may cite concurrence with the justifications as presented by the investigator on submission materials (or as modified per the IRB). This documentation may also be available in a

supporting meeting document or checklist.

16. When approving research that involves populations covered by Subparts B, C, or D of 45 CFR 46, the minutes and/or supporting meeting document(s) will document the IRB's justifications and findings regarding the determinations stated in the Subparts. Supporting documents may include the checklist for research on children; the checklist for pregnant women, fetuses and neonates; the checklist for prisoners. Alternatively, the IRB may cite concurrence with the justifications as presented by the investigator on submission materials (or as modified per the IRB).
17. The rationale for significant risk/non-significant risk device determinations.
18. Determinations of COI and review of management plans.
19. Identification of any research for which there is need for verification from sources other than the investigator that no material changes are made in the research.
20. A list of research approved since the last meeting utilizing expedited review procedures, including limited IRB reviews conducted using expedited procedures.
21. An indication that, when an IRB member has a conflicting interest (see Section 23.2) with the research under review, the IRB member did not vote.
22. Key information provided by consultants will be documented in the minutes or in a report provided by the consultant.

12.4. IRB Membership Roster

A membership list of IRB members will be maintained. The list will contain the following information about members:

1. Name
2. Earned degrees.
3. Affiliated or non-affiliated status (neither the member nor an immediate family member of the member may be affiliated with the SJH/SPHP).
4. Status as scientist or non-scientist. Members whose training, background, and occupation would incline them to view scientific activities from the standpoint of someone within a behavioral or biomedical research discipline are considered a scientist for the purposes of the roster. Members whose training, background, and occupation would incline them to view research activities from a standpoint outside of any biomedical or behavioral scientific discipline are considered a nonscientist. Physicians, nurses, and pharmacists are considered scientists.
5. Indications of experience (specialties, etc.) sufficient to describe each member's chief anticipated contributions to IRB deliberations.
6. Role on the IRB (Chair, Vice-Chair, etc.).
7. For alternate members, the primary member for whom the member could substitute.

The IRB office must keep the IRB membership list current. The IO or designee reports changes in IRB membership to the OHRP and DHHS. Changes in IO or IRB Chair will be reported promptly.

12.5. Documentation of Exemptions

Documentation of the specific exempt category will be included in IRBManager in order to ensure that the activity described in the investigator's request satisfies the conditions of the cited exempt category

as detailed in Section 5. When an exemption includes limited IRB review, the documentation will include this fact and the IRB action taken on those aspects of the research subject to limited IRB review in accordance with the procedures described for the review procedures used (expedited or convened board) elsewhere in this manual.

12.6. Documentation of Expedited Reviews

IRB records for initial and continuing review by the expedited procedure must include the specific permissible category and that the activity described by the investigator satisfies all of the criteria for approval under expedited review (as detailed in section 10.3). If the expedited reviewer determines that continuing review is required, the justification will be documented along with the approval period. Any determinations required by the regulations including study-specific information supporting those determinations will also be documented.

12.7. Access to IRB Records

IRB protocol files are secured in IRBManager with administrative access controlled by the IRB office. Likewise, investigators control access to investigator records in the electronic system. All other IRB records (e.g., membership rosters) are kept secure in a limited access file on SJH/SPHP computers, or in filing cabinets within a locked office. Access to IRB records is limited to the IO, HRPP and HRPP Administrator, IRB Chair, Vice Chair and members, authorized organizational officials, and officials of federal and state regulatory agencies (e.g., OHRP, FDA). Appropriate accreditation bodies are provided access.

Records are accessible for inspection and copying by authorized representatives of federal and state regulatory agencies during regular business hours.

Paper records may not be removed from the IRB Office; however, the HRPP Administrator will provide copies of records for authorized personnel if requested.

All other access to IRB records is limited to those who have legitimate need for them, as determined by the IO and HRPP Administrator.

12.8. IRB Record Retention

In order to comply with the requirements of OHRP, FDA, and HIPAA, IRB records are maintained for at least six (6) years after completion of the research.

IRB records for research cancelled without participant enrollment will be retained for at least three (3) years after closure.

IRB minutes are retained until all of the studies that were reviewed at that meeting have been completed for at least three (3) years.

After the noted times, IRB records may be shredded or otherwise securely destroyed.

All documentation related to studies granted initial approval by the IRB from January 1, 2004 through October 26, 2017 will have been filed by study name or SJH/SPHP-IRB numeric assignment and maintained in a manner such that they are reasonably available to the IRB, regulatory agencies, and accreditation organizations. All

documentation related to studies submitted after October 26, 2017 will be filed by chronological date of receipt in IRBManager.

13. Obtaining Informed Consent from Research Subjects

No investigator conducting research under the auspices of SJH/SPHP may involve a human being as a subject in research without obtaining the legally effective informed consent of the subject or the subject's legally authorized representative (LAR) unless a waiver of consent has been approved by the IRB of record. Except as provided in Sections 13.10, 13.11, and 13.12 of these procedures, informed consent must be documented using a written consent form approved by the IRB.

The IRB will evaluate both the consent process and the procedures for documenting informed consent to ensure that adequate informed consent is obtained from subjects.

The following procedures describe the requirements for obtaining consent from subjects in research conducted under the auspices of SJH/SPHP.

13.1. General Requirements

The requirement to obtain the legally effective informed consent of individuals before involving them in research is one of the central protections provided for by the federal regulations and the SJH/SPHP HRPP. Investigators are required to obtain legally effective informed consent from a subject or their LAR unless the requirement has been waived by the IRB. When informed consent is required, it must be sought prospectively, and properly documented

Except as provided elsewhere in these SOPs:

1. Before involving a human subject in research, an investigator shall obtain the legally effective informed consent of the subject or their LAR.
2. An investigator shall seek informed consent only under circumstances that provide the prospective subject or the LAR sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or undue influence.
3. The information that is given to the subject or the LAR shall be in a language understandable to the subject or the LAR.
4. The prospective subject or the LAR must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.
5. Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or LAR in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension

   Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or LAR's understanding of the reasons why one might or might not want to participate.

6. No informed consent may include any exculpatory language through which the subject or the LAR is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

7. If a participant enrolls in a study without valid informed consent (e.g. participation in a study without the presence of a valid informed consent document or participant comprehension of the elements of informed consent is called into question), the principal investigator (PI) must immediately notify the IRB Chairperson or HRPP Administrator to explain the situation. The IRB will provide guidance on how to proceed.

   The PI should request that the participant re-consent to participate. If the participant agrees and the complete informed consent process is repeated, including signatures on the consent document and documentation of consent in the research record, data obtained during the period of invalid consent may be used with approval of the Study Sponsor and IRB.

These informed consent requirements are not intended to preempt any applicable federal, state, or local laws (including tribal laws passed by the official governing body of an American Indian or Alaska Native tribe) that have additional requirements for informed consent to be legally effective.

The informed consent process involves three key features: (1) disclosing to the prospective human subject information needed to make an informed decision; (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether or not to participate in the Research.

Informed consent is more than just a signature on a form. It is a process of information exchange to include reading, discussing, receiving answers to any questions, and signing the consent document. The informed consent process is the critical communication link between the prospective human subject and an investigator, beginning with the initial approach by an investigator and continuing through the completion of the research study. Investigators must have received the appropriate training and be knowledgeable about the study procedures, potential risks, anticipated benefits, and alternatives in order that they may appropriately describe the research and answer questions. The exchange of information between the investigator and study participant can occur via one or more of the following modes of communication, among others; face to face dialogue; mail; electronic interface, telephone, or fax; however, obtaining informed consent must allow for a dialogue so that the potential subject has the opportunity to ask questions and receive responses. Investigators must obtain consent prior to entering a subject into a study, gathering data about a subject, and/or conducting any procedures required by the research plan, unless consent is waived by the IRB. *See Section 13.10.1 for an exclusion for certain screening and recruitment activities.*

If someone other than the investigator conducts the interview and obtains consent, the investigator needs to formally delegate this responsibility, and the person so delegated must have received appropriate training to perform this activity. The person so delegated must be knowledgeable about the research to be conducted and the consenting process and must have the expertise be able to answer questions about the study including those regarding risks, procedures, and alternatives. The SJH/SPHP Application form solicits information regarding who will obtain consent; proposed changes to the

personnel authorized to obtain consent must be submitted to the SJH/SPHP IRB for approval.

Sample or draft consent documents may be developed by a sponsor or network. However, the IRB of record is the final authority on the content of the consent documents that are presented to prospective subjects

13.2. Additional Requirements

Informed consent must be obtained under the following circumstances:

1 Informed consent may only be obtained from subjects who have the legal and mental capacity to give consent. For subjects without that capacity, permission must be obtained from a legal guardian with appropriate authority to make decisions regarding the activities called for in the research or a legally authorized representative (LAR);
2. The informed consent information must be presented in language that is understandable to the subject (or LAR/guardian). To the extent possible, the language should be understandable by a person who is educated to 8th grade level and layman's terms shall be used in the description of the research. The IRB may require or allow different readability standards based upon the characteristics of the target subject population;
3. For subjects with Limited English Proficiency (LEP), informed consent must be obtained in a language that is understandable to the subject (or LAR/guardian). In accordance with this policy, the SJH/SPHP IRB requires that informed consent discussions include a reliable interpreter when the prospective subject does not understand the language of the person who is obtaining consent, and, in most circumstances, that consent materials are translated;
4. The investigator is responsible for ensuring that each prospective subject is adequately informed about all aspects of the research and understands the information provided.

13.3. Legally Authorized Representative (LAR)

It is SJH/SPHP's policy to follow the NY state law for LAR's for treatment (see below).

A Legally Authorized Representative (LAR) is defined by 45 CFR 46.102(c) and 21 CFR 50.3 as *"an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research."*

New York State: Per the Family Health Care Decisions Act (FHCDA), a person in the highest category on the following surrogate list who is available, willing and competent to make decisions for the incapable patient, and is identified when there is no health care agent:

1. A court-appointed guardian (per NYS Mental Health Law Article 81);
2. An individual designated as a representative/agent through a health care proxy that is appropriately executed. For a health care proxy to be effective, it must have been signed at a time when the subject had decision-making capacity. The subject's wishes, if any, with regard to research as expressed in the health care proxy govern (e.g. prohibiting all research or permitting only research which may provide a direct benefit);
3. The spouse, if not legally separated from the patient, or the domestic partner;
4. A son or daughter eighteen years of age or older;

5. A parent;
6. A brother or sister eighteen years of age or older; or
7. A close friend (meaning a person eighteen (18) years of age or older who has maintained such regular contact with the subject as to be familiar with the subject's activities, health and beliefs).

LARs should be well informed regarding their roles and responsibilities when asked to provide surrogate consent. In addition to the consent information, LARs should be informed that their obligation is to try to determine what the potential subject would do if able to provide consent, or if the potential subject's wishes cannot be determined, what they think is in the person's best interest.

Investigators must describe the intended use of LARs in their submission to the IRB. The IRB determines whether the use of LARs is appropriate for a given research study. Further discussion and procedures for assessment of capacity and inclusion of adults with impaired decision-making capacity in research are described in Section 14.7.

13.4. Basic Elements of Informed Consent

To be valid, the consent process must provide the following basic elements of information to potential subjects:

1. A 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 others which 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 must be maintained;
6. **For research involving more than minimal risk**, an explanation as to whether any compensation **and** an explanation as to whether any medical treatments are available if injury occurs **and**, if so, what they consist of, or where further information may be obtained;
7. An **explanation of whom to contact** for answers to pertinent questions about the research **and** research subjects' rights, **and** whom to contact in the event of a research-related injury to the subject;
8. A statement that participation is **voluntary**, refusal to participate will involve **no penalty or loss of benefits** to which the subject is otherwise entitled, and the subject **may discontinue participation** at any time without penalty or loss of benefits to which the subject is otherwise entitled;
9. One of the following statements about any research that involves the **collection of identifiable private information or identifiable biospecimens**:
    a. A statement that **identifiers might be removed** from the identifiable private information or identifiable biospecimens **and that**, after such removal, the information or biospecimens **could be used** for future research studies or distributed to another investigator for future

research studies **without additional informed consent** from the subject or the legally authorized representative, if this might be a possibility; or

b. A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, **will not be used or distributed** for future research studies.

10. For **FDA-regulated studies**, a statement that notes the possibility that the Food and Drug Administration may inspect the records;

11. For applicable **FDA-regulated clinical trials,** the following statement must be included verbatim:

"A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this website at any time."

13.5. Additional elements of informed consent to be applied, as appropriate:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
3. Any additional costs to the subject that may result from participation in the research;
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject;
6. The approximate number of subjects involved in the study (e.g. include when the research involves more than minimal risk);
7. A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
8. A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions;
9. For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

13.6. SJH/SPHP Requirements

In addition to the federal elements of consent described above, SJH/SPHP has defined specific additional information that must be included in consent documents when applicable to the research (e.g., Injury information, HIPAA language). A list of these requirements is provided in the IRBManager and the IRB Website for investigator and reviewer reference. Template consent forms, also include SJH/SPHP required language.

13.7. Subject Withdrawal or Termination

A subject enrolled in a research study may decide to withdraw from the research, or an investigator may decide to terminate a subject's participation in research regardless of whether the subject wishes to continue participating. Investigators must plan for the possibility that subjects will withdraw from research and include a discussion of what withdrawal will mean and how it will be handled in their research protocols and consent documents.

When seeking informed consent from subjects, the following information regarding data retention and use must be included:

i. For FDA-regulated clinical trials: When a subject withdraws from a study, the data collected on the subject to the point of withdrawal remain part of the study database and may not be removed. This should be disclosed in the consent; or

ii. For research not subject to FDA regulations: The investigator should inform subjects whether the investigator or study sponsor intends to either: (1) retain and analyze already collected data relating to the subject up to the time of subject withdrawal; or (2) honor a research subject's request that the investigator or study sponsor will destroy the subject's data or that the investigator or study sponsor will exclude the subject's data from any analysis.

When a subject's withdrawal request is limited to discontinuation of the primary interventional component of a research study, research activities involving other types of participation for which the subject previously gave consent may continue. Investigators should ask a subject who is withdrawing whether the subject wishes to participate in continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and procedures and continued follow-up in person, by phone, or via records review.

If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up as described in the previous paragraph, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original consent document). IRB approval of consent documents for these purposes would be required.

If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up, the investigator must not access or gather private information about the subject for purposes related to the study. However, an investigator may review study data related to the subject collected prior to the withdrawal of the subject from the study, and may consult public records, such as those establishing survival status.

13.8. Documentation of Informed Consent

Except as provided in Sections 13.10, 13.11 and 13.12, of this document, informed consent must be documented by the use of a written consent form approved by the IRB.

1. Informed consent is documented by the use of a written consent form approved by the IRB and signed (including in an electronic format) and dated by the subject or the subject's LAR at the time of consent;

2. For research conducted in accordance with ICH-GCP E6 (See Section 25) or in facilities subject to Joint Commission requirements, the name of the person who obtained consent and the date they did so is documented on the written consent form;
3. A written copy of the signed and dated consent form must be given to the person signing the form. The investigator should retain the signed original in the research records. When appropriate, a copy of the consent form is uploaded into the electronic health record;

The consent form may be either of the following:

1. A written consent document that embodies the basic and required additional elements of informed consent. The investigator shall give either the subject or the subject's LAR adequate opportunity to read the informed consent form before it is signed; alternatively, this form may be read to the subject or the subject's legally authorized representative; **or**

   A short form written consent document stating that the elements of informed consent have been presented orally to the subject or their LAR and that the key information required by Section 13.1 #5 was presented first to the subject, before other information, if any, was provided. When this method is used:

   a. The oral presentation and the short form written document should be in a language understandable to the subject; and
   b. There must be a witness to the oral presentation; and
   c. The IRB must approve a written summary of what is to be said to the subject (the approved full consent document may serve as this summary); and
   d. The short form document is signed by the subject or representative;
   e. The witness must sign both the short form and a copy of the summary; and
   f. The person actually obtaining consent must sign a copy of the summary; and
   g. A copy of the summary must be given to the subject or representative, in addition to a copy of the short form.

   When the short form procedure is used with subjects who do not speak English, or have Limited English Proficiency (LEP);

   i. the oral presentation and the short form written document should be in a language understandable to the subject;
   ii. the IRB-approved English language informed consent document may serve as the summary;
   iii. the witness should be fluent in both English and the language of the subject. When the person obtaining consent is assisted by an interpreter, the interpreter may serve as the witness.

   The IRB must receive all foreign language versions of the short form document as a condition of approval. Expedited review of these versions is acceptable if the protocol/research plan, the full English language informed consent document, and the English version of the short form document have already been approved by the convened IRB.

   In addition to receiving a copy of the (English) summary and a copy of the short form at the time of consenting, the IRB may require that the subject be provided with a copy of the summary,

translated into their native language, as soon as possible after their enrollment into the study.

13.9. Special Consent Circumstances

13.9.1. Enrollment of Non-English Speakers as Research Subjects

1. **Expected enrollment**: In some studies, the investigator may be able to anticipate enrollment of persons who do not speak or read, or have limited proficiency in, oral or written English. When the target subject population includes such persons or the investigator or the IRB otherwise anticipates that consent will be conducted in a language other than English, the IRB requires a translated consent document and other subject materials, as applicable. Generally, translated consent forms should not be prepared until the final approved version of the English-language version is available. To ensure that translated documents are accurate, the IRB requires a certified translation.
2. **Unexpected enrollment:** If a person who does not speak or read, or has limited proficiency in, English unexpectedly presents for possible enrollment, an IRB-approved translated version of the written consent may not be available for use. Investigators should carefully consider the ethical and legal ramifications of enrolling subjects when a language barrier exists. If the subject does not clearly understand the information presented during the consent process or in subsequent discussions, his/her consent may not be informed or legally effective.

   If an investigator decides to enroll a subject into a study for which there is not an existing IRB-approved consent document in the prospective subject's language, the investigator must receive IRB approval to follow the procedures for a "short form" written consent as described in Section 13.8.
3. **Use of interpreters in the consent process:** Unless the person obtaining consent is fluent in the prospective subject's language, an interpreter will be necessary to facilitate the consent discussion. Preferably someone who is independent of the subject (i.e., not a family member) should assist in presenting information and obtaining consent. Whenever possible, interpreters should be provided copies of the translated consent, or short form and the IRB-approved consent script (typically the English-language version of the consent document), well before (24 to 48 hours if possible) the consent discussion with the subject. If the interpreter also serves as the witness, she/he may sign the translated consent, or short form consent document and summary, as the witness and should note "Interpreter" under the signature line. The person obtaining consent must document that the "short form" process was used in the subject's research record, including the name of the interpreter.

13.9.2. Braille consent

For blind subjects who read Braille, the IRB may approve a consent document prepared in Braille. To ensure that a Braille consent document is accurate, the IRB may require a transcription into print text or review of the document by an IRB member or other person who reads Braille. If possible, the subject will sign the Braille consent; otherwise verbal consent will be obtained, witnessed and documented as described under "Verbal Consent" (see Section 13.9.4).

13.9.3. Consenting in American Sign Language

For deaf subjects who are fluent in American Sign Language (ASL), the IRB may approve a consent process using ASL and the IRB-approved written consent form. When this process is approved, the individual authorized to consent prospective subjects must use an interpreter fluent in ASL to conduct the consent process and the documentation of the consent process must conform to the requirements set forth in Section 13.8.

13.9.4. Verbal (oral) Consent

When subjects are unable to read a written consent form (such as blind or illiterate subjects), the IRB may approve a verbal consent process, provided the subject (1) retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally and (2) is able to indicate approval or disapproval to study entry.

For research that is no more than minimal risk, documentation of consent may be waived if the criteria in Section 13.11 are met.

For greater than minimal risk research, the consent form must be read to the subjects and the subjects must be given an opportunity to ask questions. An audiotape approved by the IRB may also be used. If capable of doing so, the subject signs, or marks an X to signify consent. If that is not possible, the subject will provide verbal consent. The person obtaining consent and a witness will sign the written study consent form with a statement that documents that a verbal process was used and that the subject gave verbal consent or made their mark. The consent process will also be documented in the subject's research record. Signed copies of the consent form are given to the subject and, whenever possible, these documents should be provided to the subject on audio or video-tape.

13.9.5. Physically-Challenged Subjects

A person who is physically challenged (e.g., physically unable to talk or write) can enroll in research if competent and able to indicate voluntary consent to participate. Whenever possible, the subjects should sign the consent form or make their mark by initialing or making an X. As with verbal consent, a witness to the consent process is recommended and the circumstances and consent process should be carefully documented in the research records.

13.10. Waiver or Alteration of Informed Consent

An IRB may waive the requirement to obtain informed consent, provided the IRB finds and documents that all the below criteria are satisfied. An IRB may also approve a consent procedure that omits some, or alters some or all, of the basic and additional elements of informed consent (an "alteration"), provided that the IRB finds and documents that the below criteria are satisfied.

1. The research or clinical investigation involves no more than minimal risk to the subjects;
2. The research or clinical investigation could not practicably be carried out without requested waiver or alteration;
3. If the research involves using identifiable private information or identifiable biospecimens,

the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
4. The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
5. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

This option applies to both FDA-regulated and DHHS-conducted or supported research.

Public Benefit or Service Programs Waiver or Alterations

An IRB may waive the requirement to obtain informed consent in public benefit or service programs, provided the IRB finds and documents that all the below criteria are satisfied.

An IRB may also approve a consent procedure that omits some, or alters some or all, of the basic and additional elements of informed consent (an "alteration") (See Sections 13.4 and 13.5), provided that the IRB finds and documents that the below criteria are satisfied.

1. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
    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; and
2. The research could not practicably be carried out without the waiver or alteration. This option **does not** apply to FDA-regulated research.

13.10.1. Screening, recruiting, or determining eligibility

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

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

This option **does not** apply to FDA-regulated research.

13.11. Waiver of Documentation of Informed Consent

The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds **any** of the following:

1. The only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm from a breach of confidentiality (e.g., domestic violence research where the primary risk is discovery by the abuser). Each subject (or LAR) will be asked

whether they want documentation linking them with the research, and their wishes must govern. This option **does not** apply to FDA-regulated research.

OR

2. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Procedures such as non-sensitive surveys, questionnaires and interviews generally do not require written consent.
   This option **does** apply to FDA-regulated research (most commonly in the context of minimal risk screening activities that are necessary to determine eligibility for enrollment in a clinical trial).
3. If the subjects or LARs are members of a distinct cultural group or community in which signing forms is not the norm, the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.
   This option **does not** apply to FDA-regulated research.

Unless the IRB has granted a full waiver of the requirement to obtain informed consent, investigators who seek and receive approval for a waiver of documentation of consent still must perform an appropriate consent process.

In cases in which the documentation requirement is waived, the IRB requires the investigator to provide in the application materials a written summary of the information to be communicated to the subject, and the IRB will consider whether to require the investigator to provide subjects with a written statement regarding the research.

13.12. Waiver of Informed Consent for Planned Emergency Research

The conduct of planned research in life-threatening emergencies where the requirement to obtain prospective informed consent has been waived by the IRB is covered by 21 CFR 50.24 for FDA-regulated research and by the waiver articulated by DHHS at 61 FR 51531-33 for research that is not FDA-regulated.

The FDA exception from informed consent requirements for emergency research under FDA regulations permits planned research in an emergency setting when human subjects who are in need of emergency medical intervention cannot provide legally effective informed consent themselves, and there is generally insufficient time and opportunity to locate and obtain consent from their legally authorized representatives (LARs).

The Secretary of Health and Human Services (DHHS) has implemented an Emergency Research Consent Waiver under 45 CFR 46.101(i) with provisions equivalent to those of the FDA with the exception of the requirements specified in Sections 13.12.2.1 and 13.12.2.2 below. The DHHS waiver is not applicable to research involving prisoners, pregnant women, fetuses, or in vitro fertilization.

An exception from consent in emergency medicine research supported by the DoD is prohibited unless a waiver is obtained from the Secretary of Defense.

Most planned emergency research involves the use of an FDA regulated test article and is subject to FDA regulations *(21 CFR 50.24)*. The IRB recommends PIs who are planning emergency research to contact the compliance office for assistance at least 4-5 months prior to the planned start date. The requirements are very complex and include consultation within the organization, the community in which the research is to be conducted, the FDA, and the DHHS.

These Emergency Research policies and procedures apply to Planned Emergency Research. Planned Emergency Research is different from Emergency Single Time Use of a Test Article as regulated under FDA *21 CFR 56.104(c).*

13.12.1. Definitions

Planned Emergency Research. It is research that involves subjects who, are in a life-threatening situation for which available therapies or diagnostics are unproven or unsatisfactory, and because of the subjects' medical condition and the unavailability of legally authorized representatives of the subjects, it is generally not possible to obtain legally effective informed consent.

Family Member. For this section means any one of the following adult and legally competent persons: spouses; 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.

13.12.2. Procedures

The IRB may approve the planned emergency research without requiring informed consent of all research subjects prior to initiating the research intervention if the IRB finds and documents that the following conditions have been met:

1. 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.
2. Obtaining informed consent is not feasible because:
    a. The subjects will not be able to give their informed consent as a result of their medical condition;
    b. The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
    c. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.
3. Participation in the research holds out the prospect of direct benefit to the subjects because:
    a. Subjects are facing a life-threatening situation that necessitates intervention;
    b. 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
    c. Risks associated with the research 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.

4. The research could not practicably be carried out without the waiver.
5. The proposed research plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.
6. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sections 46.116 and 46.117 of 45 CFR 46 and Sections 50.20, 50.25 and 50.27 of 21 CFR 50. These procedures 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. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the research consistent with section 7(e) of this section.
7. Additional protections of the rights and welfare of the subjects will be provided, including, at least:
    a. Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the research will be conducted and from which the subjects will be drawn;
    b. Public disclosure to the communities in which the research 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;
    c. Public disclosure of sufficient information following completion of the research to apprise the community and investigators of the study, including the demographic characteristics of the research population, and its results;
    d. Establishment of an independent data monitoring committee to exercise oversight of the research; and
    e. If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the research. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

In addition, the IRB is responsible for ensuring that procedures are in place 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, of the subject's inclusion in the research, the details of the research and other information contained in the

informed consent document. The IRB shall also ensure that there is a procedure to inform the 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, 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. If a legally authorized representative or family member is told about the research and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into research with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the research is to be provided to the subject's legally authorized representative or family member, if feasible.

13.12.2.1. FDA-regulated Planned Emergency Research

A licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation must concur that the conditions described in Section 13.12.2 are satisfied.

Studies involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies that such studies may include subjects who are unable to consent. The submission of those studies in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for such investigations may not be submitted as amendments under 312.30 or 812.35.

If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided in the regulations 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.

The IRB determinations and documentation required in Section 13.12.2 and the above paragraph are to be 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 56.115(b).

13.12.2.2. Documentation and Reporting of Planned Emergency Research Not Subject to FDA Regulations

The IRB responsible for the review, approval, and continuing review of the research must approve both the research and a waiver of informed consent and have (i) found and documented that the research **is not** subject to regulations codified by the FDA at 21 CFR Part 50, and (ii) found and documented **and** reported to the OHRP that the conditions required in Section 13.12.2 have been met relative to the research.

13.13. Posting of Clinical Trial Consent Forms

For each clinical trial conducted or supported by a (Common Rule department or agency) Federal

department or agency, one IRB approved informed consent form used to enroll subjects **must be posted by the awardee or the Federal department or agency component conducting the trial** on a publicly available Federal Web site established as a repository for such informed consent forms. ClinicalTrials.gov has been identified as a publicly available federal website that will satisfy the consent form posting requirement.

If the Federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a Federal Web site (e.g. confidential commercial information), such Federal department or agency may permit or require redactions to the information posted.

The informed consent form must be posted on the Federal Web site after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

13.14. Need to Re-consent/assent

There may be situations where the researcher will need to re-consent/assent research participants. These include:

The IRB approves a significant change in the consent/assent document(s), and/or increase participant risk, which requires re-consent / assent of participants.

If the participant refuses to re-consent, participation in the study may be halted immediately and the collected data may or may not be used according to the previously signed consent form.

13.14.1. Procedures Re-Consenting/assent

Re-consenting should be carried out following the same procedures as the initial consent/assent and take place in person if possible.

However, re-consent by telephone may be approved by the IRB. If the IRB approves the use of the telephone the following steps must be taken:

1. The consent/assent document (revised consent/assent form or addendum) must be provided to the participant for review prior to the telephone consent process.
    a. The process requires the following: Study Participant, Study Personnel conducting re-consent and a Witness (the witness does not need to be part of the study team).
2. An executed copy must be provided to the participant to keep for his/her records.
3. No new research procedures can be conducted until a signed copy (fax, digital copy, or original) of the form has been received by the investigator.

14. Vulnerable Subjects in Research

When subjects in research conducted under the auspices of SJH/SPHP are likely to be vulnerable to coercion or undue influence or have diminished decision-making capacity, the research must include additional safeguards to protect the rights and welfare of these participants. The IRB must ensure that all

of the regulatory requirements for the protection of subjects are met and that appropriate additional protections for vulnerable subjects are in place. The following procedures describe the requirements for involving vulnerable subjects in research under the auspices of SJH/SPHP.

14.1. Definitions

Children. Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. Consistent with New York State Law, the IRB generally defines children as persons under eighteen years of age. For the purposes of these SOPs, children and minors both imply persons under eighteen years of age. NYS Public Health Law, at section 2504 speaks to who may consent (to medical care in general, but NY state law does not specifically reference who may consent to participation in research) as follows:

1. (Any person) 18 or older or is the parent of a child or is married may give effective consent for medical, dental health and hospital services for himself or herself and the consent of no other person shall be necessary.
2. Any person who has been married or who has borne a child may give effective consent for medical, dental health and hospital services for his or her child.
3. Any person who is pregnant may give effective consent for medical, dental health and hospital services related to the pregnancy.

While consent by 'emancipated' individuals is not the general rule, there are other statutory provisions relating to consent for minors who are in military service or are seeking treatment for AIDS (PHL '2781) and other sexually transmitted diseases (PHL '2305).

In general, where the individual is a minor, the presumption is that he or she is not emancipated and the burden of proof rests on the individual asserting it. Because New York State law does not specifically address consent of children with majority status by virtue of "emancipation" with respect to research, the IRB will review issues of consent related to enrollment of these minor children in research on a case-by-case basis.

NOTE: For research conducted in jurisdictions other than New York State, the research must comply with the laws regarding the legal age of consent in the relevant jurisdictions. Legal counsel should be consulted with regard to the laws in other jurisdictions or such "local context" information will be sought through other mean (e.g., according to the terms of a reliance agreement).

Guardian. A guardian is an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care [45 CFR 46.402(e)].

In New York State, there are at least two separate and distinct types of guardian appointment. Generally, the power of a guardian is dictated by the 'legally appointed guardian powers', which are determined in scope and duration by a court and described in the guardian papers.

Guardian powers can be very limited (e.g. to financial matters only) or much broader. Prior to relying on guardian consent for a specific subject, a copy of the legal guardian papers must be carefully reviewed to assess whether the scope and powers (if any exist at all) of the Guardian do or do not include the authority to consent to research. SJH/SPHP Legal Counsel may be consulted as needed.

NOTE: For research conducted in jurisdictions other than New York State, the research must comply with the laws regarding guardianship in all relevant jurisdictions. Legal counsel should be consulted with regard to the laws in other jurisdictions or such "local context" information will be sought through other mean (e.g., according to the terms of a reliance agreement).

Fetus. A fetus means the product of conception from implantation until delivery [45 CFR 46.202(c)].

Dead fetus. A fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord [45 CFR 46.202(a)].

Delivery. Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means [45 CFR 46.202(b)].

Neonate. A neonate is a newborn [45 CFR 46.202(d)].

Viable. As it pertains to the neonate, viable means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration [45 CFR 46.202(h)]. If a neonate is viable, then, for the purposes of participation in research, the neonate is considered a child and the rules regarding participation of children in research apply.

Nonviable neonate. A nonviable neonate means a neonate after delivery that, although living, is not viable [45 CFR 46.202(e)].

Pregnancy. Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery [45 CFR 46.202(f)].

Prisoner. Prisoner means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing [45 CFR 303(c)].

14.2. Involvement of Vulnerable Populations in Research

When the IRB reviews research that involves categories of participants vulnerable to coercion or undue influence, the review process should include one or more individuals who are knowledgeable about or experienced in working with these participants. When the IRB does not have the relevant expertise among its membership, expertise may be sought through the use of a scientific reviewer or consultants.

45 CFR 46 has additional subparts designed to provide extra protections for certain defined vulnerable populations which also have additional requirements for IRBs.

Subpart B - Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Subpart C - Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Subpart D - Additional Protections for Children Involved as Subjects in Research

Non-exempt DHHS-conducted or supported research that involves any of these populations must comply with the requirements of the relevant subparts. **Research regulated by the FDA includes equivalent protections and obligations when research involves children (Subpart D).** Research conducted, supported, or otherwise regulated by other federal departments or agencies may or may not be covered by the subparts. See the Special Topics section of this manual for additional information on department or agency requirements.

14.3. Procedures

The following policies and procedures apply to all research involving vulnerable populations under the oversight of the SJH/SPHP IRB regardless of funding. Subsequent sections address additional procedures and requirements that apply to specific populations.

Initial Review of Research Proposal:

1. The investigator identifies the potential to enroll vulnerable subjects in the proposed research at initial review and provides the justification for their inclusion in the study;
2. The investigator describes safeguards to protect the subject's rights and welfare in the research proposal;
3. HRPP Administrator, in collaboration with the IRB Chair as needed, ensure that the IRB has the relevant expertise with the vulnerable population, and, if necessary, arrange for consultation. When the research involves no more that minimal risk and is eligible for expedited review, the designated reviewer may determine the need for additional expertise to ensure the protection of the vulnerable population(s);
4. The IRB evaluates the proposed inclusion of vulnerable population(s) in the research and the safeguards proposed by the investigator, taking into consideration the following factors, as applicable to the research:
    a. Whether inclusion of vulnerable populations is ethically and scientifically appropriate;
    b. Whether the proposed plans, including the settings and circumstances, for the identification and recruitment of subjects, and for obtaining consent or parental permission, ensure equitable selection of subjects and promote voluntariness;
    c. Whether the proposed research confers any direct benefit, whether the benefit is available outside of the research, and whether access to the benefit may unduly influence participation by vulnerable populations;
    d. Whether any costs or plans for subject reimbursement or compensation, may exclude or unduly influence participation by vulnerable populations;
    e. Whether the provisions for privacy and confidentiality adequately protect vulnerable populations; and
    f. Other relevant considerations as appropriate for the population(s) and the circumstances of the research
5. The IRB will determine whether the inclusion of the vulnerable population(s) is appropriate and whether the proposed plan adequately safeguards the rights and welfare of these subjects. When appropriate, the IRB may restrict or disallow the inclusion of vulnerable subjects or may require modifications to the research plan to enhance protections or to monitor the effectiveness of protections. For example, the IRB could require review more than annually,

periodic QAIP reviews, independent routine monitoring, or the use of a research subject advocate or consent monitor.

Modifications to Research

1. When an investigator proposes to add inclusion of a vulnerable population after research has already been approved by the IRB, the investigator must submit a modification request to the IRB identifying the population they would like to add, justification for inclusion of the population, and any modifications to the research plan to ensure protection of the subjects' rights and welfare;
2. The HRPP Administrator and IRB will follow the procedures outlined for initial review above.

Continuing Review

1. At continuing review, the investigator should identify any problems that arose relevant to the rights and welfare of vulnerable subjects, if any such subjects have been enrolled.
2. HRPP Administrator, in collaboration with the IRB Chair as needed, ensure that the IRB has the relevant expertise with the vulnerable population, and, if necessary, arrange for consultation. When the research involves no more that minimal risk and is eligible for expedited review, the designated reviewer may determine the need for additional expertise to ensure the protection of the vulnerable population(s);
3. The IRB reviews the continuing review information, and any relevant information reported to the IRB during the period of approval and determines whether the inclusion of vulnerable populations and the plans to protect the rights and welfare of vulnerable subjects remains appropriate.

14.4. Research Involving Pregnant Women, Human Fetuses and Neonates

The following applies to all research involving pregnant women, human fetuses, and neonates reviewed by the SJH/SPHP IRB. DHHS-specific requirements are noted in the appropriate sections.

If a woman becomes pregnant while participating in a study that has not been approved for inclusion of pregnant women, the IRB must be notified immediately so that the IRB can determine whether the subject may continue in the research, whether additional safeguards are needed, and to make the determinations required by the regulations and these policies.

a. ***The Ethical and Religious Directives for Catholic Healthcare Services,*** **directive #51 states**, "Nontherapeutic experiments on a living embryo or fetus are not permitted, even with the consent of the parents. Therapeutic experiments are permitted for a proportionate reason with the informed consent of the parents, or if the father cannot be contacted, at least the mother. Medical research that will not harm the life or physical integrity of an unborn child is permitted with parental consent."

14.4.1. Research Involving Pregnant Women or Fetuses

14.4.1.1. Research Not Conducted or Supported by DHHS

For research not conducted or supported by DHHS, where the risk to the pregnant women and fetus is no more than minimal, no additional safeguards are required by policy and there are no restrictions on the involvement of pregnant women in research. However, the IRB may determine that additional safeguards

or restrictions are warranted for a specific study.

Pregnant women or fetuses may be involved in research not funded by DHHS **involving more than minimal risk** to pregnant women and/or fetuses if all of the following conditions are met:

1. Where scientifically appropriate, pre-clinical 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;
3. Any risk is the least possible for achieving the objectives of the research;
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent;
5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, 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 paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children (as defined in Section 14.1) who are pregnant, assent and permission are obtained in accord with the requirements of state law and the IRB;
8. The IRB may allow individuals whose normal responsibilities include determining the viability of fetuses to be engaged in the research, if their involvement in the determination of viability for an individual fetus cannot be avoided. Confirmation of the determination regarding viability will be sought from a qualified individual who is not otherwise engaged in the research whenever possible prior to involving the subject(s) in the research. The opinion of the independent qualified individual will be documented and made available upon request to the IRB or HRPP representative. When advance confirmation is not possible, the investigator will obtain it as soon as s/he can after enrollment, but in all cases within 5 business days. The circumstances that prohibited prospective confirmation of viability and the outcome of the subsequent consultation will be reported to the IRB within 10 business days.

14.4.1.2. Research Conducted or Supported by DHHS

For DHHS-conducted or supported research, 45 CFR Subpart B applies to all non-exempt human subject research involving pregnant women, fetuses, and neonates.

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

1. Where scientifically appropriate, pre-clinical 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 the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent.
5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, 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 paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children (as defined in Section 14.1) who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in Section 14.6.2;
8. Individuals engaged in the research will have no part in determining the viability of a neonate.

14.4.2. Research involving Neonates of Uncertain Viability or Nonviable Neonates

14.4.2.1. Research Not Conducted or Supported by DHHS

Neonates of uncertain viability and nonviable neonates may be involved in research **involving more than minimal risk** if all of the conditions listed below are met. The IRB will determine on a case-by-case basis whether safeguards or restrictions should be required for minimal risk research.

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. The IRB may allow individuals whose normal responsibilities include determining the viability of neonates to be engaged in the research, if their involvement in the determination of viability for an individual neonate cannot be avoided. In such cases, confirmation of the determination regarding viability must be made by a qualified individual who is not otherwise engaged in the research whenever possible prior to involving the subject(s) in the research. The opinion of the independent qualified individual will be documented and made available upon request to the IRB or HRPP representative. When advance confirmation is not possible, the investigator will obtain it as soon as s/he can after enrollment, but in all cases within 5 business days. The circumstances that prohibited prospective confirmation of viability and the outcome of the subsequent consultation will be reported to the IRB within 10 business days.
4. The requirements of Neonates of Uncertain Viability or Nonviable Neonates (see below) have

been met as applicable.

Neonates of Uncertain Viability. Until it has been ascertained whether a neonate is viable, a neonate may not be involved in research unless the following additional conditions have been met:
The IRB determines that:

1. 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
2. The purpose of the research is the development of important knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
3. 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 LAR is obtained in accord with the provisions of permission and assent, except that the consent of the father or his LAR need not be obtained if the pregnancy resulted from rape or incest.

Nonviable Neonates. After delivery, nonviable neonates may not be involved in research unless all of the following additional conditions are met:

1. Vital functions of the neonate will not be artificially maintained;
2. The research will not terminate the heartbeat or respiration of the neonate;
3. There will be no added risk to the neonate resulting from the research;
4. The purpose of the research is the development of important knowledge that cannot be obtained by other means; and
5. The legally effective informed consent of both parents of the neonate is obtained in accord with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent 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 LAR of either or both of the parents of a nonviable neonate will not suffice.

14.4.2.2. Research Conducted or Supported by DHHS

Neonates of uncertain viability and nonviable neonates may be involved in research conducted or supported by DHHS if all of the following conditions are met:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
3. Individuals engaged in the research will have no part in determining the viability of a neonate.
4. The requirements of Neonates of Uncertain Viability or Nonviable Neonates (see below) have been met as applicable.

Neonates of Uncertain Viability. Until it has been ascertained whether a neonate is viable, a neonate

may not be involved in research unless the following additional conditions have been met:

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

1. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
2. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's LAR is obtained in accord with the provisions of permission and assent, except that the consent of the father or his LAR need not be obtained if the pregnancy resulted from rape or incest.

Nonviable Neonates. After delivery, nonviable neonates may not be involved in research unless all of the following additional conditions are met:

1. Vital functions of the neonate will not be artificially maintained;
2. The research will not terminate the heartbeat or respiration of the neonate;
3. There will be no added risk to the neonate resulting from the research;
4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
5. The legally effective informed consent of both parents of the neonate is obtained in accord with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent do not apply. However, if either parent is unable to consent because of unavailability or 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 LAR of either or both of the parents of a nonviable neonate will not suffice.

14.4.3. Viable Neonates

A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements for research Involving children (i.e., a viable neonate is a child for purposes of applying federal research regulations).

14.4.4. Research Involving, After Delivery, the Placenta, the Dead Fetus or Fetal Material

Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, must be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.

If information associated with material described above in this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent sections of these policies and procedures are applicable.

14.4.5. Research Not Otherwise Approvable

14.4.5.1. Research Not Conducted or Supported by DHHS

If the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; **and** the research is not approvable under the provisions described previously in this section, the IRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research based on either:

1. That the research in fact satisfies the conditions detailed above, as applicable; or
2. The following:
    a. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;
    b. The research will be conducted in accord with sound ethical principles; and
    c. Informed consent will be obtained in accord with the requirements for informed consent described in this manual.

14.4.5.2. Research Conducted or Supported by DHHS

DHHS-conducted or supported research that falls in this category must be approved by the Secretary of Health and Human Services. If the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and the research is not approvable under the above provisions, then the research will be sent to OHRP for DHHS review.

14.5. Research Involving Prisoners

14.5.1. Applicability

For research not conducted or supported by DHHS, where the risk to prisoners is no more than minimal (as defined in Section 14.5.2), no additional safeguards or procedures are required under these policies and procedures. However, the IRB may determine that additional safeguards or restrictions are warranted for a specific study.

For research involving more than minimal risk, and for research conducted or supported by DHHS (unless the research qualifies for exemption and only incidentally includes prisoners (See Section 5)), the requirements outlined in this section apply.

As applicable, investigators must obtain permission from and abide by the requirements of \correctional authorities and state or local law.

14.5.2. Minimal Risk

Minimal risk, in studies involving prisoners, means 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.

14.5.3. Composition of the IRB

In addition to satisfying the general membership requirements detailed in other sections of these policies and procedures, when reviewing research involving prisoners, the IRB must also meet the following requirements:

1. A majority of the IRB (exclusive of prisoner members) must have no association with the prison(s) involved, apart from their membership on the IRB;
2. At least one member of the IRB must be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement; and
3. The prisoner representative must be a voting member of the IRB. A comment may be added to the roster indicating that the prisoner representative will only count towards quorum when s/he is in attendance and reviewing studies involving prisoners.

14.5.4. Review of Research Involving Prisoners

Initial Review of Research Proposal

1. The prisoner representative must review research involving prisoners, focusing on the requirements outlined in Subpart C and these policies;
2. The prisoner representative must receive all review materials pertaining to the research (same as primary reviewer); and
3. The prisoner representative must be present at a convened meeting when the research involving prisoners is reviewed. If the prisoner representative is not present, research involving prisoners cannot be reviewed or approved. The prisoner representative may attend the meeting by phone, video-conference, or webinar, so long as the representative is able to participate in the meeting as if they were present in person at the meeting.

Modifications to Research

1. Minor modifications to research involving prisoners may be reviewed using the expedited procedure described below;
2. Modifications reviewed by the convened IRB must use the same procedures for initial review including the responsibility of the prisoner representative to review the modification and participate in the meeting (as described above).

Continuing Review

1. Continuing review will follow the same procedures as initial review including the responsibility of the prisoner representative to review the continuing review materials and participate in the meeting (as described above)

Expedited Review

1. Research **involving interaction** with prisoners may be reviewed by the expedited procedure if a determination is made that the research involves no greater than minimal risk for the prison

population being studied and the research falls within the categories of research eligible for expedited review. Whenever possible, the prisoner representative will be consulted to verify that they agree that the research is minimal risk and to conduct (if designated by the IRB Chair as an expedited reviewer) or participate in the expedited review as a consultant. Review of more than minor modifications and continuing review (when required) will follow these same procedures;

2. Research **that does not involve interaction** with prisoners (e.g., records review) may be reviewed by the expedited procedure if a determination is made that the research involves no greater than minimal risk for the prison population being studied. Review by a prisoner representative is not required. The prisoner representative may review the research as a reviewer (if designated by the IRB Chair as an expedited reviewer) or consultant. Review of modifications and continuing review (when required) will follow these same procedures.

14.5.5. Incarceration of Enrolled Subjects

1. If a subject becomes a prisoner while enrolled in a research study that was not reviewed according to these procedures, the investigator must promptly notify the IRB and the IRB shall:
    a. Confirm that the subject meets the definition of a prisoner;
    b. Consult with the investigator to determine if it is in the best interests of the subject to continue participation in the study, in part or in full, and if so, if there are specific study activities which are in the best interests of the subject that should continue until the IRB is able to review the research applying the standards and requirements for research involving prisoners.
2. If the subject should continue, one of two options are available:
    a. Keep the subject enrolled in the study and review the research applying the standards and requirements for research involving prisoners. If some of the requirements cannot be met or are not applicable (e.g., procedures for the selection of subjects within the prison), but it is in the best interests of the subject to remain in the study, keep the subject enrolled and, if the research is DHHS-conducted or supported, inform OHRP of the decision along with the justification; or
    b. Remove the subject from the study and keep the subject on the study intervention under an alternate mechanism such as compassionate use or off-label use.
3. If a subject is incarcerated temporarily while enrolled in a study:
    a. If the temporary incarceration has no effect on the study (i.e., there is no need for study activities involving the prisoner subject to take place during the temporary incarceration), keep the subject enrolled.
    b. If the temporary incarceration has an effect on the study, follow the guidance outlined above.

14.5.6. Additional Duties of the IRB

In addition to the responsibilities of the IRB described in other sections of this manual, the IRB will review research involving prisoners and approve such research only if it finds that:

1. The research falls into one of the following **permitted categories** [45 CFR 46.306(a)(2)]:
    a. 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;

b. 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;
c. Research on conditions particularly affecting prisoners as a class (for example, research on diseases or social and psychological problems much more prevalent in prisons) provided that the study may proceed only after the DHHS Secretary has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of his/her intent to approve the research;
d. 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/research plans approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the DHHS Secretary has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of his/her intent to approve the research; or
e. The research qualifies under the HHS Secretarial waiver that applies to certain epidemiological research (68 FR 36929, June 20, 2003). The criteria for this category are that the research must have as its sole purpose (i) to describe the prevalence or incidence of a disease by identifying all cases, or (ii) to study potential risk factor associations for a disease.

2. Any possible advantages accruing to the prisoner through his or 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 or 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;
3. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;
4. 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 investigator provides to the IRB 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 proposal;
5. The information is presented in language which is understandable to the subject population;
6. 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; and
7. Where the IRB finds there may be a need for follow-up examination or care of subjects 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 subjects of this fact.

14.5.7. Certification to DHHS

Under 45 CFR 46.305(c), the institution responsible for conducting research involving prisoners that is conducted or supported by DHHS shall certify to the Secretary (through OHRP) that the IRB has made the seven findings required under 45 CFR 46.305(a) (as noted above) and receive OHRP authorization prior to initiating any research involving prisoners.

Certifications, and requests for DHHS Secretarial consultation, do not need to be submitted to OHRP for research not conducted or supported by DHHS.

For all DHHS-conducted or supported research, SJH/SPHP will send to OHRP a certification letter to this effect, which will also include the name and address of the institution and specifically identify the research study in question and any relevant DHHS grant application or protocol/research plan. DHHS-conducted or supported research involving prisoners as subjects may not proceed until OHRP issues its authorization in writing to SJH/SPHP on behalf of the Secretary.

Under its authority at 45 CFR 46.115(b), OHRP requires that the institution responsible for the conduct of the proposed research also submit to OHRP a copy of the research proposal so that OHRP can determine whether the proposed research involves one of the categories of research permissible under 45 CFR 46.306(a)(2), and if so, which one.
The term "research proposal" includes:

1. The IRB-approved protocol; any relevant DHHS grant application or proposal;
2. Any IRB application forms required by the IRB; and
3. And any other information requested or required by the IRB to be considered during initial IRB review.

OHRP also encourages the organization to include the following information in its prisoner research certification letter to facilitate processing:

1. The OHRP Federalwide Assurance (FWA) number;
2. The IRB registration number for the designated IRB; and
3. The date(s) of IRB meeting(s) in which the study was considered, including a brief chronology that encompasses:
    a. The date of initial IRB review; and
    b. The date of Subpart C review, if not done at the time of initial IRB review.

14.6. Research Involving Children

The following applies to FDA-regulated or conducted or supported by DHHS research involving children, regardless of funding source. The requirements in this section are consistent with Subpart D of 45 CFR 46, which applies to DHHS-funded research and Subpart D of 21 CFR 50, which applies to FDA-regulated research involving children.

14.6.1. Allowable Categories

In addition to the IRB's normal duties, non-exempt research involving children must be reviewed by the IRB to determine if it fits within and is permissible under one or more federally-defined categories (OHRP/FDA). Each procedure or intervention that the child will undergo for the research must be taken into consideration, and, if the research includes more than one study group assignment (e.g., placebo vs. active, investigational agent vs. comparator) the category determination must be made for each group assignment. In other words, a component analysis must be conducted by the IRB. The categories are as follows:

1. Research/Clinical Investigations not involving greater than minimal risk [45 CFR 46.404/21 CFR 50.51]. Research determined to not involve greater than minimal risk to child subjects may be approved by the IRB only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in Section 14.6.2.
2. Research/Clinical Investigations involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects [45 CFR 46.405/21 CFR 50.52]. Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may be approved by the IRB only if the IRB finds and documents 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 options; and
   c. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 14.6.2.
3. Research/Clinical Investigations involving greater than minimal risk and no prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition [45 CFR 46.406/21 CFR 50.53]. Research in which 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, may be approved by the IRB only if the IRB finds and documents that:
   a. The risk represents a minor increase over minimal risk;
   b. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
   c. The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
   d. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 14.6.2.

4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children [45 CFR 46.407/21 CFR 50.54]. When the IRB does not believe that the research meets the requirements of any of the above categories, and the IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, the IRB shall refer the research for further review as follows:
    a. DHHS-conducted or supported research in this category will be referred for review by the Secretary of Health and Human Services. However, before doing so the IRB must determine that the proposed research also meets all of the requirements of the Common Rule.
    b. FDA-regulated research in this category will be referred for review by the Commissioner of Food and Drugs.
    c. For research that is not DHHS conducted or supported and not FDA-regulated, the IRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research based on either:
        i. That the research in fact satisfies the conditions of the previous categories, as applicable; or
        ii. The following:
            1. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
            2. The research will be conducted in accord with sound ethical principles; and
            3. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 14.6.2.

14.6.2. Parental Permission and Assent

14.6.2.1. Parental Permission

The IRB must determine that adequate provisions have been made for soliciting the permission of each child's parent or guardian.

Parents or guardians must be provided with the basic elements of consent and any additional elements the IRB deems necessary, as described in Section 13.

The IRB may find that the permission of one parent is sufficient for research to be conducted under Categories 1 [45 CFR 46.404/21 CFR 50.51] & 2 [45 CFR 46.405/21 CFR 50.52] above. The IRB's determination of whether permission must be obtained from one or both parents will be documented on the children's checklist when a study receives expedited review, and in meeting minutes when reviewed by the convened committee.

Permission from both parents is required for research to be conducted under Categories 3 [45 CFR 46.406/21 CFR 50.53] & 4 [45 CFR 46.407/21 CFR 50.54] above 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.

The IRB may waive the requirement for obtaining permission from a parent or legal guardian if:

1. The research meets the provisions for waiver in Section 13.10; or
2. For research that is not FDA-regulated, if the IRB determines that the research is designed to study conditions in children or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children) provided that an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and that the waiver is not inconsistent with Federal, State, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol/research plan, the risk and anticipated benefit to the research subjects, and the child's age, maturity, status, and condition.

Permission from parents or legal guardians must be documented in accordance with and to the extent required by Section 13.8.

14.6.2.2. Assent from Children

The IRB is responsible for determining that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. This judgment may be made for all children to be involved in the study, or for each child, as the IRB deems appropriate.

If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accordance with the applicable regulations.

It is important to note that the FDA regulations do permit the IRB to waive the assent requirement if it finds and documents that:

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

Because "assent" means a child's affirmative agreement to participate in research, the child must actively show his or her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way.

The IRB should take into account the nature of the proposed research activity and the ages, maturity, and psychological state of the children involved when reviewing the proposed assent procedure and the form and content of the information conveyed to the prospective subjects. For research activities

involving adolescents whose capacity to understand resembles that of adults, the assent procedure should likewise include information similar to what would be provided for informed consent by adults or for parental permission. For children whose age and maturity level limits their ability to fully comprehend the nature of the research activity, but who are still capable of being consulted about participation in research, it may be appropriate to focus on conveying an accurate picture of what the actual experience of participation in research is likely to be (for example, what the experience will be, how long it will take, whether it might involve any pain or discomfort). The assent procedure should reflect a reasonable effort to enable the child to understand, to the degree they are capable, what their participation in research would involve.

Parents and children will not always agree on whether the child should participate in research. Where the IRB has indicated that the assent of the child is required in order for him or her to be enrolled in the study, dissent from the child overrides permission from a parent. Similarly, a child typically cannot decide to be in research over the objections of a parent. There are individual exceptions to these guidelines but in general, children should not be forced to be research subjects, even when permission has been given by their parents.

Documentation of Assent

When the IRB determines that assent is required, it is also responsible for determining whether and how assent must be documented. When the research targets the very young child or children unable or with limited capacity to read or write, an oral presentation accompanied perhaps by some pictures with documentation of assent by the person obtaining assent in a research note is likely more appropriate than providing the child a form to sign. In this case, the investigator should provide the IRB with a proposed script and any materials that they intend to use in explaining the research.

When the research targets children who are likely able to read and write, investigators should propose a process and form that is age appropriate and study specific, taking into account the typical child's experience and level of understanding, and composing a document that treats the child respectfully and conveys the essential information about the study. The assent form should:

1. Tell why the research is being conducted.
2. Describe what will happen and for how long or how often.
3. Say it's up to the child to participate and that it's okay to say no.
4. Explain if it will hurt and if so for how long and how often.
5. Say what the child's other choices are.
6. Describe any good things that might happen.
7. Say whether there is any compensation for participating; and
8. Ask for questions.

Whenever possible, the document should be limited to one page. Illustrations might be helpful, and larger type and other age appropriate improvements are encouraged when they have the potential to enhance comprehension. Studies involving older children or adolescents should include more information and may use more complex language.

14.6.2.3. Children Who are Wards of the State ("Foster Children")

Children who are wards of the State or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406/21 CFR 50.53 or 45 CFR 46.407/21 CFR 50.54 (Categories 3 & 4 in Section 14.6.1), **only if such research** is:

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

If the research meets the condition(s) above, an advocate must be appointed for each child who is a ward (one individual may serve as advocate for more than one child), in addition to any other individual acting on behalf of the child as legal guardian or in *loco parentis.*

The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

14.7. Adults with Impaired Decision-Making Capacity

When vulnerable populations are included in research, regulations require that additional safeguards are put in place to protect the rights and welfare of these subjects. [45 CFR 46.111(b)/21 CFR 56.111(b)]. Adults who lack or who have impaired, fluctuating, or diminishing decision-making capacity (collectively referred to as "adults with impaired decision-making capacity" in this section) are particularly vulnerable. Investigators and IRBs must carefully consider whether inclusion of such subjects in a research study is appropriate; and when it is, must consider how best to ensure that these subjects are adequately protected. The principals and procedures outlined in this section are intended to assist SJH/SPHP investigators and the IRB with the development and review of research involving adults with impaired decision-making capacity.

14.7.1. Informed Consent

Obtaining legally effective informed consent before involving human subjects in research is one of the central ethical principles described in the Belmont Report and provided for by federal regulations governing research.

As discussed previously, the informed consent process involves three key features: (1) providing the prospective subject the information needed to make an informed decision (in language understandable to him or her); (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether to participate in the research.

Among other requirements, for consent to be legally effective, the potential subject or their LAR must have the necessary decision-making capacity to make a rational and meaningful choice about whether to participate (or continue participating) in a study.

14.7.2. Decision-Making Capacity

For the purpose of this section, a subject has the capacity to consent to his or her own participation in a research activity if s/he demonstrates an appreciation:

1. That the activity is research, not standard treatment;
2. Of the risks and benefits of a study;
3. Of the alternatives that are available if s/he does not participate; and
4. That, if she/he chooses not to participate, this decision will be accepted without penalty, i.e. without jeopardizing clinical care.

In reaching a decision about participation, it is essential for the potential subject to demonstrate an ability to use this information in a rational manner. Thus, in considering risks, benefits, and available alternatives, subjects must show they understand the aspects of these factors that are unique to them as individuals. To highlight this distinction, a person who is suffering with severe depression may be able to demonstrate an appreciation of 1, 2, 3 and 4 above, but may not care, or may actually want to take risks. Such individuals should not be considered able to provide consent for themselves.

14.7.3. Inclusion of Adults with Impaired Decision-Making Capacity in Research

Research involving adult subjects without the ability to provide consent or with impaired decision-making capacity should only be conducted when the aims of the research cannot reasonably be achieved without their participation. A decisionally-impaired participant may participate in research involving minimal or slightly above minimal risk without direct participant benefit if a LAR or Surrogate is available and provides proxy consent.

Investigators must disclose to the IRB both plans and justification for including adults with impaired decision-making capacity in a given research proposal. If adults with questionable or fluctuating capacity will be included, investigators must specify procedures for assessing capacity prior to providing informed consent and, if appropriate, for re-evaluating capacity during study participation. If a prospective subject's capacity to consent is expected to diminish, the investigator should consider requesting that the subject designate a future LAR prior to enrollment in the research, including the future LAR in the initial consent process, and obtaining written documentation of the subject's wishes regarding participation in the research. When the study includes subjects likely to regain capacity to consent while the research is ongoing, the investigator should include provisions to inform them of their participation and seek consent for ongoing participation.

Plans for evaluation of capacity should be tailored to the subject population and the risks and nature of the research.

In general, the assessment can be made by a qualified investigator. However, the IRB may require an independent, qualified assessor evaluate subjects' capacity. This may occur when the risks of the research are more than minimal and there is no potential benefit to the subject. In all cases, the person(s) evaluating capacity must be appropriately qualified.

Assessments of capacity should be documented in the research record, and when appropriate, in the medical record.

Under some circumstances, it may be possible for investigators to enable adults with a degree of decisional impairment to make voluntary and informed decisions to consent, assent, or refuse participation in research. Potential measures include repetitive teaching, audiovisual presentations, and oral or written recall tests. Other measures might include follow-up questions to assess subject understanding, videotaping or audio-taping of consent discussions, use of waiting periods to allow more

time for the potential subject to consider the information that has been presented, or involvement of a trusted family member or friend in the disclosure and decision-making process. Audio or videotapes, electronic presentations, or written materials used to promote understanding must be provided to the IRB for review and approval prior to use.

When a prospective subject is deemed to lack capacity to consent to participate in research, investigators may obtain informed consent from the individuals' surrogate or LAR (See Section 13.3). Under these circumstances, the prospective subject should still be informed about the research in a manner compatible with the subjects' likely understanding and, if possible, be asked to assent to participate. Potential subjects who express resistance or dissent (by word, gesture, or action) to either participation or use of surrogate consent, should be excluded from the study. Some subjects may initially assent but later resist participation. Under no circumstances may an investigator or caregiver override a subject's dissent or resistance. When assent is possible for some or all subjects, the investigator should provide the IRB with an assent plan that describes when and how assent will be obtained, provisions that will be taken to promote understanding and voluntariness, how assent will be documented, and a copy of the assent form. If the investigator intends to use audio or video recordings to document assent, provisions to ensure the security of the recordings should be described to the IRB.

When inclusion of adults with impaired decision-making capacity is **not anticipated** and a plan for inclusion of such subjects **has not been** reviewed and approved by the IRB, and an enrolled subject becomes unable to provide consent or impaired in decision-making capacity, the PI is responsible for notifying the IRB (as soon as possible). The PI should consider whether continuing participation is appropriate and, if so, present a plan for surrogate consent from a LAR and, if appropriate, a plan to periodically evaluate capacity and re-obtain consent if possible.

14.7.4. IRB Review

For research involving more than minimal risk, the IRB review process will include at least one IRB member, or a scientific reviewer, who is knowledgeable about, or experienced in working with individuals with impaired decision-making capacity.

In evaluating research, the IRB must be able to determine that the risks to subjects are reasonable not only in relation to any benefits, but also in relation to the importance of the knowledge that may reasonably be expected to result. In considering the risks of research involving adults with impaired decision-making capacity, the IRB should consider whether any components of the research involve risks that are greater for participants with diminished capacity. For example, whether subjects might experience increased sensitivity or discomfort to certain stimuli or may not be able to verbalize or otherwise demonstrate when they are experiencing discomfort or pain.

In general, the IRB will only approve research involving subjects unable to provide consent or with impaired decision-making capacity when the aims of the research cannot reasonably be achieved without inclusion of the population, and there are appropriate provisions to: (1) evaluate capacity, (2) obtain consent (and assent if possible), and (3) otherwise protect subjects.

14.8. Inclusion of SJH/SPHP Employees and Students

SJH/SPHP employees and students may be asked to participate in research studies as healthy control

subjects or because they receive health care services at SJH/SPHP and are eligible to participate in a particular research study. Employees and students should be appropriate for inclusion in the study and not recruited based on convenience. The PI and research team must be aware of and sensitive to perceived pressures by employees/students to participate in research in order to appear supportive of the PI, Department or College, and take precautions to reduce the likelihood of unintended coercion. This can be accomplished by adding extra protections to ensure voluntary participation and reduce the possibility of real or perceived coercion. For example, faculty and managers should not recruit their own students or employees to participate in their study whenever possible. If a study involves regular activities that take place in the workplace or the classroom, the researcher will need to be clear what activities are part of the normal workplace or learning environment, and provide a way for employees/students to opt out of study activities if desired.

In addition, employees and students who participate in research studies should be afforded all the same protections afforded to subjects who are not employees or students, regardless of their SJH/SPHP position, education or background. Short cuts in the informed consent process (including assessing capacity to provide consent, full disclosure of all information, and use of all educational tools) and documentation of consent are not acceptable. In some cases, the IRB may require an independent party to monitor the informed consent process if a researcher enrolls subordinate employees/students into their study as subjects.

15. FDA-Regulated Research

FDA regulations apply to research that involves a FDA-regulated *test article* in a *clinical investigation* involving *human subjects* as defined by the FDA regulations. For FDA-regulated research, the IRB must apply the FDA regulations at 21 CFR 50 and 21 CFR 56. If the research is conducted or supported by a Common Rule agency or department, or if compliance with the Common Rule is required by state law or the terms of an award or contract, then the Common Rule must also be applied.

Clinical investigations of investigational drugs and biological products must be conducted according to FDA's IND regulations, 21 CFR Part 312, and other applicable FDA regulations. Evaluations of the safety or effectiveness of a medical device must be conducted according to FDA's IDE regulations, 21 CFR Part 812, and other applicable FDA regulations.

SJH/SPHP requires training through CITI of ICH-GCP requirements for all clinical trial studies. Full compliance with ICH-GCP may also be required by the sponsor. (SJH/SPHP may accept ICH-GCP training requirements from other Institutions that are not associated with CITI. Please contact the HRPP Administrator for details.)

The following procedures describe the review of FDA-regulated research by the SJH/SPHP IRB.

15.1. Definitions

Food & Drug Administration (FDA) Definitions:

Biologic. Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of

natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other technologies. In general, the term "drugs" includes therapeutic biological products.

Clinical Investigation. Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies. [21 CFR 50.3(c)]

Dietary Supplement. A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains a dietary ingredient. The dietary ingredients in these products can include vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances intended to supplement the diet, and concentrates, metabolites, constituents, extracts, or combinations of the preceding types of ingredients. [21 U.S.C. 321(ff)]

Emergency Use. Emergency use is defined as the use of a test article on a human subject 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. [21 CFR 56.102(d)]

Human Cells, Tissues, or Cellular or Tissue-based Products (HCT/P's) – HCT/P's means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue.

The following articles are not considered HCT/P's: vascularized human organs for transplantation; whole blood or blood components or blood derivative products subject to listing under parts 607 and 207, respectively; secreted or extracted human products, such as milk, collagen, and cell factors; except that semen is considered an HCT/P; minimally manipulated bone marrow for homologous use and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow); ancillary products used in the manufacture of HCT/P; cells, tissues, and organs derived from animals other than humans; in vitro diagnostic products as defined in 809.3(a); blood vessels recovered with an organ, as defined in 42 CFR 121.2, that are intended for use in organ transplantation and labeled "For use in organ transplantation only."

HCT/P's may be regulated as drugs, devices, and/or biologics when the use does not qualify for an establishment exception or regulation solely under section 361 of the PHS Act and 21 CFR 1271.

Human Subject. Human subject means an individual who is or becomes a participant in a clinical investigation, either as a recipient of the test article or as a control. A subject might be either a healthy individual or a patient. For research involving medical devices a human subject is also an individual on whose specimen an investigational device is used or as a control (regardless of whether the specimens are identifiable). [21 CFR 50.3(g), 21 CFR 312.3(b), 21 CFR 812.3(p)]

Humanitarian Use Device (HUD). A Humanitarian Use Device is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year.

Investigational Drug. Investigational *or* experimental drugs are new drugs that have not yet been approved by the FDA or approved drugs that are being studied in a clinical investigation.

Investigational Device. Investigational device means a device (including a transitional device) that is the object of an investigation. Investigation, as it pertains to devices, means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

IND. IND means an investigational new drug application in accordance with 21 CFR Part 312.

IDE. IDE means an investigational device exemption in accordance with 21 CFR 812.

In Vitro Diagnostic Product (IVD). IVD products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. [21 CFR 809.3(a)]

Non-Significant Risk (NSR) Device. A NSR device is an investigational device that does not meet the definition of a significant risk device.

Research. The FDA has defined "**research**" as being synonymous with the term "**clinical investigation**." A clinical investigation, as defined by FDA regulations, means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the FDA under these sections of the Federal Food, Drug, and Cosmetic Act, but the results of which 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. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations. [21 CFR 50.3(c), 21 CFR 56.102(c)]

Experiments that must meet the requirements for prior submission to the FDA under section 505(i) of the Federal Food, Drug, and Cosmetic Act means any use of a drug other than the use of an approved drug in the course of medical practice. [21 CFR 312.3(b)]

Experiments that must meet the requirements for prior submission to the FDA under section 520(g) of the Federal Food, Drug, and Cosmetic Act means any activity that evaluates the safety or effectiveness of a device. [21 CFR 812.2(a)]

Any activity in which results are being submitted to or held for inspection by FDA as part of an application for a research or marketing permit is considered to be FDA-regulated research. [21 CFR 50.3(c), 21 CFR 56.102(c)]

Significant Risk (SR) Device. Significant risk device means an investigational device that:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; or
2. Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or

3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. [21 CFR 812.3(m)]

Test Article. The FDA defines Test Article as meaning any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act [42 U.S.C. 262 and 263b-263n]. [21 CFR 50.3(j)]. Test articles covered under the FDA regulations include, but are not limited to:

1. **Human drugs** – A drug is defined as a substance recognized by an official pharmacopoeia or formulary; a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; a substance (other than food) intended to affect the structure or any function of the body; a substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device. Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process). The primary intended use of a drug product is achieved through chemical action or by being metabolized by the body.
2. **Medical Devices** - A device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them; intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."
3. The 21st Century Cures Act amended the FD&C Act to specifically exclude certain software functions from the definition of medical device. Summarized, these include exclusions for software functions intended for administrative support of a health care facility; for maintaining or encouraging a healthy lifestyle; to serve as electronic patient records; for transferring, storing, converting formats, or displaying clinical laboratory tests or other device data and results and related information; and for displaying, analyzing, or printing medical information, for supporting or providing recommendations to a health care professional, and enabling the health care professional to independently review the basis for such recommendations. Additional information regarding the application of these exclusions is available on FDA's "Guidances with Digital Health Content" website.
4. **Human Cells, Tissues, or Cellular or Tissue-based Products** (HCT/P's) – see definition noted above.

5. **Biological Products** – See definition for biologic noted above. In addition, gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.

6. **Dietary Supplements** – A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains one or more "dietary ingredients." The "dietary ingredients" in these products may include vitamins, minerals, herbs or other botanicals, amino acids, and other substances found in the human diet, such as enzymes. When a dietary supplement meets the definition of drug, it is regulated as such.

7. **Medical Foods** – A medical food, as defined in section 5(b) of the Orphan Drug Act (21 U.S.C. 360ee (b) (3)), is a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.

8. **Mobile Medical Apps** - Mobile apps are software applications that can be executed on a mobile platform or a web-based software application that is tailored to a mobile platform but is executed on a server. Mobile medical apps are a subset of medical devices that meet the definition of a medical device and either are intended to be used as an accessory to a regulated medical device; or to transform a mobile platform into a regulated medical device.

9. **Radioactive Drugs** – The term radioactive drug means any substance defined as a drug which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides. The term “radioactive drug” includes “radioactive biological product”.

10. **Radiation-Emitting Electronic Products** - a radiation-emitting electronic product is any electrically-powered product that can emit any form of radiation on the electromagnetic spectrum. These include a variety of medical and non-medical products such as mammography devices, magnetic resonance imaging (MRI) devices, laser toys, laser pointers, liquid crystal displays (LCDs), and light emitting diodes (LEDs).

15.2. FDA Exemptions

The following categories of clinical investigations are exempt from the requirements of FDA regulations for IRB review:

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. [21

CFR §56.104(c)]

2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or 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 FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [21 CFR §56.104(d)]

15.3. Investigator Responsibilities

The investigator holds additional responsibilities when conducting a clinical investigation subject to FDA regulations. These responsibilities include, but are not limited to, the following:

1. The investigator is responsible for indicating on the IRB application that the proposed research is FDA-regulated and for providing relevant information regarding the test article.
2. The investigator is responsible for ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs (including biological products) or agreement for clinical investigations of medical devices, the investigational plan and other applicable regulations, and any requirements imposed by the FDA or IRB.
3. The investigator is responsible for personally conducting or supervising the investigation. When study-related tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.
4. The investigator must maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks (e.g., it can refer to an individual's CV on file and/or training conducted by the investigator or sponsor), and identify the dates of involvement in the study. An investigator should maintain separate lists for each study conducted by the investigator.
5. The investigator is responsible for protecting the rights, safety, and welfare of subjects under their care during a clinical trial. This responsibility includes:
    a. Informing subjects that the test articles is being used for investigational purposes and ensuring that the requirements relating to obtaining informed consent are met
    b. Providing or arranging for reasonable medical care for study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention
    c. Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, or when specialized care is needed)
    d. Adhering to the protocol so that study subjects are not exposed to unreasonable risks
    e. As appropriate, informing the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and the subject agrees to the primary physician being informed.
6. The investigator is responsible for reading and understanding the information in the investigator brochure or device risk information, including the potential risks and side effects of the drug or

device.

7. The investigator is responsible for maintaining adequate and accurate records in accordance with FDA regulations and to making those records available for inspection by the FDA. These records include, but are not limited to: correspondence with other investigators, the IRB, the sponsor, monitors, or the FDA; drug and device accountability records; case histories; consent forms; and documentation that consent was obtained prior to any participation in the study. Records must be maintained for a minimum of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such. For clinical investigations of medical devices, required records must be maintained for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. Other regulations, such as HIPAA, organizational policies, or contractual agreements with sponsors may necessitate retention for a longer period of time.
8. The investigator is responsible for controlling test articles according to FDA regulations and the Controlled Substances Act, if applicable.
9. For research reviewed by the SJH/SPHP IRB, the investigator proposing the clinical investigation will be required to submit a plan – to be reviewed by the IRB and pharmacy- that includes storage, security, and dispensing of the test article.
    a. For studies involving Drugs & Biologics, the investigator may include a completed *Pharmacy Worksheet* in the IRB submission the SJH/SPHP Pharmacy Director. SJH/SPHP Pharmacy will provide recommendations to the IRB. All studies involving Drugs & Biologics are subject to oversight by the Department of Pharmacy, regardless of whether Pharmacy services are used or required.
    b. All devices received for a study must be stored in a locked environment under secure control with limited access. When applicable, proper instructions on the use of the device must be provided to the subjects. A log must be kept regarding the receipt, use, and/or dispensing of the device, and the disposition of remaining devices at the conclusion of the investigation.
10. The investigator shall furnish all reports required by the sponsor of the research including adverse events, progress reports, safety reports, final reports, and financial disclosure reports.
11. The investigator will permit inspection of research records by the sponsor, sponsor representatives, HRPP and IRB representatives, the FDA, accrediting bodies, and any other agencies or individuals entitled to inspect such records under regulation, organizational policy, or contractual agreement.

15.4. Digital Health

Certain medical and decision support software have been excluded from the definition of medical device under the 21st Century Cures Act and thus are not subject to FDA's regulations. These include exclusions for software functions:

- Intended for administrative support of a health care facility, including the processing and maintenance of financial records, claims or billing information, appointment schedules, business analytics, information about patient populations, admissions, practice and inventory

management, analysis of historical claims data to predict future utilization or cost-effectiveness, determination of health benefit eligibility, population health management, and laboratory workflow;

- Intended for maintaining or encouraging a healthy lifestyle and unrelated to the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition;
    - Intended to serve as electronic patient records, including patient-provided information, to the extent that such records are intended to transfer, store, convert formats, or display the equivalent of a paper medical chart, so long as—such records were created, stored, transferred, or reviewed by health care professionals, or by individuals working under supervision of such professionals;
    - such records are part of health information technology that is certified under section 300jj–11(c)(5) of title 42; and
    - such function is not intended to interpret or analyze patient records, including medical image data, for the purpose of the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition
- Intended for transferring, storing, converting formats, or displaying clinical laboratory test or other device data and results, findings by a health care professional with respect to such data and results, general information about such findings, and general background information about such laboratory test or other device, unless such function is intended to interpret or analyze clinical laboratory test or other device data, results, and findings; and
- Not intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system; and
    - Is intended for the purpose of displaying, analyzing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines);
    - Is intended for the purpose of supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition; and
    - Is intended for the purpose of enabling such health care professional to independently review the basis for such recommendations that such software presents so that it is not the intent that such health care professional rely primarily on any of such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient.

Additional information regarding the application of these exclusions is available on the FDA website referenced below.

Research involving software excluded from the definition of medical device will be evaluated by the SJH/SPHP IRB in accordance with any other applicable regulations (e.g., the Common Rule, HIPAA) and the criteria outlined in this manual.

Other digital health products may be subject to FDA regulations and will be evaluated accordingly. FDA has provided a website listing of Guidances with Digital Health Content to help the regulated community understand FDA's interpretation and application of the regulations and to describe when FDA will practice enforcement discretion in regards to certain requirements such as those for pre-market review and for device reports. Investigators are encouraged to consult these guidance's in advance of their

submission to the IRB and to consult directly with the FDA as needed.

15.5. Human Cells, Tissues, or Cellular or Tissue-based Products (HCT/P's)

Generally, research involving HCT/P's regulated as drugs, devices, and/or biologics will require an IND or IDE depending on how the HCT/P is categorized. Because the regulatory and policy framework for HCT/P's is complex, consultation with the FDA prior to submission to the IRB is encouraged to appropriately categorize the HCT/P, understand which regulations and requirements apply, and to obtain an IND or IDE if necessary (or FDA determination that such is not required).

15.6. Dietary Supplements

Research involving dietary supplements may or may not fall under FDA regulations. Under the Dietary Supplement Health and Education Act (DSHEA) of 1994, a dietary supplement is not considered a drug and is not subject to the premarket approval requirements for drugs if the intended use for which it is marketed is only to affect the structure or any function of the body (i.e., not intended to be used for a therapeutic purpose). Whether a study falls under FDA oversight is determined by the intent of the clinical investigation. If the clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, FDA research regulations do not apply. However, if the study is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, then FDA regulations do apply. Studies involving the ingestion of dietary supplements that are not subject to FDA oversight are still research, and therefore must be reviewed by the IRB.

Similarly, whether an IND is needed for a study evaluating a dietary supplement is determined by the intent of the study. If the study is intended only to evaluate the dietary supplement's effect on the structure or function of the body, an IND is not required. However, if the study is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required under part 312.

As with any research involving a test article, the investigator must supply the IRB with sufficient information to determine that the criteria for approval are satisfied and to determine or verify whether the research requires an IND. Applications should provide detail consistent with that expected on a drug protocol and consistent with the level of risk associated or anticipated with the research. At a minimum, the research plan should provide the following information regarding the supplement: Name, Manufacturer, Formulation, Dosage, Method/Route of Administration, Mechanism of Action, Known Drug Interactions, Risk Profile, IND number (or justification for why an IND is unnecessary), documentation of approval for use in humans, documentation or certification of Quality or Purity. As with drugs and devices there should be an accountability plan for the product describing where the product will be stored and how it will be dispensed, usage tracked, and disposal or return. If the study entails greater than minimal risk, a plan for DSM must be included.

15.7. Clinical Investigations of Articles Regulated as Drugs or Devices

15.7.1. IND/IDE Requirements

For studies evaluating the safety or effectiveness of medical devices or experiments using drugs, biologics, dietary supplements, and other compounds that may be considered a drug or device under

FDA regulations, the investigator must indicate on the IRB application whether an IDE or IND is in place, and, if not, the basis for why an IDE or IND is not needed.
Documentation must be provided by the sponsor or the sponsor-investigator. Documentation of the IND/IDE could be a:

1. Industry sponsored study with IND/IDE number indicated on the protocol;
2. Letter/communication from FDA;
3. Letter/communication from industry sponsor; or
4. Other document and/or communication verifying the IND/IDE.

For investigational devices, the study may be exempt from IDE requirements (IDE-exempt) or, in the case of Non-Significant Risk (NSR) device studies, follow abbreviated IDE requirements which do not require formal approval by the FDA. If a sponsor has identified a device study as IDE-exempt or NSR, then the investigator should include documentation with the submission providing the basis for IDE-exempt or NSR categorization for the IRB's consideration. If the FDA has determined that the study is IDE-exempt or NSR, documentation of that determination must be provided.

The IRB will review the application and, based upon the documentation provided, determine:

1. That there is an approved IND/IDE in place;
2. That the FDA has determined that an IND is not required or that a device study is IDE-exempt or NSR; or,
3. If neither of the above, whether an IND is necessary, or that a device study is exempt or NSR, or must be submitted to the FDA for an IDE or for a determination, using the criteria below.

The IRB cannot grant approval to the research until the IND/IDE status is determined, and, if necessary, an approved IND or IDE is in place.

15.7.2. IND Exemptions

For drugs, an IND is not necessary if the research falls in one of the following seven (7) categories:

1. The drug being used in the research is lawfully marketed in the United States and all of the following requirements are met:
    a. The research is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug;
    b. In the case of a prescription drug, the research is not intended to support a significant change in the advertising for the product;
    c. The research does not involve a route of administration, dose, subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
    d. The research is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
    e. The research is conducted in compliance with the requirements of 21 CFR 312.7 (i.e., the research is not intended to promote or commercialize the drug product); and
    f. The research does not intend to invoke FDA regulations for planned emergency

research [21 CFR 50.24].

2. The research only involves one or more of the following: (a) Blood grouping serum, (b) Reagent red blood cells or (c) Anti-human globulin;
3. For clinical investigations involving an in vitro diagnostic biological product, an IND is not necessary if a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and
   b) it is shipped in compliance with 312.160
4. A clinical investigation involving use of a placebo is exempt from the requirements of part 312 if the investigation does not otherwise require submission of an IND.
5. Bioavailability or Bioequivalence (BA/BE) studies if all of the following conditions are met:
   a. The drug product does not contain a new chemical entity [21 CFR 314.108], is not radioactively labeled, and is not cytotoxic;
   b. The dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product;
   c. The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively]; and
   d. The sponsor meets the requirements for retention of test article samples [21 CFR 320.31(d)(1)] and safety reporting [21 CFR 320.31(d)(3)].
6. Research using a radioactive drug or biological product if all of the following conditions are met:
   a. It involves basic research not intended for immediate therapeutic, diagnostic, or similar purposes, or otherwise to determine the safety and efficacy of the product;
   b. The use in humans is approved by a Radioactive Drug Research Committee (RDRC) that is composed and approved by FDA;
   c. The dose to be administered is known not to cause any clinically detectable pharmacological effect in humans, and
   d. The total amount of radiation to be administered as part of the study is the smallest radiation dose practical to perform the study without jeopardizing the benefits of the study and is within specified limits.
7. FDA practices enforcement discretion for research using cold isotopes (isotopes that lack radioactivity) of unapproved drugs being conducted without an IND if all of the following conditions are met:
   a. The research is intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a drug labeled with a cold isotope or regarding human physiology, pathophysiology, or biochemistry;
   b. The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject;
   c. The dose to be administered is known not to cause any clinically detectable pharmacologic effect in humans based on clinical data from published literature or other valid human studies;
   d. The quality of the cold isotope meets relevant quality standards; and
   e. The investigation is conducted in compliance with the requirements for IRB review and informed consent. [21 CFR parts 56 and 50, respectively]

15.7.3. IDE Exemptions

For clinical investigations of medical devices, an IDE is not necessary if:

1. The research involves a device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time;
2. The research involves a device other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR 807 in determining substantial equivalence (a "510k" device);
3. The research involves a diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
    a. Is noninvasive,
    b. Does not require an invasive sampling procedure that presents significant risk,
    c. Does not by design or intention introduce energy into a subject, and
    d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure;
4. The research involves a device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk;
5. The research involves a device intended solely for veterinary use;
6. The research involves a device shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR 812.5(c);
7. The research involves a custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

15.7.4. Significant and Non-Significant Risk Device Studies

A device study is a Non-Significant Risk (NSR) Device study if it is not IDE exempt and does not meet the definition of a Significant Risk (SR) Device study.

Under 21 CFR 812.3(m), an SR device means an investigational device that:

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

If the FDA has already determined a study to be SR or NSR, documentation evidencing such should be provided to the IRB as described in Section 15.7.1. The determination of the FDA is final and the IRB does not have to make the device risk determination.

Unless the FDA has already made a device risk determination for the study, the IRB will review studies that the sponsor or investigator have put forth as NSR at a convened meeting to determine if the device represents SR or NSR.

The sponsor or sponsor-investigator is responsible for providing the IRB with an explanation describing the basis for their initial determination of NSR and any other information that may help the IRB in evaluating the risk of the study (e.g., reports of prior investigations of the device).

The IRB will review the information provided by the sponsor and investigator including, but not limited to: the sponsor or investigator's NSR assessment, the description of the device, reports of prior investigations of the device (if applicable), the proposed investigational plan, and subject selection criteria.

The NSR/SR determination made by the IRB will be based on the proposed use of the device in the investigation, not on the device alone. The IRB will consider the nature of any harms that may result from use of the device, including potential harms from additional procedures subjects would need to undergo as part of the investigation (e.g., procedures for inserting, implanting, or deploying the device). The IRB may consult with the FDA or require the sponsor or investigator to obtain a determination from the FDA. The IRB will document the SR or NSR determination and the basis for it in the meeting minutes and provide the investigator, and sponsor when applicable, with the determination in writing.

Non-significant risk device studies do not require submission of an IDE application to the FDA but must be conducted in accordance with the abbreviated requirements of IDE regulations (21 CFR 812.2(b)). Under the abbreviated requirements, the following categories of investigations are considered to have approved applications for IDE's, unless FDA has notified a sponsor under 812.20(a) that approval of an application is required:

1. An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor (or sponsor-investigator):
    a. Labels the device in accordance with 812.5;
    b. Obtains IRB approval of the investigation after presenting the reviewing IRB with an explanation of why the device is not a significant risk device, and maintains such approval;
    c. Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless the requirement is waived by the IRB;
    d. Complies with the requirements of 812.46 with respect to monitoring investigations;
    e. Maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10);
    f. Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and
    g. Complies with the prohibitions in 812.7 against promotion and other practices.

When the FDA or IRB determines that a study is SR, the IRB may approve the study, but the study cannot begin until an IDE is obtained.

15.8. Diagnostic or Treatment Use of Humanitarian Use Devices

A Humanitarian Use Device (HUD) is an approved (marketed) medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 8,000 individuals in the United States per year [21 CFR 814.3(n)].

Federal law requires that an IRB approve the use of an HUD at a facility. Once approved, the clinical use of the HUD may be considered as any other approved device, with the caution that effectiveness has not been shown in clinical trials.

15.8.1. Definitions

Humanitarian Device Exemption. A Humanitarian Device Exemption (HDE) is a "premarket approval application" submitted to FDA pursuant to Subpart A, 21 CFR Part 814 "seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the [FD&C Act] as authorized by section 520(m)(2) of the [FD&C Act]." HDE approval is based upon, among other criteria, a determination by FDA that the HUD will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from use of the device outweighs the risk of injury or illness from its use while taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

HDE Holder. An HDE Holder is a person or entity that obtains approval of an HDE from the FDA.

15.8.2. IRB Review Requirements

A Humanitarian Use Device (HUD) may only be used in a facility after an IRB has approved its use, except in certain emergencies. The HDE holder is responsible for ensuring that a HUD is provided only to facilities having an IRB constituted and acting in accordance with the FDA's regulations governing IRBs (21 CFR Part 56), including continuing review of use of the device.

When a HUD is used in a clinical investigation (i.e., research involving one or more subjects to determine the safety or effectiveness of the HUD), the full requirements for IRB review and informed consent apply (21 CFR 50 and 56) as well as other applicable regulations. It is essential to differentiate whether the HUD is being studied for the indication(s) in its approved labeling or for different indication(s). When the HUD is being studied for the indication(s) in its approved labeling, the IDE regulations at 21 CFR 812 do not apply. However, when the HUD is being studied for a different indication(s), 21 CFR 812 does apply, including the requirement for a FDA-approved IDE before starting the clinical investigation of a Significant Risk device.

15.8.3. Procedures

The relevant requirements and procedures for research described elsewhere in this manual apply to clinical investigations of HUDs. **The material within this section applies to diagnostic or treatment uses of HUDs.**

The health care provider (PI noted on the IRB submission) seeking approval for diagnostic or treatment use of a HUD at SJH/SPHP facilities is responsible for obtaining IRB approval prior to use of the HUD at the facility and for complying with the applicable regulations, including those for medical device reporting,

organizational policies, and the requirements of the IRB.

Health care providers seeking initial IRB approval for diagnostic or treatment use of a HUD for the indication(s) in the HUDs approved labeling should submit the following materials to the IRB:

1. IRB application forms;
2. A copy of the HDE approval letter from the FDA;
3. A description of the device, such as a device brochure;
4. The patient information packet for the HUD;
5. Other relevant materials as required by the Institution.

The IRB will review the proposal at a convened meeting. The IRB will review the risks to patients that are described in the product labeling and other materials, the proposed procedures to ensure that risks are minimized, and will evaluate whether the risks are reasonable in relation to the potential benefits to patients at the facility. The IRB will evaluate the patient information packet and proposed consent process and will determine if the materials are adequate and appropriate for the patient population.

The IRB may specify limitations on the use of the device, require additional screening and follow up procedures, require interim reports to the IRB, require continuing review more often than annually, or set other conditions or requirements as appropriate to minimize risks to patients and ensure the safe use of the device in the facility.

Once use of the HUD is approved, the health care provider is responsible for submitting any proposed changes to the IRB-approved plan or patient materials and obtaining approval for those changes prior to implementation, unless the change is necessary to avoid or mitigate an apparent immediate risk to a patient. Proposed changes may be submitted using the Modification Form and should be accompanied by any revised materials or supporting documentation. The IRB may review these changes using expedited review procedures or refer the changes for review by the convened IRB.
The health care provider is responsible for submitting reports to the FDA, the IRB, and the manufacturer/HDE Holder whenever a HUD may have caused or contributed to a death, and must submit reports to the manufacturer (or to FDA and the IRB if the manufacturer is unknown) whenever a HUD may have caused or contributed to a serious injury (21 CFR 803.30 and 814.126(a)). Serious injury means an injury or illness that (1) is life-threatening, (2) results in permanent impairment of a bodily function or permanent damage to a body structure, or (3) necessitates medical or surgical intervention to preclude permanent impairment of a bodily function or permanent damage to a body structure (21 CFR 803.3). The specific requirements for this reporting are in the Medical Device Reporting (MDR) Regulation, at 21 CFR Part 803.

The IRB will review these reports via either expedited or convened review, as appropriate, and will consider whether any changes are needed to the IRB-approved plan or patient materials.

The health care provider is responsible for submitting continuing review materials to the IRB sufficiently in advance of the expiration date to ensure IRB review and re-approval. The following review materials are to be submitted:

1. The Continuing Review Report
2. The most recent periodic report to the FDA by the HDE holder.
3. The current consent, if applicable.

4. Any other new relevant information or materials

The IRB may conduct continuing review using expedited review procedures or review by the convened IRB.

15.8.4. Emergency Uses of HUDs

If an appropriately trained and licensed health care provider in an emergency 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, a HUD may be used without prior IRB approval. The health care provider must, within 5 days after the emergency use of the device, provide written notification of the use to the SJH/SPHP IRB or IRB Chair including the identification of the patient involved (MR#), the date of the use, and the reason for the use. [21 CFR 812.124]. The *Emergency Use Report Form* may be used to fulfill this requirement.

If a HUD is approved for use in a facility, but an appropriately trained and licensed health care provider wants to use the HUD outside its approved indication(s) in an emergency or determines that there is no alternative device for a patient's condition, the physician should consult with the HDE holder and IRB in advance if possible, obtain informed consent if possible, and ensure that reasonable measures are taken to protect the well-being of the patient such as a schedule and plan for follow up examinations and procedures to monitor the patient, taking into consideration the patient's specific needs and what is known about the risks and benefits of the device. The provider should submit a follow up report to the HDE holder and the IRB and must comply with medical device reporting requirements.

The IRB may require additional reports, patient protection measures, or other requirement, as appropriate given the specifics of the situation.

15.9. Expanded Access to Investigational Drugs, Biologics, and Devices

Expanded access pathways, also referred to as "**compassionate use**", are designed to make investigational medical products available as early in the drug and device evaluation process as possible to patients without therapeutic options, because they have exhausted or are not a good candidate for approved therapies and cannot enter a clinical trial. Expanded access refers to the use of investigational or unapproved/uncleared medical products (all referred to as "investigational" throughout this section) outside of a clinical trial, where the primary intent is treatment, rather than research. Because the products have not yet been approved by FDA as safe and effective, it is important to remember that the product may not be effective and there may be unexpected serious adverse effects and to take appropriate measures to ensure that this is understood by the patient or their LAR and to monitor for safety.

Charging for expanded access use of investigational products is discussed in Section 15.10.

15.9.1. Expanded Access to Investigational Drugs and Biologics

The FDA's expanded access rule for investigational drugs, including biologics classified as drugs, is intended to improve access to investigational drugs for patients with serious or immediately life-threatening diseases or conditions who lack other therapeutic options and may benefit from the investigational agent. **Expanded access is sometimes referred to as compassionate use or**

treatment use.

For the purposes of expanded access to investigational drugs, ***immediately life-threatening disease or condition*** means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. ***Serious disease or condition*** means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. [21 CFR 312.300(b)]

Expanded access may also apply to (1) situations when a drug has been withdrawn for safety reasons, but there exists a patient population for whom the benefits of the withdrawn drug continue to outweigh the risks; (2) use of a similar, but unapproved drug (e.g., foreign-approved drug product) to provide treatment during a drug shortage; (3) use of an approved drug where availability is limited by a risk evaluation and mitigation strategy (REMS); and (4) use for other reasons. All are referred to as "investigational" for the purposes of these SOPs.

Under the FDA's expanded access rule, access to investigational drugs for treatment purposes is available to:

- Individual patients, including in emergencies [21 CFR 312.310]
- Intermediate-size patient populations [21 CFR 312.315]
- Widespread use under a treatment protocol or treatment IND [21 CFR 312.320]

The following sections address expanded access for individual patients. Investigators seeking expanded access for intermediate-size populations or widespread use should consult with the SJH/SPHP IRB office. Convened IRB review is generally required for intermediate or widespread expanded access unless the FDA has issued a waiver.

Physicians seeking access to investigational drugs under expanded access should work closely with the sponsor or manufacturer, the FDA, and the SJH/SPHP HRPP, to determine the appropriate access mechanism and ensure that proper regulatory procedures are followed.

The FDA provides information about the procedures and requirements for expanded access on their website, including a link to contact information.

15.9.1.1. Expanded Access for Individual Patients

Expanded access to investigational drugs may be sought under an "Access Protocol" or an "Access IND". FDA generally encourages Access Protocols, which are managed and submitted by the sponsor of an existing IND, because it facilitates the review of safety and other information. However, Access INDs for the treatment of individual patients are also available and commonly used when: (1) a sponsor holding an existing IND declines to be the sponsor for the individual patient use (e.g., because they prefer that the physician take on the role of sponsor-investigator); or (2) there is no existing IND.

Sponsor or Manufacturer Approval:

Prior to submitting to the FDA or IRB, physicians seeking expanded access to an investigational drug

should contact the sponsor (e.g., for investigational drugs under a commercial IND) or manufacturer (e.g., for approved drugs under a REMS) to: (1) ensure that the investigational drug can be obtained; (2) determine whether the patient may be treated under an existing IND study, sponsor-held Access Protocol, or if the physician should seek an Access IND; and (3) determine if the drug will be provided free or if there will be a charge. A Letter of Authorization (LOA) from the sponsor or manufacturer should be obtained.

FDA Approval:

When a commercial sponsor agrees to provide access under an Access Protocol, the sponsor is responsible for managing and obtaining FDA approval and all other sponsor responsibilities. A licensed physician under whose immediate direction an investigational drug is administered or dispensed for expanded access is considered an "investigator" under FDA regulations and is responsible for all investigator responsibilities under 21 CFR 312, to the extent they are applicable to expanded access.

If the sponsor or manufacturer declines treatment of the patient under an existing IND study or Access Protocol but agrees to make the investigational drug available for the patient, physicians may apply to the FDA for an individual patient Access IND using Form FDA 3926, a streamlined IND application specifically designed for such requests. Form FDA 3926, and related guidance, is available on a FDA website. Form FDA 3926 includes a section where an investigator can request approval from the FDA for alternative IRB review procedures; these alternative procedures enable review by the IRB Chair (or a Chair-designated IRB member) in lieu of review by the convened IRB. This alternative review procedure is referred to as a "concurrence review" in FDA guidance; however, the IRB Chair must review the same materials and make the same determinations as the convened board would. IRB Chair review can also be used for any post-approval reviews (e.g., unanticipated problems, continuing review, closure, etc.).

When there is an emergency situation and insufficient time to submit a written application to the FDA prior to treatment, a request to FDA for emergency use may be made by telephone (or other rapid means). A written expanded access application must be submitted within 15 days of the FDA's authorization. For more information on emergency use, see Section 15.9.3.

A physician who obtains an Access IND is considered a "sponsor-investigator" and is responsible for the responsibilities of both sponsors and investigators under 21 CFR 312, as applicable, including IND safety reports, annual reports, and maintenance of adequate drug accountability records.

IRB Review:

Unless the conditions that permit an emergency use exemption (see Section 15.9.3) are satisfied, IRB approval must be obtained prior to initiating treatment with the investigational drug. When the FDA has authorized the use of alternative IRB review procedures (which can be presumed when the request is made on Form FDA 3926 unless the FDA specifically states that the request is denied), the review may be conducted by the IRB Chair (or designee). Otherwise, the review must be conducted by the convened IRB.

Physicians using investigational drugs under compassionate use should develop and submit an appropriate plan and schedule for treating and monitoring the patient, taking into consideration the nature of the drug and the needs of the patient. The plan should include monitoring to detect any

possible problems arising from the use of the drug.

To request IRB approval for single patient expanded access, investigators should notify the Investigational pharmacy & Billing, contact the IRB office (as soon as possible to coordinate a timely review), and submit the following via the IRBManager:

1. IRB Application Form;
2. A copy of the LOA from the Commercial Sponsor or Manufacturer or other documentation supporting sponsor/manufacturer approval;
3. A copy of the information submitted to the FDA (and FDA approval, if available);
4. A copy of the Investigator's Brochure or similar documentation that provides information regarding the potential risks and benefits of the investigational drug;
5. A copy of the plan for treating and monitoring the patient; and
6. A copy of the draft informed consent document.

The IRB may review the expanded access application prior to FDA approval being received but cannot finalize approval until documentation of FDA approval is provided. The IRB will provide the investigator with written documentation of its review.

SJH/SPHP will consider reliance upon an external IRB for expanded access when the IND is held by a commercial sponsor and an external IRB has approved the protocol and is willing to accept review and oversight of additional investigators/sites. Investigators should contact the HRPP Administrator or IO, to discuss IRB reliance for expanded access protocols.

Post-Approval Requirements

Investigators are responsible for complying with any sponsor or FDA reporting requirements. The post-approval requirements for research described throughout this manual apply, including, but not limited to, prospective IRB approval of any proposed modifications to the plan or materials approved by the IRB unless the change is necessary to eliminate apparent immediate hazard to the subject (in which case it must be promptly reported), reporting of unanticipated problems, noncompliance, complaints, and other reportable information, and for continuing review and study closure, as applicable. **Additionally**, copies of any follow-up submissions to the FDA related to the expanded access use should be submitted to the IRB within 7 business days of the date of submission to the FDA.

15.9.2. Expanded Access to Investigational and Unapproved Medical Devices

As with investigational drugs, unapproved medical devices may normally only be used in humans in an approved clinical trial under the supervision of a participating clinical investigator. However, there are circumstances under which a health care provider may use an unapproved device outside of a clinical study when it is not possible to enroll a patient in a clinical study and the patient is facing life-threatening circumstances or suffering from a serious disease or condition for which no other alternative therapy or diagnostic exists or is a satisfactory option for the patient.

FDA has made the following mechanisms available for these circumstances:

- Emergency Use
- Compassionate Use (or Single Patient/Small Group Access)

- Treatment Use

Investigators seeking access to investigational or unapproved devices under one of the above provisions should work closely with the sponsor or manufacturer, the FDA, and the SJH/SPHP HRPP, to ensure that proper regulatory procedures are followed.

FDA has made information about expanded access to medical devices available on their website.

15.9.2.1. Compassionate Use of Investigational/Unapproved Medical Devices

The compassionate use provision under expanded access provides a mechanism for accessing investigational devices for an individual patient or small groups of patients when the treating physician believes the device may provide a diagnostic or treatment benefit. Compassionate use can be used for devices being studied in a clinical trial under an IDE for patients who do not qualify for inclusion in the trial, and for devices for which an IDE does not exist.

The following criteria must be satisfied:

1. The patient has a life-threatening or serious disease or condition; and
2. No generally acceptable alternative treatment for the condition exists.

The medical device company must agree to make the medical device available for the proposed compassionate use. FDA and IRB approval are required before the device may be used under the compassionate use provision.

FDA Approval:

When **there is an IDE** for the device, the IDE sponsor submits an IDE supplement requesting approval for the compassionate use under 21 CFR 812.35(a).

When **there is not an IDE** for the device, the physician or manufacturer submits the following information to the FDA:

1. A description of the device (provided by the manufacturer);
2. Authorization from the device manufacturer for the use;
3. A description of the patient's condition and the circumstances necessitating treatment or diagnostics (when seeking small group access, the number of patients to be treated;
4. A discussion of why alternative therapies/diagnostics are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition; and
5. The patient protection measures that will be followed, including:
    a. A draft of the informed consent document that will be used;
    b. Clearance from the institution as specified by their policies (see below);
    c. Concurrence (approval) of the IRB Chair or Chair-designated IRB member (prior to FDA request when possible); and
    d. An independent assessment from an uninvolved physician.

When IRB Chair approval cannot be obtained in advance of the submission to the FDA, the request should indicate that approval from the IRB Chair will be obtained prior to use of the device. Proof of IRB Chair approval must be submitted with the follow-up report to the FDA after the patient is treated (or the

diagnostic is used).

When the compassionate use is conducted under an IDE, a licensed provider who receives an investigational device is an "investigator" under FDA regulations and is responsible and accountable for all applicable investigator responsibilities under 21 CFR 812 (IDE regulations), 21 CFR 50 (Informed Consent), and 21 CFR 56 (IRB).

When the provider obtains an IDE for compassionate use, the provider is considered a "sponsor-investigator" and is responsible for the responsibilities of both sponsors and investigators under 21 CFR 812, as applicable, including medical device reports and progress reports.

IRB Review:

Unless the conditions that permit an emergency use exemption are satisfied (see Section 15.9.3), IRB approval must be obtained prior to initiating treatment with the investigational device. When the request is for single-patient compassionate use, the review may be conducted by the IRB Chair (or designee). Otherwise, the review must be conducted by the convened IRB.

Physicians using medical devices under compassionate use should develop and submit an appropriate plan and schedule for treating and monitoring the patient, taking into consideration the nature of the device and the needs of the patient. The plan should include monitoring to detect any possible problems arising from the use of the device.

To request IRB approval for compassionate use, investigators should notify billing, contact the IRB office (as soon as possible to coordinate a timely review), and submit the following via the IRBManager:

1. IRB Application Form;
2. A copy of the information submitted to the FDA (and FDA approval, if available);
3. A copy of the device brochure, Instructions for Use, or other similar documentation that provides information regarding the potential risks and benefits of the device;
4. A copy of the plan for treating and monitoring the patient; and
5. A copy of the draft informed consent document.

The IRB may review the expanded access application prior to FDA approval being received but may condition approval upon receipt of FDA approval. The IRB will provide the investigator with written documentation of its review.

SJH/SPHP will consider reliance upon an external IRB for Compassionate Use protocols on a case-by-case basis when the IDE is held by a commercial sponsor and an external IRB has already approved the protocol and is willing to accept review and oversight of additional investigators/sites. Investigators should contact the HRPP Administrator or IO, to discuss IRB reliance for Compassionate Use protocols.

Post-Approval Requirements

Investigators are responsible for complying with any sponsor or FDA reporting requirements. The post-approval requirements for research described throughout this manual apply, including, but not limited to, prospective IRB approval of any proposed modifications to the plan or materials approved by the IRB unless the change is necessary to eliminate apparent immediate hazard to the subject (in which case it must be promptly reported), reporting of unanticipated problems, noncompliance, complaints, and other reportable information, and for continuing review and study closure, as applicable. **Additionally**, a

follow-up report to the FDA is required following a compassionate use by whomever submitted the original request to the FDA. The report should include summary information regarding patient outcome and any problems that occurred as a result of the device. A copy of the follow-up report to the FDA and any other post-approval submissions or reports to the FDA should be submitted to the IRB within 7 business days of the date of submission to the FDA.

15.9.2.2. Treatment Use of Investigational/Unapproved Devices

During the course of a clinical trial under an IDE, if the data suggest that the device under study is effective, the trial may be expanded to include additional patients with life-threatening or serious diseases under the Treatment Use provision for expanded access. "Treatment Use" also applies to the use of a device for diagnostic purposes under these same conditions. [21 CFR 812.36]

The following criteria must be satisfied for Treatment Use to apply:

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

The IDE sponsor is responsible for applying for a Treatment Use IDE.

A licensed provider who receives an investigational device for treatment use under a Treatment Use IDE is an "investigator" under FDA regulations and is responsible and accountable for all applicable investigator responsibilities under 21 CFR 812 (IDE regulations), 21 CFR 50 (Informed Consent), and 21 CFR 56 (IRB).

IRB Review:

IRB approval is required before the investigational device/diagnostic is used. The review may be conducted by the IRB Chair (or designee). Otherwise, the review must be conducted by the convened IRB.

To request IRB approval for Treatment use, investigators should notify billing, contact the IRB office (as soon as possible to coordinate a timely review), and submit the following via the IRB Electronic System (IRBManager):

1. IRB Application Form.
2. A copy of the information submitted to the FDA (and FDA approval);
3. Treatment Use IDE Protocol, if available.
4. A copy of the device brochure, Instructions for Use, or other similar documentation that provides information regarding the potential risks and benefits of the device.
5. A copy of the plan for treating and monitoring the patient; and
6. A copy of the draft informed consent document.

SJH/SPHP will consider reliance upon an external IRB for Treatment Use IDE protocols on a case-by-case basis when an external IRB has already approved the protocol and is willing to accept review and oversight of additional investigators/sites. Investigators should contact the HRPP Administrator or IO, to discuss IRB reliance for Treatment Use IDEs.

Post-Approval Requirements

Investigators are responsible for complying with any sponsor or FDA reporting requirements. The post-approval requirements for research described throughout this manual apply, including, but not limited to, prospective IRB approval of any proposed modifications to the plan or materials approved by the IRB unless the change is necessary to eliminate apparent immediate hazard to the subject (in which case it must be promptly reported), for reporting of unanticipated problems, noncompliance, complaints, and other reportable information, and for continuing review and study closure, as applicable. **Additionally**, the semi-annual (applicable until the marketing application is filed) or annual (applicable after the marketing application is filed) progress report from the sponsor should be submitted to the IRB within 7 business days of receipt.

15.9.3. Emergency Use of Investigational Drugs and Devices

FDA regulations permit the use of an investigational drug or device without IRB approval when an appropriately trained and licensed health care provider determines that IRB approval for the use of the drug or device cannot be obtained in time to prevent serious harm or death to a patient. The provider is expected to assess the potential for benefit from the use of the drug or device and to have substantial reason to believe that benefits will exist. The criteria and requirements for this Emergency Use Exemption are explained in Section 15.9.3.1 below.

Sponsor/Manufacturer approval must be obtained prior to initiating treatment with the drug or device.

For emergency use of drugs, FDA approval must be obtained prior to initiating treatment (see Section 15.9.3.1).

For emergency use of devices, prior FDA approval is not required if the provider determines and documents that: (1) the patient has a life-threatening or serious disease or condition that needs immediate treatment; (2) no generally acceptable alternative treatment for the condition exists; and (3) because of the immediate need to use the device, there is no time to use existing procedures to obtain FDA approval for the use.

Providers invoking the emergency use exemption must comply with any applicable FDA follow-up requirements. Information regarding follow-up report requirements for investigational drugs and devices is available on the respective FDA websites.

Note: DHHS regulations do not permit research activities to be started, even in an emergency, without prior IRB approval. When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject under 45 CFR Part 46.

However, nothing in the DHHS regulations at 45 CFR Part 46 is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state or local law.

15.9.3.1. Emergency Use Exemption from Prospective IRB Approval

Under FDA regulations [21 CFR 56.104(c)], FDA exempts the emergency use of a test article from the requirement for prospective IRB approval, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article in the facility requires IRB review. However, FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue. If in the review of the emergency use, it appears likely that the test article may be used again, the IRB may request that a study application is submitted which would cover future uses.

FDA defines emergency use as the use of a test article 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 [21 CFR 56.102(d)]. If all conditions described in 21 CFR 56.102(d) exist, then the emergency exemption from prospective IRB approval found at 21 CFR 56.104(c) may be used.

Life-threatening, for the purposes of 21 CFR 56.102(d), includes both life-threatening and severely debilitating.

Unless the provisions for an emergency exception from the informed consent requirement are satisfied (see Section 15.7.3.2), informed consent must be obtained in accordance with 21 CFR 50 and documented in writing in accordance with 21 CFR 50.27.

The IRB must be notified within **5 working days** after an emergency exemption is used. The IRB Chair or other IRB member will review the report to verify that circumstances of the emergency use conformed to FDA regulations. This must not be construed as IRB approval, as an exemption from the requirement for prospective IRB approval has been invoked. When appropriate, in the event a manufacturer requires documentation from the IRB prior to the emergency use, the IRB Chair or designee will review the proposed use, and, if appropriate, provide 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).

Investigators are reminded that they must comply with all other organizational policies and requirements applicable to the use of the investigational or unapproved drugs or device.

15.9.3.2. Emergency Exception from the Informed Consent Requirement

An exception under FDA regulations at 21 CFR 50.23(a-c) permits the emergency use of an investigational drug or device without informed consent when the investigator and an independent physician who is not otherwise participating in the clinical investigation (the emergency use) certify in writing all four of the following conditions:

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 not sufficient to obtain consent from the subject's LAR; and
4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the life of the subject.

If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the

subject, and time is not sufficient to obtain the independent physician determination in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

The IRB must be notified within **5 working days** when an emergency consent exception is invoked. Submission of the *Emergency Use Report* form or IRBManager submission and documentation of the independent physician evaluation will satisfy this requirement. The IRB Chair or other IRB member will review the report to verify that circumstances of the emergency exception conformed to FDA regulations.

15.10. Charging Subjects for Investigational Products

FDA regulations do not prohibit charging subjects or their insurers for investigational products so long as those charges comply with specified criteria. FDA approval of such charges does not obviate the investigator's and IRB's responsibility to minimize risks to subjects (Beneficence), to ensure that the risks and burdens associated with research are equitably distributed (Justice), and to ensure that subjects are properly informed and not unduly influenced to accept an otherwise unacceptable risk or cost in order to access a benefit (Respect for Persons). Any costs to subjects or insurers must be described in the IRB application and informed consent document. All studies are required to undergo billing review.

15.10.1. Charging for Investigational Medical Devices and Radiological Health Products

IDE regulations allow sponsors to charge for an investigational device, however, the charge may not exceed the amount necessary to recover the costs of manufacture, research, development, and handling of the investigational device [21 CFR 812.7(b)]. Sponsors must justify the proposed charges for the device in the IDE application, state the amount to be charged, and explain why the charge does not constitute commercialization [21 CFR 812.20(b)(8)].

15.10.2. Charging for Investigational Drugs and Biologics

In 2009, FDA updated its rules at 21 CFR 312 regarding charging for Investigational Drugs under an IND.

These rules:

- Provide general criteria for authorizing charging for an investigational drug [21 CFR 312.8(a)]
- Provide criteria for charging for an investigational drug in a clinical trial [21 CFR 312.8(b)]
- Set forth criteria for charging for an investigational drug for an expanded access for treatment use [21 CFR 312.8(c)]
- Establish criteria for determining what costs can be recovered when charging for an investigational drug [21 CFR 312.8(d)]

Additional information is available in FDA guidance: Charging for Investigational Drugs Under and IND – Question and Answers.

16. Unanticipated Problems Involving Risks to Subjects or Others

Regulations require an organization to have written procedures for ensuring prompt reporting of "unanticipated problems involving risk to subjects or others" (referred to as UAPs).

This section provides definitions and procedures for the reporting of UAPs to the SJH/SPHP IRB. Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in Section 6.1.2.

16.1. Definitions

Unanticipated problems involving risk to participants or others. Unanticipated problems involving risks to subjects or others (UAPs) refer to any incident, experience, outcome, or new information that:

1. Is unexpected; **and**
2. Is at least possibly related to participation in the research; **and**
3. Indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, legal or social harm) than was previously known or recognized

UAPs also encompass Unanticipated Adverse Device Effects, as defined below.

Unexpected. The incident, experience or outcome is not expected (in terms of nature, severity, or frequency) given the research procedures that are described in the study-related documents, such as the IRB-approved research protocol/research plan and informed consent documents; and the characteristics of the subject population being studied.

Related. There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

Adverse Event. For the purposes of these policies and procedures, an adverse event (AE) is any untoward or unfavorable occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

Unanticipated Adverse Device Effect. An Unanticipated Adverse Device Effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety, or welfare of subjects [21 CFR 812.3(s)].

16.2. Procedures

16.2.1. Reporting

Adverse events in clinical trials must be reported to the sponsor in compliance with FDA regulations and sponsor requirements. Unless specifically required by the IRB for a given protocol, SJH/SPHP IRB discourages, but may accept reports of adverse events that are not UAPs to be

submitted at the Sponsors or PI request using the Item of Information Form. These requests will be acknowledged by the IRB Office.

Investigators must report the following events or issues to the IRB. Reports should be submitted as soon as possible after they have occurred, but within **5 working days** after the investigator first learns of the event using the appropriate form in IRBManager.

If investigators are uncertain but believe that the event might represent an UAP, a report should be submitted.

Examples of UAPs include:

1. A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome);
2. A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy);
3. Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). A summary and analyses supporting the determination should accompany the report;
4. An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects. A discussion of the divergence from the expected specificity or severity should accompany the report;
5. A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). A discussion of the divergence from the expected rate should accompany the report;
6. AEs involving direct harm to subjects enrolled by the local investigator which in the opinion of the investigator or sponsor, may represent an UAP;
7. IND Safety Reports from sponsors that meet the criteria for an UAP. Such reports must be accompanied by an analysis from the sponsor explaining why the report represents an UAP and whether it has been reported to the FDA as such;
8. Unanticipated adverse device effects (UADEs);
9. Any other AE or safety finding (e.g. based on animal or epidemiologic data) that indicates subjects or others might be at risk of serious, unanticipated harms that are reasonably related to the research. These would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects. An explanation of the conclusion should

accompany the report.

10. Reports (including reports from DSMBs/DMCs) that indicate that risks are greater than previously known or that indicate that the research should be modified, suspended, or halted.
11. Any Protocol deviation that harmed subjects or others or that indicates subjects or others may be at increased risk of harm.
12. Sponsor or lead investigator/coordinating center imposed suspension or termination for risk;
13. An unanticipated event related to the research that exposes subjects to potential risk but that does not involve direct harm to subjects;
14. A breach of confidentiality or loss of research data (e.g., a laptop or thumb drive is lost or stolen);
15. An unanticipated event related to the research that results in actual harm or exposes individuals other than the research subjects (e.g., investigators, research assistants, students, the public, etc.) to potential risk;
16. New information that indicates increased risk, new risk(s), or decrease to potential benefit from what was previously understood. Examples include:
    a. An interim analysis or safety monitoring report indicates that the frequency or magnitude of harms or benefits may be different than initially presented to the IRB;
    b. A report or publication that indicates the risks, benefits, or merit of the research are different from what was previously understood.

16.2.2. Review Procedures: SJH/SPHP Subjects

Unanticipated Problem Reports will be reviewed by HRPP Administrator to confirm that the reported incident constitutes an unanticipated problem (in consultation with the IRB Chair or Vice Chair, as needed), and will make an initial determination regarding action.

If needed, the Chair, Vice Chair or designee may request additional information from the investigator, sponsor, or others (including study committees, such as data monitoring committees, DSMBs, or steering committees).

If it is determined that immediate action may be required, the unanticipated problem will be forwarded to the Chair or Vice Chair for review. If the IRB Chair deems it necessary to take action before the IRB meeting (e.g., suspension etc.), the PI will be notified regarding steps to be taken to ensure protection of rights/welfare of subjects (or staff, as appropriate), pending review and action by the full committee. If immediate action is not required, the unanticipated problem will be placed on the agenda for full review at the next IRB meeting. Pre-review may be conducted by one (1) or more IRB members.

16.2.3. Review Procedures: non-SJH/SPHP Subjects

Unanticipated Problem Reports and associated sponsor/coordinating site materials will be reviewed by the HRPP Administrator to determine if any additional local action is required.

If needed, the IRB Chair, Vice Chair or designee may request additional information from the investigator, sponsor, or others (including study committees, such as data monitoring committees, DSMBs, or steering committees).

If no action is required, an acknowledgment letter will be sent to the PI. If additional action is required, the

unanticipated problem will be placed on the agenda for full review at the next IRB meeting. If the IRB Chair deems it necessary to take immediate action (e.g., suspension etc.), the PI will be notified regarding steps to be taken to ensure protection of rights/welfare of subjects (or staff, as appropriate), pending review and action by the full committee.

16.2.4. Review Outcomes

1. Based upon the circumstances, the IRB may take any of the following actions, or others, to ensure the protection of human subjects:
    a. Requiring modifications to the protocol.
    b. Revising the continuing review timetable.
    c. Modifying the consent process.
    d. Modifying the consent document.
    e. Providing additional information to current participants (e.g., whenever the information may relate to the subject's rights, welfare, or willingness to continue participation).
    f. Providing additional information to past participants.
    g. Requiring additional training of the investigator and/or study staff.
    h. Requiring that current subject's re-consent to participation.
    i. Monitoring the research.
    j. Monitoring consent.
    k. Reporting or referral to appropriate parties (e.g., the IO, Integrity & Compliance Officer).
    l. Suspending IRB approval.
    m. Terminating IRB approval.
    n. Other actions as appropriate given the specific circumstances.
2. When the IRB determines that an event is an UAP, the HRPP Administrator will follow the procedures for reporting to regulatory agencies, sponsors, and organizational officials in Section 20. When appropriate, a preliminary report may be submitted while more information is obtained to inform the determination or actions. Suspension or termination of research by the IRB will be promptly reported in writing to OHRP, and FDA (if FDA-regulated research).
3. The results of the review will be recorded in IRBManager and communicated to the investigator.

17. Noncompliance

This section provides definitions and procedures for the reporting and review of known or suspected noncompliance for research under the oversight of the SJH/SPHP IRB. Research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in Section 6.1.2.

In conducting its review of protocol deviations, unanticipated problems, subject complaints, and other reportable events, the IRB will also consider whether the event or issue was caused by, contributed to, or otherwise related to noncompliance.

17.1. Definitions

Noncompliance is defined as the failure to follow federal, state, or local regulations governing human

subject research, institutional policies related to human subject research, or the requirements or determinations of the IRB. Noncompliance may be minor or sporadic or it may be serious or continuing.

Serious Noncompliance is defined as noncompliance that, in the judgment of the convened IRB, creates an increase in risks to subjects, adversely affects the rights, welfare, or safety of subjects, or adversely affects the scientific integrity of the study. Willful violation of institutional policies and/or federal, state or local regulations may also constitute serious noncompliance.

Continuing Noncompliance is defined as a pattern of noncompliance that, in the judgment of the convened IRB, suggests a likelihood that instances of noncompliance will continue unless the IRB or institution intervenes.

Allegation of Noncompliance. Allegation of Noncompliance is defined as an unproved assertion of noncompliance.

17.2. Reporting

Investigators and their study staff are required to report instances of possible noncompliance. The PI is responsible for reporting any possible non-compliance by study personnel to the HRPP Administrator, who will notify the IRB Chair, IO and the Integrity & Compliance Office. Any individual or employee may report observed or apparent instances of noncompliance to the Integrity & Compliance office. In such cases, the reporting party is responsible for making these reports in good faith, maintaining confidentiality and cooperating with any HRPP, IRB, and/or institutional review of these reports.

If an individual, whether investigator, study staff or other, is uncertain whether there is cause to report noncompliance, he or she may contact the HRPP Administrator, IRB Chair, IO or the Integrity & Compliance Office to discuss the situation informally.

Reports of non-compliance must be submitted to the SJH/SPHP HRPP Office or the Integrity & Compliance Office as soon as possible upon discovery of the noncompliance. The report may be verbal or written, and must include a complete description of the noncompliance, and the personnel involved. Complainants may choose to remain anonymous.

17.3. Review Procedures

1. Upon receipt of the Protocol Deviation, or other notification of suspected noncompliance, the HRPP Administrator pre-reviews the submission and, if needed, contacts the investigator for corrections or additional information. If the report came from someone other than the investigator verbally, by email, or by other means, the HRPP Administrator or assigned staff will develop a written report summarizing the available information and will upload the report into IRBManager. If the information provided suggests that subjects may be at risk of harm without immediate intervention or that research misconduct may have occurred, the IRB Chair or Vice Chair, and, when appropriate, the IO will be notified so that they can take any necessary steps to ensure the safety of subjects and/or investigate the matter.
2. The IRB Chair or Vice Chair receives and reviews the report and makes an initial determination as to whether the event represents noncompliance, and, if so, if the noncompliance may be serious or continuing. If needed, the IRB Chair/Vice Chair may

request additional information from the investigator or others. When circumstances warrant, the HRPP Administrator may bypass this step and assign the report for convened board review.

3. If the IRB Chair/Vice Chair determines that the event or issue is not noncompliance, or is noncompliance but not serious or continuing, they will review any proposed corrective and preventative action plans and determine if the plan is acceptable as proposed or if modifications to the plan or additional actions are required. As warranted, the IRB Chair/Vice Chair may refer the matter to the convened IRB for review. The results of the review will be recorded in IRBManager and communicated to the investigator.
4. If the reviewer determines that the event or issue may be serious or continuing noncompliance, the report will be referred for review by the convened IRB. The convened IRB will determine whether the event is serious or continuing noncompliance. The IRB will review any proposed corrective and preventative action plans and determine if the plan is acceptable as proposed or if modifications to the plan or additional actions, such as those outline below, are necessary to ensure the protection of human subjects. If needed, the IRB may request additional information from the investigator or others. The results of the review will be recorded in the IRB minutes and communicated to the investigator.
5. When the IRB determines that an event is serious or continuing noncompliance, the IRB may take any of the following actions, or others, to ensure the protection of human subjects:
    a. Requiring modifications to the protocol
    b. Revising the continuing review timetable
    c. Modifying the consent process
    d. Modifying the consent document
    e. Providing additional information to current participants (e.g., whenever the information may relate to the subject's willingness to continue participation)
    f. Providing additional information to past participants
    g. Requiring additional training of the investigator and/or study staff
    h. Requiring that current subjects re-consent to participation
    i. Monitoring the research
    j. Monitoring consent
    k. Reporting or referral to appropriate parties (e.g., the IO, Integrity & Compliance Officer)
    l. Suspending IRB approval
    m. Terminating IRB approval
    n. Other actions as appropriate given the specific circumstances
6. When the IRB determines that an event is serious or continuing noncompliance, the HRPP Administrator will follow the procedures for reporting to regulatory agencies, sponsors, and organizational officials in Section 20. When appropriate, a preliminary report may be submitted while more information is obtained to inform the determination or actions.
7. Investigators may request that the IRB reconsider its determination by following the procedures in Section 9.4.

18. Complaints

The HRPP & IRB will be responsive and sensitive to the complaints or concerns expressed by subjects or others and will respond to all complaints or concerns in a confidential and timely manner. The PI and all other research team members are responsible for the safety and welfare of all subjects enrolled in their studies. When investigators or team members hear complaints or concerns from subjects, he or she will try to resolve them.

Investigators conducting research under the auspices of SJH/SPHP must report complaints to the SJH/SPHP HRPP regardless of who serves as the IRB of record. Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in Section 6.1.2.

Investigators report complaints to the SJH/SPHP IRB in IRBManager. Investigators are encouraged to contact the HRPP Administrator or Office of Patient Experience (patient.relations@SJH/SPHPsyr.org) when they are having difficulty resolving a complaint or concern, and whenever circumstances warrant (e.g., immediate attention is needed).

When the HRPP or IRB office is the direct recipient of complaints or concerns, the following will occur:

1. Document the complaint or allegation. When appropriate, the staff may request that the subject submit the complaint in writing.
2. Reassure the subject that the HRPP/IRB will take all necessary measures to inquire into the circumstances and to address the issue.
3. When appropriate, contact the investigator for additional information or to assist with resolution.
4. When appropriate, contact other resources to assist with information-gathering or resolution.
5. Provide written confirmation of receipt of the complaint to the subject, if the subject is willing to provide contact information.
6. Convey the information to the IRB of record in a timely manner.

For research under the oversight of the SJH/SPHP IRB, the IRB Chair or designee will consider the complaint or concern and take any reasonable steps necessary to investigate and/or resolve the issue, if appropriate, prior to review and consideration by the IRB. A report will be provided to the IRB at the next available meeting or provided to the designated expedited reviewer if the research is eligible for expedited review.

When reviewing complaints, the IRB will consider whether the complaint was the result of, or related to, an UAP or noncompliance, and, if so, will follow the relevant procedures. The IRB Chair or designated expedited reviewer may refer any complaint for review by the convened IRB. The IRB minutes, or reviewer comments for expedited reviews, will reflect the action(s) taken and, if necessary, notice to the appropriate officials and/or agencies.

The HRPP will maintain written copies of complaints and concerns and will document the investigation and resolution. The complainant will be notified promptly following resolution of the complaint or concern, when appropriate, and if contact information has been provided. If the HRPP or IRB receives a complaint, or identifies information while investigating a complaint, that is indicative of possible misconduct in research, SJH/SPHP's Integrity and Compliance Office will be notified immediately.

19. Other Reportable Information

When research is under the oversight of the SJH/SPHP IRB, in addition to UAPs, noncompliance, and complaints, any change to the research implemented without IRB approval and any information that may impact the rights, safety, or welfare of subjects or inform the IRB's oversight of the research must be reported to the IRB as soon as possible upon discovery using the Protocol Deviation or Item of Information Form. Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in Section 6.1.2.

Other reportable information includes, but is not limited to, the following:

1. Changes made to the research without prior IRB approval to eliminate apparent immediate hazards to the subject(s).
2. Protocol Deviations - any variation from the IRB approved research plan that happens without prior review and approval of the IRB and isn't necessary to eliminate apparent immediate hazards to the subject(s);
3. Monitoring, audit, and inspection reports in accordance with Section 2.1 of this manual.
4. Sponsor or coordinating center reports.
5. Data Safety Monitoring reports, including reports from DSMBs, DMCs, and others.
6. Enrollment or inclusion of vulnerable populations not previously approved by the IRB for the study (e.g., prisoner, pregnant woman, neonate, child, adult with impaired decision-making capacity).
7. When an existing subject becomes a member of a vulnerable population not previously approved by the IRB for inclusion in the study (e.g., incarceration, pregnancy, or change in decision-making capacity of an already enrolled subject).
8. Holds, suspensions, or terminations of a study, in part or in full, by an investigator, sponsor, or others.
9. Changes that impact the ability of the PI to conduct or supervise the study, temporarily or permanently.
10. Changes that impact the qualifications of investigators or research staff members such as actions taken by regulatory authorities, licensing boards, or credentialing committees.
11. New information that may impact the rights, welfare, or willingness of subjects to continue in the research.

19.1. Review Procedures

1. Upon receipt of the report, the HRPP Administrator reviews the submission and, if needed, contact the investigator for corrections or additional information. If the information provided suggests that subjects may be at risk of harm without immediate intervention or that research misconduct may have occurred, the HRPP Administrator, IRB Chair/Vice Chair, and, when appropriate, the IO and/or Integrity & Compliance Officer will be notified so that they can take any necessary steps to ensure the safety of subjects or investigate the matter.
2. The IRB Chair, Vice Chair, or designated IRB member receives and reviews the report and if the report may represent an UAP or noncompliance, reviews the report as described in Section 16 or 17. When circumstances warrant, the HRPP Administrator may bypass this

step and assign the report for convened board review.

3. If the IRB Chair/Vice Chair, or designated IRB member determines that the event or issue is not noncompliance or an UAP, they will review the event or issue, any proposed corrective and preventative action plans, and determine if any additional actions are needed to ensure the protection of human subjects. As warranted, the IRB Chair/Vice Chair, or designated IRB member may refer the matter to the convened IRB for review. The results of the review will be recorded in IRBManager and communicated to the investigator.

20. Reporting to Federal Agencies, Departments, and Organizational Officials

Federal regulations require prompt reporting to appropriate institutional officials and, as applicable, the federal department or agency (e.g., OHRP, FDA), of (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance with the applicable federal regulations or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval. The SJH/SPHP IRB complies with this requirement as described in section 20.1 below. When research is under the oversight of an external IRB, the terms of the reliance agreement (Section 6.2.2) with the IRB of record will guide reporting.

20.1. Procedures

HRPP Administrator will initiate these procedures as soon as the IRB takes any of the following actions:

1. Determines that an event may be considered an unanticipated problem involving risks to participants or others
2. Determines that noncompliance was serious or continuing
3. Suspends or terminates approval of research

The HRPP Administrator or designee is responsible for preparing reports or letters, which include the following information:

1. Reason for the report (Unanticipated problem involving risks to subjects or others, serious or continuing noncompliance, suspension or termination of IRB approval)
2. Name of the involved institution(s)
3. Title of the research project and/or grant proposal in which the problem occurred
4. Name of the investigator on the project
5. Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement)
6. A detailed description of the problem including the findings of the organization and the reasons for the IRB's decision
7. Actions the institution is taking or plans to take to address the problem (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring, etc.)
8. Any applicable reports from IRB consultants
9. Plans, if any, to send a follow-up or final report by the earlier of
    a. A specific date

b. When an investigation has been completed or a corrective action plan has been implemented

The IRB Chair and the IO review the report or letter and recommend modifications as needed. The IO is the signatory.

The HRPP Administrator or designee sends a copy of the report or letter to:

- The IRB Chair
- The IO
- The PI
- Sponsor, if the study is sponsored
- Others as deemed appropriate by the IO
- Federal agencies, as follows:
  c. OHRP,
  d. FDA, if the study is subject to FDA regulations.
  e. If the study is conducted or supported by a federal agency and reporting is required, the report is sent to the head of the federal agency or the party identified by the agency.

Note: Reporting to a regulatory agency may not be required if the event occurred at another site and the regulatory agency/sponsor has been notified of the event by another party (e.g., sponsor or other institution).

The HRPP Administrator ensures that all steps of this policy are completed within 30 working days of the convened IRB's determination of an unanticipated problem, serious or continuing noncompliance, suspension, or termination.

21. Investigators

Principal Investigators (PIs) are ultimately responsible for the compliant and ethical conduct of research. PIs may delegate tasks to appropriately trained and qualified members of their research team. However, PIs must maintain oversight and retain ultimate responsibility for the proper conduct of those to whom they delegate responsibility.

The IRB recognizes one PI for each study. The PI has ultimate responsibility for the research activities.

Protocols that require skills beyond those held by the PI must be modified to meet the investigator's skills or have one or more additional qualified physicians as co-investigator(s).

Students, residents, fellows and staff may serve as PIs.

The research team consists of individuals who intervene or interact directly with subjects (including the recruitment or consenting thereof), or who analyze data and/or tissue derived from humans for the purposes of the activity in question.

21.1. Responsibilities

Investigators who conduct research involving human subjects must:

1. Develop and conduct research that is in accordance with the ethical principles in the Belmont

Report.

2. Develop a research plan that is scientifically sound and minimizes risk to the subjects.
3. Develop a research plan that ensures the just, fair, and equitable recruitment and selection of subjects.
4. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, include additional safeguards in the study to protect the rights and welfare of these subjects.
5. Ensure that the research plan includes adequate provisions for the monitoring of subjects and data to ensure the safety of subjects.
6. Ensure that there are adequate provisions to protect the privacy interests of subjects.
7. Ensure that there are adequate provisions to protect the confidentiality of data.
8. Have sufficient resources necessary to protect human subjects, including:
    a. Access to a population that would allow recruitment of the required number of subjects.
    b. Sufficient time to conduct and complete the research.
    c. Adequate numbers of qualified staff.
    d. Adequate facilities.
    e. Necessary equipment.
    f. A plan to ensure proper supervision of the research including a plan for periods of absence or decreased availability; and
    g. When appropriate, a plan to ensure the availability of medical, psychological, or other services that subjects might require as a result of their participation.
9. Ensure that all procedures in a study are performed with the appropriate level of supervision and only by individuals who are licensed or otherwise qualified to perform such under the laws of NY State and the policies of SJH/SPHP
10. Ensure that all study personnel are educated in the regulatory requirements regarding the conduct of research and the ethical principles upon which they are based (e.g. completed required CITI training),
11. Ensure that all persons assisting with the research are adequately trained and informed about the protocol and research implementation plan and their specific duties and functions.
12. Promptly report any changes in, addition to, or departure of investigators or research staff to the IRB for evaluation and approval (note that investigators and staff may not begin work on the research until IRB-approved).
13. Protect the rights, safety, and welfare of participants.
14. Ensure that when Protected Health Information (PHI) is used, legally effective HIPAA authorization is obtained for each subject unless a Privacy Board or IRB has approved a waiver of the requirement.
15. Ensure that the language in the consent form is consistent with that in the protocol, any associated grant or contract, and, when applicable, the HIPAA authorization.
16. Obtain and document informed consent and ensure that no human subject is involved in the research prior to obtaining consent or consent/permission from their LAR, unless a waiver of the requirement has been approved by the IRB.
17. Have a procedure to receive questions, complaints, or requests for additional information from subjects and respond appropriately.
18. Ensure that all information provided to the IRB is accurate and complete so that the IRB may fulfill its responsibilities to review the research and make the required determinations.

19. Ensure that all research involving human subjects receives IRB review and approval in writing or a determination of exemption before the research begins.
20. Ensure that all other required reviews, signoffs and approvals are in place before initiating the research.
21. Comply with all IRB decisions, conditions, and requirements.
22. Ensure that studies receive timely continuing IRB review and approval.
23. Report unanticipated problems, deviations, complaints, noncompliance, suspensions, terminations, and any other reportable events to the IRB and the organization, as required by regulations and policy.
24. Notify the IRB if information becomes available that suggests a change to the potential risks, benefits, merit, or feasibility of the research.
25. Obtain IRB review and approval before changes are made to the research unless a change is necessary to eliminate apparent immediate hazards to the subject(s).
26. Seek HRPP or IRB assistance when in doubt about whether proposed research requires IRB review.
27. Retain records for the time-period and in the manner described to and approved by the IRB and as required by regulations, agreements, and policies.

Additional investigator responsibilities, including specific responsibilities for investigators engaged in FDA-regulated research are described throughout this manual.

21.1.1. Record Retention

Investigator research records, including, but not limited to, signed consent forms and HIPAA authorizations, subject records and data, test article records, IRB records (submission materials, IRB determinations and associated documentation, correspondence to and from the IRB, etc.), and sponsor/grant records must be retained in accordance with regulatory, organizational, IRB, sponsor or grantor, and journal or publication standards. Records must be maintained securely with limited access. Disposal of investigator records must be done in such a manner that no identifying information can be linked to research data. When research is sponsored or grant supported, consult the contract, grant terms, or other relevant agreements prior to destroying or transferring any records. If there are questions or allegations about the validity of the data or the appropriate conduct of the research, all records must be retained until such questions or allegations have been completely resolved.

Records pertaining to IRB-approved research must be retained for a defined time period (as noted) once the research is permanently closed.

Research is permanently closed if all of the following conditions are met:

- No new subjects will be enrolled; **and**
- There will be no more intervention or interaction with enrolled subjects; **and**
- No further analysis of identifiable data/tissue will be conducted. Either analyses are complete, or data/tissue have been permanently de-identified (i.e., with all identifiers and keys to codes destroyed).

The following summarizes a few of the more common regulatory requirements:

1. **OHRP** – research records must be retained for at least 3 years after the completion of the research
2. **HIPAA** – Research authorizations (including combined consent and authorizations), or documentation of waivers or alterations of authorization, must be held for a minimum of 6 years after the authorization or waiver/alterations was last obtained or in effect, whichever is later
3. **FDA – Drugs** (& biologics classified as drugs) - For a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified
4. **FDA – Devices** (& biologics classified as devices) - For a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

21.2. Investigator Concerns

Investigators who have concerns or suggestions regarding SJH/SPHP's HRPP should convey them to the HRPP Administrator, the IO or other responsible parties when appropriate. The recipient of the concern will consider the issue, and when deemed necessary, seek additional information and convene the parties involved to form a response for the investigator or make necessary procedural or policy modifications, as warranted. In addition, the IRB Chair and HRPP Administrator are available to address investigators' questions, concerns, and suggestions.

Consistent with SJH/SPHP policies, there will be no retaliation against employees, physicians, students, staff, etc. who report concerns in good faith.

22. Sponsored Research

It is SJH/SPHP's policy that any sponsored research conducted under the auspices of SJH/SPHP is conducted in accordance with federal guidelines and ethical standards.

The following describe the procedures required to ensure that all sponsored research meets this requirement.

22.1. Definitions

Sponsor. Sponsor means the company, institution, individual donor, or organization responsible for the initiation, management or financing of a research study.

Sponsored research. Sponsored research means research funded by external entities (public, industry, or private) through a grant or contract that involves a specified statement of work (e.g., the research proposal), including clinical trials involving investigational drugs, devices or biologics.

22.2. Responsibility

Sponsor grants, contracts, and other written agreements will be reviewed with consultation with the IRB, as necessary:

1. All sponsor contracts have a written agreement with the Sponsor that addresses medical care for research participants with a research-related injury, when appropriate.
2. In studies where Sponsors conduct research site monitoring visits or conduct monitoring activities remotely, the sponsor contracts have a written agreement with the Sponsor that the Sponsor promptly reports to the SJH/SPHP IRB findings that could affect the safety of participants or influence the conduct of the study.
3. When the Sponsor has the responsibility to conduct DSM, the sponsor contracts have a written agreement with the Sponsor that addresses provisions for monitoring the data to ensure the safety of participants and for providing DSM reports to the IRB of record.
4. Sponsor contracts have a written agreement with the Sponsor about plans for disseminating findings from the research and the roles that investigators and Sponsors will play in the publication or disclosure of results.
5. When participant safety could be directly affected by study results after the study has ended, the sponsor contracts have a written agreement with the Sponsor that the investigator, the IRB of record or the SJH/SPHP IRB will be notified of the results in order to consider informing participants.
6. Payment in exchange for referrals of prospective participants from investigators (physicians) (finder's fees) is not permitted. Similarly, payments designed to accelerate recruitment that are tied to the rate or timing of enrollment (bonus payments) are also not permitted.

23. Conflict of Interest in Research

It is SJH/SPHP's policy to preserve public trust in the integrity and quality of research by reducing actual or perceived COI in the conduct of research.

COI in research can be broadly described as any interest that competes with an organization's or individual's obligation to protect the rights and welfare of research subjects, the integrity of a research study, or the credibility of the research program. COI can be financial or non-financial.

In the environment of research, openness and honesty are indicators of integrity and responsibility, characteristics that promote quality research and strengthen the research process. Therefore, COI should be eliminated, managed and/or disclosed.

23.1. Researcher Conflicts of Interest

Identification and Management of COI by Members of the SJH/SPHP Community Involved in Sponsored Research, SJH/SPHP IRB will collaborate with the Office of Integrity & Compliance to ensure that COI of investigators and research team members (investigators) are identified and managed before the IRB completes its review of any research application.

23.1.1. Procedures

23.1.1.1. Disclosure of Researcher COI

For IRB purposes, investigator conflict review occurs at the time of new study submission or personnel change form, for addition of a new investigator, and whenever an investigator signs off on the COI

disclosure indicating a new or changed interest. HRPP Administrator notify the Integrity & Compliance Office whenever a submission requiring conflict review is received.

For new study submissions, COI review must be completed before electronic submission through IRBManager are submitted to the IRB Office. The SJH/SPHP IRB may defer the review of the new research study until COI review is completed and the results are made available to the IRB.

When the research is under an external IRB, any conflicts identified as the result of COI review and any Management Plans (MPs) are provided to the external IRB in accordance with the IRB reliance agreement.

23.1.1.2. Evaluation of COI

The IRB will review the results of the COI review and MPs to determine whether the MP effectively protects research subjects and the integrity and credibility of the research and the research program.

In evaluating COIs and MPs, among other factors the IRB will consider:

1. How the research is supported or financed.
2. The nature and extent of the conflict.
3. The role and responsibilities of the conflicted individual in the design, conduct, and reporting of the research; and
4. The ability of the conflicted individual to influence the outcome of the research.

23.1.1.3. Management of COI

The IRB has final authority to determine whether the research, the COI, and the MP, if any, allow the research to be approved. The IRB can require additional measures to manage a COI so that the research may be approved.

For example, in addition to the MP, the IRB may require:

1. Disclosure of the COI to subjects through the consent process;
2. Modification of the research plan or safety monitoring plan;
3. Monitoring of research by a third party;
4. Disqualification of the conflicted party from participation in all or a portion of the research;
5. Appointment of a non-conflicted PI;
6. Divestiture of significant financial interests; and/or
7. Severance of relationships that create actual or potential conflicts.

In the event the conflict cannot be effectively managed, the IRB may disapprove the research.

23.2. IRB Member Conflict of Interest

COI disclosures are required to be completed yearly by IRB members. No IRB member or alternate may participate in the review of any research project in which the member has a COI, except to provide information as requested. It is the responsibility of each IRB member to disclose any COI related to a study submitted for review and recuse himself or herself from the deliberations and vote by leaving the room.

The HRPP Administrator ensures that IRB members and alternates are not assigned to conduct reviews of studies for which the member has a known conflict and reminds members of conflicts at convened meetings as needed to ensure recusal. HRPP Administrator may consult with the Integrity & Compliance Office to clarify whether a specific study involves a member COI.

IRB members, alternates, or consultants may be considered to have a conflicting interest requiring recusal when they, or an immediate member of their family, have any of the following:

1. Involvement in the design, conduct, and reporting of the research;
2. Significant financial interests related to the research being reviewed; or
3. Any other situation where an IRB member believes that another interest conflicts with his or her ability to deliberate objectively on a study.

The IRB Chair will ask IRB members at the beginning of each convened meeting if any members have an unknown (i.e., other than being part of the study team) COI regarding any of the items to be reviewed and reminds members that they must recuse themselves by leaving the room during the discussion and vote of the specific research study. If a conflicted member is participating by conference call, the HRPP Administrator will mute the phone line during discussion and voting.

IRB members with a conflicting interest are excluded from being counted towards quorum. Recusals of members with COIs are recorded in the minutes.

23.3. Recruitment Incentives

Payment arrangements between or among sponsors, organizations, investigators, research personnel, and those referring research participants present a COI and may place participants at risk of coercion or undue influence or cause inequitable selection. Payment in exchange for referrals of prospective participants (finder's fees) is not permitted. Similarly, payments designed to accelerate recruitment that is tied to the rate or timing of enrollment (bonus payments) are also not permitted. Bonus payments do not include payments for bona fide items or services.

24. Health Insurance Portability and Accountability Act (HIPAA)

The *Health Insurance Portability and Accountability Act of 1996* (HIPAA) required the creation of a Privacy Rule for identifiable health information. While the primary impact of the Privacy Rule is on the routine provision of and billing for health care, the Rule also affects the conduct and oversight of research.

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule as, "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge." See 45 CFR 164.501. A covered entity may always use or disclose for research purposes health information which has been de-identified (in accordance with 45 CFR 164.502(d), and 164.514(a)-(c) of the Rule) without regard to the provisions below.

Except as otherwise permitted, The Privacy Rule also defines the means by which individuals will be informed of uses and disclosures of their medical information for research purposes, and their rights to access information about them held by covered entities. Where research is concerned, the Privacy Rule protects the privacy of individually identifiable health information, while at the same time ensuring that

researchers continue to have access to medical information necessary to conduct vital research. Currently, most research involving human subjects operates under the Common Rule (45 CFR Part 46, Subpart A) and/or the Food and Drug Administration's (FDA) human subject protection regulations (21 CFR Parts 50 and 56), which have some provisions that are similar to, but separate from, the Privacy Rule's provisions for research. These human subject protection regulations, which apply to most Federally-funded and to some privately funded research, include protections to help ensure the privacy of subjects and the confidentiality of information. The Privacy Rule builds upon these existing Federal protections. More importantly, the Privacy Rule creates equal standards of privacy protection for research governed by the existing Federal human subject regulations and research that is not.

The use of PHI for research done at SJH/SPHP will be in full compliance with regulations at 1) Health and Human
Services (HHS) 45 CFR §46; 2) HIPAA Privacy and Security Act 45 CFR §46.111(a)(7) and 45 CFR §164.512(i);
3) other applicable Federal, state, and local laws; and 4) will ensure that the individual who will use the records has
permitted access for research purposes.

- All patients have a right to privacy which precludes the use of their records containing any PHI by an individual who does not have permitted access as defined in this policy.
- Records containing PHI, in any form, are the property of SJH/SPHP. The PHI contained in the record is the property
  of the individual who is the subject of the record.
- When using or disclosing PHI or when requesting or receiving PHI from a covered entity, SJH/SPHP must make
  reasonable efforts to limit PHI to the minimum necessary to accomplish the research.
- SJH/SPHP will use a compound authorization process for research where the HIPAA authorization is merged within
  the research informed consent.

In the course of conducting research, researchers may obtain, create, use, and/or disclose individually identifiable health information. Under the Privacy Rule, covered entities are permitted to use and disclose protected health information for research with individual authorization, or without individual authorization under limited circumstances set forth in the Privacy Rule.

IRB applications will be processed and reviewed in either an exempt, expedited or full board category when research involves either the collection, creation and / or use of PHI:

1. **Exempt Research**
Research involving medical records is exempt provided the records utilized in the research are existing and the data are recorded in such a manner that participants cannot be de-identified (e.g., *either all 18-HIPAA specified identifiers are removed or a bio-statistical consult indicated there is only a "small risk" of re-identification of a participant)*

2. **Non-exempt Research**
Research involving the study of medical records is not exempt if the investigator records the data in such a manner that participants can be identified either directly or through identifiers linked to the participant or if

the study involves prospective collection of records. If participant identifiers must be temporarily maintained in order to permit the investigator to identify additional records for inclusion in the study, informed consent / authorizations required unless the IRB grants a waiver of informed consent and waiver of Authorization in accordance with the following specific requirements of HIPAA and 45 CFR §46.116(d):

a) Only the minimum amount of participant identifier data is recorded. Whenever possible, data should be recorded without PHI.

b) The use or disclosure of PHI or data, which is not PHI, involves no more than minimal risk.

c) The alteration or waiver of informed consent will not adversely affect the rights and welfare of the participants.

d) The research cannot practicably be carried out without the alteration or waiver.

e) There must be an adequate plan to protect participant identifiers from improper use and disclosure.

f) There must be an adequate plan to destroy the identifiers associated with PHI at the earliest opportunity unless there is a health or research justification for retaining the identifiers or retention is required by law.

g) When appropriate, the participants will be provided with additional pertinent information after participation.

h) If identifiers are recorded for the purpose of selecting a prospective participant population and the investigator intends to subsequently solicit informed consent to participate in a prospective study, specific guidelines must be followed regarding initial contact with potential participants. Contact with potential participants should originate with an individual who has the appropriate professional relationship with the potential participant (e.g. primary care physician, counselor, teacher, etc.). If an investigator does not have such a relationship, they shall obtain assistance from someone who does. Once the appropriate professional has originated the contact, negotiation for informed consent can begin as with any other research protocol.

24.1. Definitions

Access. Access is the mechanism of obtaining or using information electronically, on paper, or other medium for the purpose of performing an official function.

Accounting of Disclosures. Information that describes a covered entity's disclosures of PHI other than for treatment, payment, and health care operations; disclosures made with Authorization; and certain other limited disclosures. For those categories of disclosures that need to be in the accounting, the accounting must include disclosures that have occurred during the 6 years (or a shorter time period at the request of the individual) prior to the date of the request for an accounting.

Authorization. An individual's written permission to allow a covered entity to use or disclose specified PHI for a particular purpose. Except as otherwise permitted by the Privacy Rule, a covered entity may not use or disclose PHI for research purposes without a valid Authorization that includes all of the required elements under the Privacy Rule.

Covered entity. A health plan, a health care clearinghouse, or a health care provider who or that transmits health information in electronic form in connection with a transaction for which DHHS has adopted a standard.

Data Use Agreement. An agreement into which the covered entity enters with the intended recipient of a limited data set that establishes the ways in which the information in the limited data set may be used

and disclosed and how it will be protected.

De-identified. Data is considered de-identified under HIPAA when they do not identify an individual, and there is no reasonable basis to believe that the data can be used to identify an individual. The Privacy Rule defines two methods for de-identifying PHI: (1) when the PHI is stripped of all 18 HIPAA-defined identifying elements and the 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 (Safe Harbor method); or (2) when an appropriate expert determines that the risk is very small that the information could be used, alone or in combination with other reasonably available information, by an anticipated recipient to identify an individual who is a subject of the information (Expert Determination method).

Designated Record Set. A group of records maintained by or for a covered entity that includes (1) medical and billing records about individuals maintained by or for a covered health care provider; (2) enrollment, payment, claims adjudication, and case or medical management record systems maintained by or for a health plan; or (3) used, in whole or in part, by or for the covered entity to make decisions about individuals. A record is any item, collection, or grouping of information that includes PHI and is maintained, collected, used, or disseminated by or for a covered entity.

Disclosure. The release, transfer, provision of access to, or divulging in any manner, of information outside the entity holding the information.

Genetic Information. Genetic information means, with respect to an individual, information about: (i) The individual's genetic tests; (ii) The genetic tests of family members of the individual; (iii) The manifestation of a disease or disorder in family members of such individual; or iv) Any request for, or receipt of, genetic services, or participation in clinical research which includes genetic services, by the individual or any family member of the individual.

Genetic information concerning an individual or family member of an individual includes the genetic information of: (i) A fetus carried by the individual or family member who is a pregnant woman; and (ii) Any embryo legally held by an individual or family member utilizing an assisted reproductive technology. Genetic information excludes information about the sex or age of any individual.

Genetic services. A genetic test; genetic counseling (including obtaining, interpreting, or assessing genetic information); or genetic education.

Genetic test means an analysis of human DNA, RNA, chromosomes, proteins, or metabolites, if the analysis detects genotypes, mutations, or chromosomal changes. Genetic test does not include an analysis of proteins or metabolites that is directly related to a manifested disease, disorder, or pathological condition.

Health Information. Health Information means any information, including genetic information, whether oral or recorded in any form or medium, that (1) is created or received by a health care provider, health plan, public health authority, employer, life insurer, school or university, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual.

Individually Identifiable Health Information. Information that is a subset of health information,

including demographic information collected from an individual, and (1) is created or received by a health care provider, health plan, employer, or health care clearinghouse; and
(2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual; and (a) that identifies the individual; or (b) with respect to which there is a reasonable basis to believe the information can be used to identify the individual.

Limited Data Set. Refers to data sets that exclude 16 categories of direct identifiers that are specified in the Privacy Rule. Limited Data Sets may be used or disclosed, for purposes of research, public health, or health care operations, without obtaining either an individual's Authorization or a waiver or an alteration of Authorization for its use and disclosure, only if the covered entity obtains satisfactory assurances in the form of a Data Use Agreement. Limited Data Sets are not de-identified information under the Privacy Rule.

Minimum Necessary. The least PHI reasonably necessary to accomplish the intended purpose of the use, disclosure, or request. Unless an exception applies, this standard applies to a covered entity when using or disclosing PHI or when requesting PHI from another covered entity. A covered entity that is using or disclosing PHI for research without Authorization must make reasonable efforts to limit PHI to the minimum necessary. A covered entity may rely, if reasonable under the circumstances, on documentation of IRB or Privacy Board approval or other appropriate representations and documentation under section 164.512(i) as establishing that the request for PHI for the research meets the minimum necessary requirements.

Privacy Board. A board that is established to review and approve requests for waivers or alterations of Authorization in connection with a use or disclosure of PHI as an alternative to obtaining such waivers or alterations from an IRB. A Privacy Board consists of members with varying backgrounds and appropriate professional competencies as necessary to review the effect of the research protocol on an individual's privacy rights and related interests. The board must include at least one member who is not affiliated with the covered entity, is not affiliated with any entity conducting or sponsoring the research and is not related to any person who is affiliated with any such entities. A Privacy Board cannot have any member participating in a review of any project in which the member has a COI.

Protected Health Information. Protected Health Information (PHI) means individually identifiable health information that is transmitted by electronic media; maintained in electronic media; or transmitted or maintained in any other form or medium. PHI excludes individually identifiable health information in education records covered by the Family Educational Rights and Privacy Act (FERPA), as amended, 20 U.S.C. 1232g; in records described at 20 U.S.C. 1232g(a)(4)(B)(iv); in employment records held by a covered entity in its role as employer; and regarding a person who has been deceased for more than 50 years.

Psychotherapy Notes. Psychotherapy notes means notes recorded (in any medium) by a health care provider who is a mental health professional documenting or analyzing the contents of conversation during a private counseling session or a group, joint, or family counseling session and that are separated from the rest of the individual's medical record. Psychotherapy notes excludes medication prescription and monitoring, counseling session start and stop times, the modalities and frequencies of treatment furnished, results of clinical tests, and any summary of the following items: Diagnosis, functional status, the treatment plan, symptoms, prognosis, and progress to date.

Research. A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. This includes the development of research repositories and databases for research.

Use. With respect to individually identifiable health information, the sharing, employment, application, utilization, examination, or analysis of such information within the covered entity or health care component (for hybrid entities) that maintains such information.

Waiver or Alteration of Authorization. The documentation that the covered entity obtains from a researcher or an IRB or a Privacy Board that states that the IRB or Privacy Board has waived or altered the Privacy Rule's requirement that an individual must authorize a covered entity to use or disclose the individual's PHI for research purposes.

Workforce. Employees, volunteers, trainees, and other persons whose conduct, in the performance of work for a covered entity, is under the direct control of the covered entity, whether or not they are paid by the covered entity.

24.2. The IRB's Role under the Privacy Rule

Under the Privacy Rule, IRBs have authority to consider, and act upon, requests for a partial or complete waiver or alteration of the Privacy Rule's Authorization requirement for uses and disclosures of PHI for research. Although the Common Rule and FDA regulations include protections to help ensure the privacy of subjects and the confidentiality of information (as applicable, to research activities that are regulated under those sets of regulations), the Privacy Rule supplements these protections where HIPAA is applicable, by requiring covered entities to implement specific measures to safeguard the privacy of PHI. If certain conditions are met, an IRB may grant a waiver or an alteration of the Authorization requirement for research uses or disclosures of PHI.

The SJH/SPHP IRB and, when mutually agreed, the external IRBs it relies upon, fulfill the functions of a Privacy Board for human subject research.

The Privacy Rule does not change the composition of an IRB. When acting upon a request to waive or alter the Authorization requirement, an IRB must follow the procedural requirements of the Common Rule and FDA regulations, if applicable, including using either the normal review procedures (review by the convened IRB) or, as appropriate, the expedited review procedures.

When a request for a waiver or an alteration of the Authorization requirement is considered by the convened IRB, a majority of the IRB members must be present at the meeting, including at least one member whose primary concerns are in nonscientific areas. In order for an approval of a waiver or an alteration of the Privacy Rule's Authorization requirement to be effective, it must be approved by a majority of the IRB members present at the convened meeting. If a member of the IRB has a conflicting interest with respect to the PHI use and disclosure for which a waiver or an alteration approval is being sought, that member may not participate in the review. Expedited review of a request for a waiver or an alteration of the Authorization requirement is permitted if the research qualifies for expedited review under Common Rule requirements (See Section 10.1). 45 CFR 46.110 and 21 CFR 56.110 permit an IRB to use an expedited review procedure to review minor changes in previously approved research. A modification to a previously approved research protocol, which only involves the addition of an Authorization for the use or disclosure of PHI to the IRB-approved informed consent, may be reviewed by

the IRB through an expedited review procedure, because this type of modification may be considered to be no more than a minor change to research. If expedited review procedures are appropriate for acting on the request, the review may be carried out by the IRB Chair, Vice Chair or by one or more experienced reviewers designated by the Chair from among the IRB members. A member with a conflicting interest may not participate in an expedited review. If an IRB uses expedited review procedures, it must adopt methods for keeping all its members advised of all requests for waivers or alterations of the Authorization requirement as well as those requests that have been granted under an expedited review procedure.

IRB documentation of approval of a waiver or alteration of the authorization requirement includes:

1. The identity of the approving IRB;
2. The date on which the waiver or alteration was approved;
3. A statement that the IRB has determined that the alteration or waiver or authorization, in whole or in part, satisfies the three criteria in the Rule;
4. A brief description of the PHI for which use or access has been determined by the IRB to be necessary;
5. A statement that the waiver or alteration was reviewed and approved under either normal or expedited review procedures; and
6. Signature of the IRB Chair, Vice Chair, or other IRB member (designated by the Chair), as applicable.

SJH/SPHP will not release PHI to investigators or other third parties without individual authorization or proper documentation of an IRB or Privacy Board approval of a waiver or alteration of the requirement.

24.3. Authorization

Except as otherwise permitted, the Privacy Rule requires that a research subject "authorize" the use or disclosure of his/her PHI to be used in research. This authorization is distinct from the subject's consent to participate in research, which is required for research to which the Common Rule, FDA regulations, and/or state laws regarding certain categories of health information apply (although certain research that is subject to the Privacy Rule may be exempt from Common Rule requirements). Just as a valid consent under Common Rule and FDA regulations must meet certain requirements, a valid authorization must be written in plain language and contain certain statements and core elements [45 CFR 164.508.6(c)]. At SJH/SPHP, the HIPAA authorization is combined with the consent document, with limited exceptions at the discretion of the HRPP Administrator in consultation with the Integrity & Compliance Office. All HIPAA authorizations are submitted to the IRB office to verify that the appropriate template is used without inappropriate substantive modification.

Once executed, a signed copy must be provided to the individual providing authorization. Signed authorizations must be retained by the covered entity for 6 years from the date of creation or the date it was last in effect, whichever is later.

A research subject has the right to revoke their authorization at any time. See Section 25.12 for more information regarding an individual's right to revoke, procedures, and exceptions.

When an Authorization permits disclosure of PHI to a person or organization that is not a covered entity (such as a sponsor or funding source), the Privacy Rule does not continue to protect the PHI disclosed to

such entity. However, other federal and state laws and agreements between the covered entity and recipient such as a Business Associate Agreement (BAA) or Confidentiality Agreement may establish continuing protections for the disclosed information. Under the Common rule or FDA regulations, an IRB may impose further restrictions on the use or disclosure of research information to protect subjects.

Authorization Core Elements:

1. A description of the PHI to be used or disclosed, identifying the information in a specific and meaningful manner;
2. The names or other specific identification of the person or persons (or class of persons) authorized to make the requested use or disclosure;
3. The names or other specific identification of the person or persons (or class of persons) to whom the covered entity may make the requested use or disclosure;
4. A description of each purpose of the requested use or disclosure;
5. Authorization expiration date or expiration event that relates to the individual or to the purpose of the use or disclosure (A statement that there is "no expiration date or event" or that authorization expires at the "end of the research study" or "unless and until revoked" by the individual are permissible for research, including authorizations for future research); and
6. The signature of the individual and date. If the individual's legally authorized representative signs the Authorization, a description of the representative's authority to act for the individual must also be provided.

Authorization Required Statements:

1. A statement of the individual's right to revoke his/her Authorization and how to do so, and, if applicable, the exceptions to the right to revoke his/her Authorization or reference to the corresponding section of the covered entity's notice of privacy practices;
2. Whether treatment, payment, enrollment, or eligibility of benefits can be conditioned on Authorization (if such conditioning is permitted under the Privacy Rule), including research-related treatment and consequences of refusing to sign the Authorization; and
3. A statement of the potential risk that PHI will be re-disclosed by the recipient. This may be a general statement that the Privacy Rule may no longer protect health information disclosed to the recipient.

24.4. Waiver or Alteration of the Authorization Requirement

Obtaining signed authorization to access and use PHI for research is not always feasible. The Privacy Rule contains criteria for waiver or alterations of authorization. If a covered entity has used or disclosed PHI for research pursuant to a waiver or alteration of authorization, documentation of the approval of the waiver or alteration must be retained for 6 years from the date of its creation or the date it was last in effect, whichever is later. This is in addition to any other documentation requirements that might apply.

For research uses and disclosures of PHI, an IRB or Privacy Board may approve a waiver or an alteration of the authorization requirement in whole or in part. A complete waiver occurs when the IRB or Privacy Board determines that no authorization will be required for a covered entity to use and disclose the PHI contemplated to be used or disclosed for that particular research project. A partial waiver of authorization occurs when the IRB or Privacy Board determines that a covered entity does not need authorization for

all PHI uses and disclosures for some defined group of research purposes, such as accessing PHI for research recruitment purposes. An IRB or Privacy Board may also approve a request that removes some, but not all, required elements or statements of an authorization (an alteration).

In order for an IRB or Privacy Board to waive or alter authorization, the Privacy Rule (45 CFR 164.512(i)(2)(ii)) requires the IRB or Privacy Board to determine the following:

1. The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
    a. An adequate plan to protect health information identifiers from improper use and disclosure;
    b. An adequate plan to destroy 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
    c. Adequate written assurances that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule;
2. The research could not practicably be conducted without the waiver or alteration; and
3. The research could not practicably be conducted without access to and use of the PHI.

The Privacy Rule allows institutions to rely on a waiver or an alteration of Authorization obtained from a single IRB or Privacy Board to be used to obtain or release PHI in connection with a multi-site project.

Transition Provisions
Under the HIPAA Privacy Rule, a covered entity may use and disclose PHI that was created or received for research, either before or after the compliance date, if the covered entity obtained any one (1) of the following
prior to the compliance date:

- An authorization or other express legal permission from an individual to use or disclose protected health
  information for the research;
- The informed consent of the individual to participate in the research; **OR**
- A waiver of informed consent by the IRB in accordance with the Common Rule or an exception under FDA's human subject protection regulations at 21 CFR §50.24.

However, if a waiver of informed consent was obtained prior to the compliance date, but informed consent is
subsequently sought after the compliance date, the covered entity must obtain the individual's authorization as required at 45 CFR §164.508.

For example, if there was a temporary waiver of informed consent for emergency research under the FDA's human subject protection regulations, and informed consent was later sought after the compliance date, individual authorization would be required before the covered entity could use or disclose PHI for the research after the waiver of informed consent was no longer valid.

24.5. Activities Preparatory to Research

Under the preparatory to research provision of the Privacy Rule, a covered entity may permit a researcher to use PHI for purposes preparatory to research such as assessing the feasibility of conducting a research project, developing a grant application or protocol, or identifying potential subjects.

The covered entity must obtain from the investigator representations, either in writing or orally, that (1) the use or disclosure of the PHI is solely to prepare a research protocol or for similar purposes preparatory to research, (2) that the investigator will not remove any PHI from the covered entity (e.g., physically taken out of a facility, or downloaded and retained on the investigator's device) in the course of the review, and (3) the PHI for which access is sought is necessary for the research purpose. [45 CFR 164.512(i)(1)(ii)]

Federal guidance has drawn a distinction between activities that may be undertaken by a researcher who is a member of the covered entity's workforce, e.g., an employee of the covered entity, and a researcher who is not part of the covered entity's workforce. This guidance indicates that researchers may use PHI under the preparatory to research provision to *identify* potential study participants, so long as no PHI is removed from the covered entity and the remaining two representations set forth above can be made. However, the guidance also indicates that researchers may not use PHI obtained pursuant to the "preparatory to research" provision to *contact* potential study subjects unless (i) the researcher is a member of the covered entity's workforce, or (ii) the researcher enters into a BAA with the covered entity.
Therefore, if the researcher is not a workforce member or business associate of the covered entity, then the researcher may contact potential subjects only pursuant to a partial waiver of authorization from the cognizant IRB or privacy board, or pursuant to the Authorization of the subject.

At SJH/SPHP, access and/or use of PHI for purposes preparatory to research may be requested by SJH/SPHP physicians, staff or students. This is accomplished by the investigator submitting a HIPAA Review Preparatory to Research Request Form or including appropriate information in the IRB submission, to use PHI to identify and contact potential study participants as explained above.

24.6. Research Using Decedent's Information

The HIPAA Privacy Rule protects the individually identifiable health information about a decedent for 50 years following the date of death of the individual. When a researcher seeks to use PHI from decedents for a research protocol, the researcher must (1) obtain authorization from the personal representative of the decedent (i.e., the person under applicable law with authority to act on behalf of the decedent or the decedent's estate), (2) obtain a waiver of the requirement to obtain authorization from an IRB or Privacy Board, or (3) attest to the covered entity holding the PHI that the use or disclosure is solely for research on the PHI of decedents, that the PHI being sought is necessary for the research, and, if requested by the covered entity, provide documentation of the death of the individuals about whom information is being sought.

At SJH/SPHP, the attestation option referenced above is accomplished by the investigator submitting a HIPAA Research on Decedents Information Request Form

24.7. Corollary and Sub-studies

Consistent with the discussion above relating to future uses of research databases or repositories, the Privacy Rule mandates that subject participation in corollary or sub-studies not essential to the primary aims of the research, such as when PHI from an interventional clinical trial is used to create or to contribute to a central research repository, must be on a voluntary, "opt-in" basis. This is particularly important when the primary research offers a potential direct benefit to the research subject, such as treatment, that might compel the potential subject to agree to an ancillary study, even if the subject would prefer not to do so.

HIPAA reinforces this ethical principle by explicitly stating that authorization for "unconditioned" activities, for which there is no associated treatment, benefit or other effect on the individual subject associated with participation, cannot be required. The published preamble to HIPAA Omnibus clarifies the basis for this position, and the requirement that authorization for unconditioned activities involve a clear opt-in mechanism, stating:

> *"This limitation on certain compound authorizations was intended to help ensure that individuals understand that they may decline the activity described in the unconditioned authorization yet still receive treatment or other benefits or services by agreeing to the conditioned authorization." and "an opt out option does not provide individuals with a clear ability to authorize the optional research activity, and may be viewed as coercive by individuals."*

As with authorization for future research (which is one form of "unconditioned activity"), it is acceptable to combine in a single document the authorization for a conditioned activity, such as a clinical trial, with authorization for other forms of unconditioned activities such as a corollary or sub-study that does not directly benefit or effect the individual participant, **provided that**:

1. The authorization clearly differentiates between the conditioned and unconditioned research activities;
2. The authorization clearly allows the individual the option to opt in to the unconditioned research activities; and
3. Sufficient information is provided for the individual to be able to make an informed choice about both the conditioned and unconditioned activities.

Separate authorization must be obtained for research activity that involves the use and disclosure of psychotherapy notes. For example, authorization for the use and disclosure of psychotherapy notes for a clinical trial cannot be combined with an authorization for the use and disclosure of those psychotherapy notes for a corollary research activity.

24.8. De-identification of PHI under the Privacy Rule

Covered entities may use or disclose health information that is de-identified without restriction under the Privacy Rule, because information that has been de-identified consistent with the Privacy Rule requirements is not considered individually identifiable health information. The "Safe Harbor" method permits a covered entity to de-identify data by removing all 18 data elements specified in the Privacy Rule that could be used to identify the individual who is the subject of the information or the individual's relatives, employers, or household members. To satisfy the Safe Harbor method of de-identification, the covered entity also must have no actual knowledge that the remaining information could be used alone or

in combination with other information to identify individuals. Under this method, the identifiers of the individual or his or her relatives, employers, or household members that must be removed are the following:

1. Names;
2. All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP Code, and their equivalent geographical codes, except for the initial three digits of a ZIP Code if, according to the current publicly available data from the Bureau of the Census:
    a. The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people;
    b. The initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people are changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older;
4. Telephone numbers;
5. Facsimile numbers;
6. Electronic mail addresses;
7. Social security numbers;
8. Medical record numbers;
9. Health plan beneficiary numbers;
10. Account numbers;
11. Certificate/license numbers;
12. Vehicle identifiers and serial numbers, including license plate numbers;
13. Device identifiers and serial numbers;
14. Web universal resource locators (URLs);
15. Internet Protocol (IP) address numbers;
16. Biometric identifiers, including fingerprints and voiceprints;
17. Full-face photographic images and any comparable images; and
18. Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification.

Alternatively, a qualified statistician may certify that the risk is very small that the health information could be used, alone or in combination with other reasonably available information, to identify individuals. The qualified statistician must document the methods and results of the analysis that justify such a determination. This analysis must be retained by the covered entity for 6 years from the date of its creation or when it was last acted on, whichever is later.

The Privacy Rule permits a covered entity to assign to, and retain with, the de-identified health information, a code or other means of record re-identification if that code **is not** derived from or related to the information about the individual and is not otherwise capable of being translated to identify the individual. The covered entity may not use or disclose the code or other means of record identification for any other purpose and may not disclose its method of re-identifying the information.

NOTE: Data that are considered de-identified under HIPAA may still be considered human subject data

under the Common Rule and may require IRB review and approval. Removal of HIPAA-identifying elements does not necessarily mean that the identity of the subject is not or may not readily be ascertained by the investigator or associated with the information and thus be considered identifiable private information under the Common Rule. The reverse can also be true (and, in practice, is more likely to occur): information may not be "identifiable" under the Common Rule but, because it contains certain HIPAA identifiers, it is considered identifiable under HIPAA.

24.9. Limited Data Sets and Data Use Agreements

Limited data sets are data sets stripped of certain direct identifiers. Limited data sets may be used or disclosed only for public health, research, or health care operations purposes. Because limited data sets may contain identifiable information, they are still PHI and as such are not considered de-identified under the Privacy Rule. Unlike de-identified data, PHI in limited data sets may include: addresses other than street name or street address or post office boxes, all elements of dates (such as admission and discharge dates) and unique codes or identifiers not listed as direct identifiers. The following direct identifiers must be removed for PHI to qualify as a limited data set:

1. Names, including initials (of the individual, employer, relatives, etc.).
2. Postal address information, other than town or city, state, and ZIP code.
3. Telephone numbers.
4. Fax numbers.
5. Email addresses.
6. Social Security numbers.
7. Medical Record numbers.
8. Health Plan Beneficiary numbers.
9. Account numbers.
10. Certificate or license numbers.
11. Vehicle identifiers and license plate numbers.
12. Device identifiers and serial numbers.
13. URLs.
14. IP addresses.
15. Biometric identifiers; and
16. Full-face photographs and any comparable images.

Before disclosing a limited data set, a covered entity must enter into a Data Use Agreement (DUA) with the recipient. The DUA establishes the parameters around the proposed uses and disclosures of the data, who is permitted to have access to the data, and stipulates that no other use or disclosure will be made other than as permitted by the DUA or as otherwise required by law, no attempt will be made to identify or contact individuals whose data are included in the limited data set, that appropriate safeguards are in place to protect the data from unauthorized use or disclosure, that any agents, including subcontractors, to whom the recipient provides the LDS will agree to the same restrictions and conditions that apply to the recipient, and that the recipient will report any uses or disclosures of the information that they become aware of that are not in keeping with the terms of the DUA.

24.10. Research Subject Access to PHI

With few exceptions, the Privacy Rule guarantees individuals access to their medical records and other types of health information. One exception is during a clinical trial, when the subject's right of access can be suspended while the research is in progress. The subject must have been notified of and agreed to the temporary denial of access when providing consent and authorization. Any such notice must also inform the individual that the right to access will be restored upon conclusion of the clinical trial. Language accommodating this exclusion is included in the applicable SJH/SPHP Consent and Authorization Form template.

24.11. Revoking Authorization

The Privacy Rule establishes the right for an individual to revoke their authorization for uses and disclosures of PHI for research, in writing, at any time, except to the extent that the covered entity has taken action in reliance on the authorization. [45 CFR 164.508(b)(5)] However, individuals providing authorization should be made aware that revoking authorization does not mean that the individual's PHI may no longer be used in the research or be used or disclosed for other purposes.

At SJH/SPHP, individual subjects may revoke authorization by putting their request in writing to the investigator (or designee) in charge of the study. When an investigator receives a withdrawal of authorization, s/he should inform SJH/SPHP by including this information in the continuing review report (study withdrawals).

A covered entity may continue to use and disclose PHI that was obtained **before** the individual revoked authorization to the extent that the entity has taken action in reliance on the authorization. When the research is being conducted by the covered entity, the covered entity is permitted to continuing using or disclosing the **already obtained** PHI to the extent necessary to maintain the integrity of the research (e.g., to account for a subject's withdrawal from a study, to report adverse events, or to conduct an investigation of misconduct). A covered entity may also continue to use the PHI for other activities that are permitted under the Rule without authorization (e.g., health care operations such as QA/QI). Additionally, revoking an authorization does not prevent the continued use or disclosure of PHI by a non-covered entity that had **already received** it pursuant to the authorization.

24.12. Accounting of Disclosures

The Privacy Rule generally grants individuals the right to a written "Accounting of Disclosures" of their Protected Health Information made by a covered entity without the individual's authorization in the six years prior to their request for an Accounting. A covered entity must therefore keep records of such PHI disclosures for 6 years.

It is important to understand the difference between a use and a disclosure of PHI. In general, the use of PHI means use of that information within the covered entity. A disclosure of PHI means "the release, transfer, provision of access to, or divulging in any manner of information outside of the entity holding the information." The Privacy Rule restricts both uses and disclosures of PHI, but it requires an accounting only for certain PHI disclosures.

Generally, an Accounting of Disclosures is required for:

1. Routinely Permitted Disclosures (e.g., under public health authority, to regulatory agencies, to persons with FDA-related responsibilities) with limited exceptions (e.g., law enforcement,

national security, etc.);
2. Disclosures made pursuant to:
    a. Waiver of Authorization;
    b. Research on Decedents' Information; or
    c. Reviews Preparatory to Research.

An accounting is not needed when the PHI disclosure is made:

1. For treatment, payment, or health care operations;
2. Under an Authorization for the disclosure;
3. To an individual about himself or herself; or
4. As part of a limited data set under a data use agreement.

The Privacy Rule allows three methods for accounting for research-related disclosures that are made without the individual's Authorization or other than a limited data set: (1) A standard approach, (2) a multiple-disclosures approach, and (3) an alternative for disclosures involving 50 or more individuals. Whatever approach is selected, the accounting is made in writing and provided to the requesting individual. Accounting reports to individuals may include results from more than one accounting method.

24.13. HIPAA Documents Required with IRB Submissions

Where health information is proposed for use or disclosure in a human subject research activity, applicable HIPAA documents must be included with the IRB submission, e.g.:

- Consent/authorization
- HIPAA Limited Data Set
- HIPAA Waiver of Authorization

25. Special Topics

25.1. Mandatory Reporting

New York State Sanitary Code (10NYCRR 2.10) requires reporting of suspected and/or confirmed communicable diseases. Specific diseases requiring reporting can be found via the following link http://www.health.ny.gov/forms/instructions/doh-389_instructions.pdf.

Any SJH/SPHP employee, agent, medical staff, resident, student or affiliate (personnel) who in good faith believes or becomes aware of any known or suspected violations of SJH/SPHP policies, the Code of Conduct, applicable Federal, State or local laws and other regulations affecting compliance or research under the auspices of SJH/SPHP HRPP/IRB is expected to fulfill several significant obligations by reporting the activity in person, by phone, or in writing to your supervisor and/or to the SJH/SPHP Integrity & Compliance Office.

SJH/SPHP Integrity & Compliance Office (315) 448-5756

Reporting Research Misconduct:
All SJH/SPHP physicians and staff are encouraged to report any suspected incidences of research misconduct to the HRPP Administrator or the SJH/SPHP Integrity & Compliance Office. Good faith

allegations can be made in person, or via phone or email. All reasonable efforts will be made to protect the anonymity of complainants making good faith allegations of research misconduct.

25.2. Registration of Clinical Trials

In support of the idea that researchers and the public at large should have access to relevant information about ongoing clinical trials involving human subjects, SJH/SPHP expects that all clinical research studies conducted at SJH/SPHP or by SJH/SPHP physicians or affiliate be registered through ClinicalTrials.gov This expectation ensures that research data generated by SJH/SPHP physicians will be eligible for publication and trial information will be made available to the public at large. See section 13.13 (Posting of Clinical Trial Consent Forms).

The NIH, FDA and other entities require registration for certain studies. In addition, many Journals require registration in order to consider articles for publication. Some examples are:

- Studies that are funded (wholly or in part) by NIH, and meet the NIH definition of a clinical trial.
  See https://grants.nih.gov/policy/clinical-trials/definition.htm for details.
- Studies that are clinical trials of drugs and/or biological products subject to FDA regulations.
  See https://clinicaltrials.gov/ct2/manage-recs/fdaaa) for details.
- Prospective clinical study of health outcomes comparing an intervention with a device product against a control in humans (other than a small feasibility study), or any pediatric post-market surveillance study, as required under the Federal Food, Drug and Cosmetic Act See https://clinicaltrials.gov/ct2/manage-recs/fdaaa for details.
- ICMJE journals. See http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/ for details.
  Note that for these journals, registration must occur before the first patient is enrolled.

25.3. Certificates of Confidentiality

Certificates of Confidentiality (CoC) protect research information by prohibiting certain disclosures and conditioning others upon consent from the subject. The protections and requirements of CoCs are outlined in 42 U.S.C. 241(d) and NIH policy (when applicable), and summarized below.

CoCs are obtained as follows:

- CoCs are issued automatically when research is conducted or supported by NIH and falls within the scope of the NIH policy.
- Research that is not funded by NIH (non-NIH research) may still have the protections afforded by CoCs through successful application to the NIH, FDA, or other authorized Federal agencies or departments.

Additional information about CoCs and the application process for non-NIH research is available on the NIH CoC Website.

25.3.1. Definitions

Identifiable, sensitive information means information that is about an individual and that is gathered

or used during the course of biomedical, behavioral, clinical, or other research and

1. Through which an individual is identified; or
2. For which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.

Examples of Sensitive Research

a. Information relating to sexual attitudes, preferences, or practices.
b. Information relating to the use of alcohol, drugs, or other addictive substances.
c. Information pertaining to illegal conduct.
d. Information that, if released, could damage a participant's financial standing, employability, or reputation within the community.
e. Information that would normally be recorded in a patient's medical record, and the disclosure of which could reasonably lead to social stigmatization or discrimination.
f. Information pertaining to an individual's psychological well-being or mental health.
g. Genetic information

25.3.2. Protections and Requirements

When a CoC is issued, whether automatically or under an approved application, the person(s) engaged in the research must not disclose or provide the name of a subject or any information, document, or biospecimen that contains identifiable, sensitive information about the subject and that was compiled for the purposes of the research:

1. In any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, unless the disclosure is made with the consent of the individual to whom the information, document, or biospecimen pertains; or
2. To any other person not connected with the research, unless:
    a. Required by Federal, State or local laws (e.g., adverse event reporting to the FDA, transmissible disease reporting required under State law), but excluding proceedings as described in "1" above;
    b. Necessary for the medical treatment of the subject to whom the information, document, or biospecimen pertains and made with the consent of the subject;
    c. Made with the consent of the individual to whom the information, document, or biospecimens pertains; or
    d. Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.
    e.

Additional Protections

Identifiable, sensitive information protected under a CoC, and all copies thereof, are immune from the legal process, and shall not, without the consent of the of the individual to whom the information pertains, be admissible as evidence or used in any action, suit, or other judicial, legislative, or administrative proceeding.

Identifiable, sensitive information that has been collected under a CoC, and all copies thereof, are protected for perpetuity. If identifiable, sensitive information covered by a CoC is shared with other researchers or organizations, the researchers or organizations must be informed that the information is covered by a CoC and of their responsibility to protect the information accordingly.

Nothing in the rule (42 U.S.C. 241(d)) may be construed to limit the access of a subject to information about himself or herself collected during the research.

When consent is obtained, the consent should inform subjects that a CoC is in place and describe the protections and limitations.

25.3.3. NIH Policy

The NIH Policy on CoCs applies to *"all biomedical, behavioral, clinical, or other research funded wholly or in part by the NIH, whether supported through grants, cooperative agreements, contracts, other transaction awards, or conducted by the NIH Intramural Research Program that collects or uses identifiable, sensitive information"* that was commenced or ongoing on or after December 13, 2016.

CoCs are automatically granted, and the requirements of such must be complied with, whenever a NIH-funded activity falls within the scope of the policy. Investigators and institutions are responsible for determining when a NIH-funded activity falls within the scope of the policy.

NIH policy expands upon 42 U.S.C. 241(d) by explaining that NIH considers research in which identifiable, sensitive information is collected or used, to include:

- Human subjects research as defined in 45 CFR 46, including research determined to be exempt (except for exempt research when the information obtained is recorded in such a manner that human subjects cannot be identified or the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects);
- Research involving the collection or use of biospecimens that are identifiable to an individual or for which there is at least a very small risk that some combination of the biospecimen, a request for the biospecimen, and other available data sources could be used to deduce the identity of an individual;
- Research that involves the generation of individual level, human genomic data from biospecimens, or the use of such data, **regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained;** or
- Any other research that involves information about an individual for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual, as defined in subsection 301(d) of the Public Health Service Act.

25.3.4. NIH CoC Policy Determination

At SJH/SPHP, IRB Staff will, in consultation with the investigator(s) or Program or Project Director, if applicable, determine if the NIH policy applies to any NIH-funded activity. The questions outlined in the NIH policy will be used to guide the analysis. When it has been determined that the NIH policy does not

apply, investigators (or Program or Project Directors, if applicable) are responsible for consulting with IRB whenever they are proposing changes to the NIH-funded activity that may impact or change the analysis.

The NIH policy includes additional responsibilities and requirements for internal controls and for ensuring that recipients of identifiable, sensitive information protected by a CoC understand that they are also subject to the requirements of subsection 301(d) of the Public Health Service Act. For additional information see [https://humansubjects.nih.gov/coc/index].

25.3.5. Application Procedures for non-NIH Research

Any person engaged in human subjects research that collects or uses identifiable, sensitive information may apply for a CoC. For most research, CoCs are obtained from NIH, an investigator may apply for a CoC through the NIH Institute or Center funding research in a scientific area similar to the project.

If the researcher is conducting a sensitive research project that is covered by the Agency for Healthcare Research and Quality (AHRQ) confidentiality statute (42 U.S.C. section 299c-3(c)) then a CoC may not be needed.

If there is an IND Application or an IDE, the sponsor can request a CoC from the FDA.

CoCs may also be issued by other Federal agencies and departments, such as CDC, SAMSHA, or HRSA.
For more information, see the NIH CoC Website.

25.3.6. IRB Review

Investigators are responsible for clearly representing in the IRB submission that a CoC is in place, or that an application for CoC has been submitted. When the CoC application is in process or pending, the IRB may condition final approval upon its receipt.

For studies that are already underway, investigators must submit an Amendment Request to the IRB, along with updated consent language (if applicable), when a CoC is applied for, or when automatically issued under the NIH policy.
When reviewing research under a CoC, the SJH/SPHP IRB will evaluate whether the research plan is consistent with the obligations to protect information and specimens under a CoC and whether the consent language, if applicable, discloses the CoC and appropriately describes the associated protections and limitations. Sample consent language is available on the NIH CoC Website.

When non-NIH research is not under a CoC, the IRB may require an investigator to apply for a CoC if the research includes identifiable, sensitive information and the IRB determines that a CoC is necessary to minimize risks and adequately protect subjects' privacy and the confidentiality of subjects' information or specimens.

25.4. Case Reports Requiring IRB Review

Federal regulations at 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 SJH/SPHP IRB does not consider the retrospective review and analysis

of medical records for publication of a single case report or a case series involving data from two or three patients to be research, and therefore such a report of 1-3 medical cases does not need to be submitted to the IRB. This is because reporting on such a small number of patients does not involve a systematic investigation, including defining a hypothesis that is then investigated prospectively and systematically, to develop or contribute to generalizable knowledge. Investigators should use the Case Reports Using Existing Data - Author Worksheet to help determine whether submission to the IRB is required. The completed form should be retained by the investigator as documentation.

When a larger series of patients is being evaluated, the commonalities of those patients are typically explored and conclusions are drawn (i.e., a systematic investigation). Such a systematic investigation more closely resembles prospectively designed clinical research and as such requires IRB review and approval. While drawing such a "bright line" to distinguish non-research from research may seem arbitrary, it serves as a guide to those who would prepare case reports. If a researcher ever does intend a report of 1-3 medical cases to develop or contribute to generalizable knowledge, or to otherwise constitute research, the report should be submitted to the IRB with a request for a determination whether the case report constitutes research using the procedures outlined in Section 4. As always, anyone who is unsure whether a project requires IRB review should contact the IRB /HRPP office for assistance.

Regardless of the number of cases, providers must comply with all applicable laws and SJH/SPHP policies related to the use and release of health information. Permission from the patients who will be included in the report should be sought whenever possible, and journals may require such as a condition of publication. Providers should consult with the Privacy Office and/or HRPP/IRB Office for guidance on patient privacy and HIPAA.

A copy of this policy and the completed Author Worksheet can be provided to journal editors or others who request confirmation of IRB review or waiver.

25.5. Databases & Registries

Databases and registries (all referred to as registries throughout this section) are used to store data for future use.

There are two type of registries:

- Non-research repositories created and maintained for purposes that are unrelated to research. Such purposes may include diagnosis, treatment, billing, marketing, quality control, and public health surveillance.
- Research repositories created and maintained specifically for research purposes. Such purposes may include databases to identify prospective subjects, patient outcome information to evaluate treatment effectiveness, and tissues samples for future research. Non-research repositories that are altered to facilitate research (e.g., through the addition of data fields not necessary for the core purpose of the repository) are considered research repositories.

25.5.1. Non-research Registries

Even though registries were not created for research purposes, they may contain information that is of great interest to researchers. The creation (or operation) of non-research databases or registries does not involve human subject research and does not require IRB oversight. However, IRB approval is required

for the research use of identifiable private information or identifiable human specimens from non-research registries, and, regardless of identifiability, when data will be used to evaluate the safety or effectiveness of a medical device. Research under the auspices of SJH/SPHP that includes the use of coded private information, must either be submitted for IRB review or for a "Human Subjects Research Determination" (See Section 4).

Researchers submitting an application for research using data from non-research registries must describe the source of the data and any terms, conditions, or restrictions on use. Data cannot be used for research if the person from whom the data originated objected to its use for research. Informed consent and HIPAA authorization (when applicable) must be obtained unless the IRB determines that the criteria for a waiver are satisfied.

25.5.2. IRB Oversight

IRB approval is required for the establishment and operation of a research registries when the data that are accessed, received, stored, or distributed are identifiable. In general, private information is considered individually identifiable when the identities of the subjects are known to investigators/registry operators or when the data can be linked to specific individuals either directly or indirectly through coding systems.

Separate IRB approval is required for the use of data from a registry when the recipient investigator(s) know or may readily ascertain the identity of individual subjects, and, regardless of identifiability, when data will be used to evaluate the safety or effectiveness of a medical device. Research under the auspices of SJH/SPHP that includes the use of coded private information, must either be submitted for IRB review or for a "Human Subjects Research Determination" (See Section 4). The only exception to this policy is when the coded private information are to be obtained from an IRB-approved registry and the rules of that registry forbid the release of identifiable information, the release of the key to the code or other means that would allow re-identification, or the release of sufficient information that investigators could readily ascertain the identity of subjects.

25.6. Research Involving or Generating Genetic Information

Research that generates or uses genetic information may create special risks to human subjects and their relatives. These involve medical, psychosocial, legal and economic risks, such as the possible loss of privacy, insurability, and employability, and may result in stigmatization and discrimination. Information about one's own genetic make-up may also provide information about family members.

In studies involving genetic testing or analysis of genetic information, several questions should be addressed to ensure that potential risks are well understood and that the rights and interests of subjects and their family members are carefully considered and planned for. For example:

1. Is the testing intrinsic to the study? If not, has participation in the genetic testing component been provided as an opt-in?
2. Will test results be given? Will the subject or family member be provided the option to receive or not receive results? How will this decision be recorded? Is there an appropriate plan for return of results? (See section 26.6.2)
3. Could the results provide information about individual disease risk? Disease risk for family

members?

4. Could other clinically relevant information or incidental findings be uncovered by the study? Is there a plan for the management of such findings?
5. Could a change in a family relationship be disclosed, such as mistaken paternity?
6. Could/will the research provide information about the origins, ancestry, or natural history of families, indigenous peoples, tribal populations, or other populations? What are the possible risks?
7. Could/will the research generate information that could place subjects or family members at risk or be stigmatizing?
8. Could/will the research generate information of other value or importance to subjects/families?
9. Are there any practical limitations on the subject's right to withdraw from the research, withdraw data, and/or withdraw biological materials (e.g., specimens, cell lines, extracted genomic DNA)? If so, what are they?
10. How will the information and/or biological materials be protected and who will have access?
11. What is the potential for re-identification of individual subjects (e.g., through the combination of their genetic information and/or materials with other sources of information (e.g., public records))? What measures can be taken to mitigate these risks?
12. Is a CoC in place or should one be considered? (See Section 26.3)
13. Will the specimens, cell lines, or genetic information be stored and/or made available for future research? Is this provided as an opt-in when not intrinsic to the study? (See Section 26.7.2)

Investigators should carefully consider the above and other factors relevant to their specific study when developing the protocol, consent process, and consent form. The President's Bioethics Commission, the National Academies of Sciences, Engineering, and Medicine, and others have produced reports, recommendations, and materials that investigators and the IRB may find helpful in protocol development and review, including:

- Returning Individual Research Results to Participants: Guidance for a New Research Paradigm
- Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts
- Privacy and Progress in Whole Genome Sequencing
- Genetics Research and American Indian and Alaska Native Communities
- National Human Genome Research Institute:
  - Human Subjects Research in Genomics
  - Return of Research Results
  - Data Sharing and Privacy
  - Informed Consent for Genomics Research

In addition to the ethical considerations, investigators must ensure that research involving genetic testing or use of genetic information is consistent with applicable law (e.g., GINA, HIPAA, EU GDPR, state law) and policy (e.g., NIH).

25.6.1. The Genetic Information Nondiscrimination Act

The Genetic Information Nondiscrimination Act of 2008 (GINA) is a federal law that protects people from genetic discrimination in health insurance and employment. GINA generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against an individual based on their genetic information. This law helps to lower the risk of health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long-term care insurance. This law protects individuals, including research subjects, in the following ways:

- Health insurance companies and health plans are generally prohibited from requesting or requiring genetic information of an individual or their family members, including genetic information generated from research;
- If health insurance companies and health plans do receive such genetic information, they may not use it to make decisions regarding coverage, rates, or preexisting conditions; and
- Employers with 15 or more employees generally may not use genetic information for hiring, firing, promotion, or other decisions regarding terms of employment.

GINA does not apply to employers with fewer than 15 employees.

This law does not protect individuals against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

GINA defines genetic information as information about:

- An individual's genetic tests.
- Genetic tests of an individual's family members.
- Genetic tests of any fetus of an individual or family member who is a pregnant woman, and genetic tests of any embryo legally held by an individual or family member utilizing assisted reproductive technology.
- The manifestation of a disease or disorder in an individual's family members (family history); or
- Any request for, or receipt of, genetic services or participation in clinical research that includes genetic services (genetic testing, counseling, or education) by an individual or an individual's family members.

GINA includes a "research exception" that allows health insurers and health plans who are engaged in research to request, but not require, that an individual undergo a genetic test so long as certain requirements are satisfied. Additional information on GINA and this exception are available on this OHRP website.

The health insurance protections of GINA do not apply to:

- Members of the US military who receive their care through Tricare
- Veterans who receive their care through the Veterans Administration
- The Indian Health Service
- Federal Employees enrolled in the Federal Employee Health Benefits Plan
  These groups have policies in place that provide protections similar to GINA.

The SJH/SPHP IRB will consider the protections and limitations of GINA when it assesses the risks of

research generating or using genetic information and the adequacy of the measures to protect privacy and maintain confidentiality. Generally, the IRB will also require that the protections and limitations of GINA are disclosed in the consent process when applicable.

25.6.2. Genetics and State Law

Investigators must ensure that the research they conduct conforms with applicable law. When developing and conducting research involving genetic testing, genetic information in NY State, the following should be considered:

NYS law definition of genetic test: "Genetic test shall mean any laboratory test of human DNA, chromosomes, genes, or gene products to diagnose the presence of a genetic variation linked to a predisposition to a genetic disease or disability in the individual or the individual's offspring; such term shall also include DNA profile analysis.'

Genetic Test Results (NYS DOH): may not be provided to research subjects who are New York State residents if the genetic test is not FDA approved and New York State validated, and is not being performed in a New York State (NYS) approved laboratory. The study doctor may refer the research subject to a geneticist or recommend that the test be repeated for non- study purposes in a NYS approved clinical laboratory. *(The NYS DOH requires submission of validation materials from an approved lab before an FDA cleared/approved lab test can be performed for patients/subjects).* If the test performed is not NYS approved, results can only be released to a physician if an "orphan disease exemption" is obtained from the NYS DOH. A separate exemption must be obtained for each subject for whom results will be released.

Please note, that in these cases there are additional requirements which must be met as mandated by the New York State Civil Rights Act, Section 79-l.

When conducting research in other jurisdictions, investigators must ensure that the research conforms with applicable law in that jurisdiction. Investigators should be prepared to provide information on relevant law and their plans to ensure compliance to the IRB of record for the study, whether it is SJH/SPHP IRB or another.

25.7. Genomic Data Sharing (GDS)

SJH/SPHP complies with the NIH GDS Policy, which allows for "broad and responsible sharing of genomic research data", via submission of said data into an NIH-designated data repository. The intent of NIH's policy is to speed discoveries to diagnose, treat, and prevent disease.

The NIH policy applies to grant activities requesting support from NIH for research involving the generation of large-scale human (and/or non-human) genomic data, regardless of funding level, such as:

- Research project grants (Rs).
- Program projects (Ps) and SCORs (Ss) (Gender Factors Affecting Women's Health).
- Cooperative agreements for research (Us).
- Individual career development awards (Ks) that include a research component.
- S activities that include a research component; and
- All other activities that include a research component.

Also covered under this policy is research involving data derived from these activities for subsequent research. All basic and clinical research, including clinical trials, supported by NIH that involves the generation or use of large-scale genomic data fall within the scope of the policy.

The policy does not apply to:

- Institutional training grants (T32s, T34s, T35s, and TL2s).
- K12 career development awards (KL2s).
- Individual fellowships (Fs).
- Resource grants and contracts (Ss).
- Linked awards derived from previously reviewed applications (KL1, KL2, RL1, RL2, RL5, RL9, TL1, UL1).
- Facilities or coordinating centers funded through related initiatives to provide genotyping, sequencing, or other core services in support of GDS.

Because of the potential for re-identification of genomic data, CoCs are automatically issued by the NIH for any research it supports, in part or in whole, that involves *"the generation of individual level, human genomic data from biospecimens, or the use of such data, regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained as defined in the Federal Policy for the Protection of Human Subjects (45 CFR 46)."* Research covered by the NIH policy and/or the underlying PHS Act is protected by the CoC in perpetuity; as such any downstream recipients of such information must comply with the requirements of the PHS Act.

Investigators without NIH support who intend to submit genomic data to a NIH repository are encouraged to obtain a CoC. Investigators conducting research generating or using genomic data are encouraged to obtain a CoC when one is not already in place (e.g., for downstream use of data that was collected under a CoC).

For more information on CoCs, see Section 26.3.

25.7.1. Definitions

Genomic data: information derived from study of an organism's genome, i.e., the set of DNA (including all the genes within) in every cell that provides all of the information needed to build and maintain that organism.

Genomic Summary Results (GSR): GSR (also referred to as "aggregate genomic data" or "genomic summary statistics") are results from primary analyses of genomic research that convey information relevant to genomic associations with traits or diseases across datasets rather than associations specific to any one individual research participant (e.g., genotype counts and frequencies; allele counts and frequencies; effect size estimates and standard errors; likelihood; and p-values). **Sensitive GSR** refers to GSR where the privacy risks may be heightened for study populations (e.g., populations from isolated geographic regions or with rare traits) or the study populations may be more vulnerable to group harm (e.g., because the data includes potentially stigmatizing traits). Information regarding NIH's updated policy on the access, use, and management of GSR may be found here: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-19-023.html

Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data. Examples of genomic research projects that are subject to the Policy and the timeline for submission and sharing of data from such projects may be found here: https://osp.od.nih.gov/wp-content/uploads/Supplemental_Info_GDS_Policy.pdf

NIH-Designated Data Repository: any data repository maintained or supported by NIH either directly or through collaboration. Examples of such repositories is available here: https://osp.od.nih.gov/scientific-sharing/data-repositories-and-trusted-partners/. Data may be unrestricted or controlled access:

- **Unrestricted-Access ("Open Access"):** data are publicly available to anyone (e.g., The 1000 Genomes Project)
- **Controlled-Access:** the data are available to an investigator for a specific project only after the investigators and institution certify to abide by specified terms and conditions and NIH has approved the use (e.g., dbGaP)

25.7.2. Procedures

IRB Submissions and GDS

For any cell lines created or specimens to be collected, analyzed, and shared subject to the GDS Policy, the IRB expects that informed consent will be obtained from the research subject for the future research uses and broad sharing of data required under the policy. **This is the case even if the specimens or cell lines are de-identified.** If there are compelling scientific or legal reasons that necessitate the use of genomic data from cell lines or clinical specimens that lack consent for research use and data sharing, investigators will need to provide a justification in the funding request to NIH for their use. The funding NIH institute/center will review the justification and decide whether to make an exception to the consent expectation. Exceptions from the NIH are not required if only some participants decline to consent to broad sharing, rather an exception request must be granted by NIH for research when consent for broad sharing has not or will not be sought.

Subjects asked to allow for future research uses and broad sharing of their genomic data have the ability to decline, and still remain in the research (however their data cannot be placed into a repository or otherwise broadly shared). The only exception to this is when sharing of the data is intrinsic to the study (e.g., the purpose of the study is to establish a repository for sharing biological specimens and/or data for future research).

NIH and NHGRI provide guidance and resources to assist in the development of appropriate consent forms for research involving or generating genetic or genomic data. Sample consent forms for studies subject to GDS is also available at https://www.genome.gov/27559023/informed-consent-sample-consent-forms/

Applications to the SJH/SPHP IRB should include information about the proposed generation or use of genomic data including, as applicable:

- Whether the research will generate or use data subject to the NIH GDS policy;
- The name of the NIH data repository/database, or other repository or database, that data will be submitted to or acquired from;

- Whether the data is or should be classified as restricted access or unrestricted access;
- Whether the data is or should be classified as sensitive (e.g., studies involving populations from isolated geographic regions or with rare traits, studies that include data on potentially stigmatizing traits, etc.)
- Whether there are any data use limitations or modifiers (e.g., use limited to a specific disease, restricted to not-for-profit organizations, IRB approval requirement, etc.);
- The plan for informed consent and the proposed consent language;
- A copy of the genomic data sharing plan.

The IRB will review the proposal for genomic data sharing or subsequent use of such genomic data in accordance with the criteria for approval of research and the guidelines for IRBs provided by NIH.

When SJH/SPHP is responsible for NIH Institutional Certification (see below), the IRB review will specifically address the required assurances outlined on the Extramural Institutional Certification. When appropriate, if the IRB is unable to confirm that a certification element is satisfied (e.g., because the IRB has not yet granted final approval), Provisional Institutional Certification will be provided.

Grant Applications and GDS

Investigators planning to apply to NIH for research that will generate large-scale human genomic data as defined above should contact the appropriate NIH Program/Project officials to discuss expectations and timelines for complying with this policy. Along with the grant, the following will need to be submitted:

- **Notification in a cover letter** of the intent to generate large-scale human genomic data
- **A genomic data sharing plan,** within the grant's resource sharing plan section (NIH guidance on these plans is available here: https://osp.od.nih.gov/wp-content/uploads/NIH_Guidance_Developing-GDS_Plans.pdf)
- **An Institutional Certification** should be provided to the funding NIH Institute or Center prior to award, along with any other Just in Time information (templates available here: https://osp.od.nih.gov/scientific-sharing/institutional-certifications. Certification must be provided for all sites contributing samples. If more than one site is contributing samples, the primary site may submit one certification on behalf of all collaborating sites (or each site may provide their own certification if this is the site's preference). This certification assures that:
    - The data submission is consistent with applicable national, tribal, and state laws and regulations, and institutional policies.
    - Any limitations on the research use of the data, as expressed in the informed consent documents, are delineated within the certification.
    - The identities of research participants will not be disclosed to the repositories.
    - An IRB and/or Privacy Board has reviewed the investigator's proposal for data submission and assures that:
        - the protocol for the collection of genomic and phenotypic data is consistent with human subjects regulations.
        - data submission and subsequent data sharing for research purposes are consistent with the informed consent of study participants from whom the data were obtained.
        - consideration was given to the risks to participants and their families, and, to

the extent relevant and possible, to groups or populations associated with the submission and subsequent sharing of the data; and
    - that the investigator's plan for de-identifying datasets is consistent with the standards outlined in the NIH Genomic Data Sharing (GDS) Policy.
- **In situations where the sharing of human data is not possible** (i.e., the Institutional Certification criteria cannot be met), a justification is required to explain why these data cannot be shared, and an alternative data sharing plan will need to be provided. Exceptions to NIH expectations for data submission to an NIH-designated data repository will be considered on a case-by-case basis by the NIH funding Institute or Center (IC).

Use of human genomic data from NIH controlled-access & unrestricted-access repositories

Investigators who wish to use controlled-access human genomic data from NIH-designated data repositories (e.g., dbGaP) should briefly address their plans for requesting access to the data and state their intention to abide by the NIH Genomic Data User Code of Conduct in the Research Plan of the application. The code of conduct is available here: https://osp.od.nih.gov/wp-content/uploads/Genomic_Data_User_Code_of_Conduct.pdf.
Access to controlled-access data is dependent on an approval process that involves the relevant NIH Data Access Committee(s). Applicants may wish to secure access to the data prior to submitting their application for NIH support. Secondary users of controlled-access data are not expected to deposit their findings into NIH-designated data repositories, unless appropriate.

Investigators who wish to use/download data from NIH unrestricted-access repositories should not attempt to identify individual human research participants from whom the data were obtained, and, in all oral and written presentations, disclosures, or publications, acknowledge the specific dataset or accession numbers and the repository through which the data were accessed.

Procedures for submitting data into, or requesting access for data from an NIH-designated repository, are available here: https://osp.od.nih.gov/scientific-sharing/institutional-certifications/

25.8. Community Based Research

Community based research (CBR) is research that is based in a community and conducted in collaboration with members of that community. *Community* is often self-defined, but general categories of community include geographic community, a community of individuals with a common problem or issue, or a community of individuals with a common interest or goal.

Where research is being conducted in communities, investigators are encouraged to involve members of the community in the research process, including the design and implementation of research and the dissemination of results when appropriate.

The most significant community involvement is in a subset of CBR called Community Based Participatory Research (CBPR) where there is an equal partnership between the academic investigators and members of a community, with the latter actively participating in all phases of the research process including the design and implementation of research and the dissemination of results when appropriate.

Questions to be considered as CBR studies are developed, and issues that the IRB will consider when reviewing CBR, are as follows:

- How was the community involved or consulted in defining the need for the proposed research (i.e., getting the community's agreement to conduct the research)?
- How was the community involved or consulted in generating the study research plan?
- How will the research procedures, including recruitment strategies and consent processes be assessed to ensure sensitivity and appropriateness to various communities (e.g., literacy issues, language barriers, cultural sensitivities, etc.)?
- How will the community be involved in the conduct of the proposed research?
- How will community members who participate in the implementation of the research be trained and supervised?
- How have "power" relationships between investigators and community members on the research team, and in subject recruitment strategies been considered to minimize coercion and undue influence?
- What are the risks and benefits of the research for the community as a whole?
- How will boundaries between multiple roles (e.g., investigator, counselor, peer) be maintained i.e., what happens when the investigator/research staff is the friend, peer, service provider, doctor, nurse, social worker, educator, funder, etc.?
- How will the research outcomes be disseminated to the community?
- Is there a partnership agreement or memorandum of understanding to be signed by the investigator and community partners that describes how they will work together?

25.9. Department of Education

The U.S. Department of Education (ED) is a signatory to the Common Rule with regulations equivalent to 45 CFR 46 published under 34 CFR 97. Research conducted or supported by ED is reviewed by the SJH/SPHP IRB in accordance with the Common Rule as described throughout this manual with the following variations and additional requirements.

ED has not adopted Subpart B (Pregnant Women, Fetuses, or Neonates) or Subpart C (Prisoners) of the Common Rule.

ED requires reporting of **alleged** (1) unanticipated problems involving risks to subjects or others; and, (2) serious or continuing noncompliance with the Common Rule or Subpart D (protection of children in research). Other mandated reports, as described in Section 20, are submitted to ED instead of OHRP when the research is funded or sponsored by ED. When applicable, SJH/SPHP will follow the directions for incident reporting provided on ED's Protection of Human Subjects in Research website.

25.9.1. Family Educational Rights and Privacy Act (FERPA)

The Family Educational Rights and Privacy Act (FERPA) is a Federal law that protects the privacy of student education records at educational entities that receive funds from the ED. In general, schools must have written permission from the parent or eligible student to release any information from a student's education record. However, FERPA allows schools to disclose personally identifiable information from an education record of a student without consent if the disclosure is to organizations conducting studies for, or on behalf of, educational agencies or institutions to:

1. Develop, validate, or administer predictive tests;
2. Administer student aid programs; or
3. Improve instruction. [34 CFR 99.31(a)(6)]

A written agreement with the receiving organization is required, including:

1. The purpose, scope, and duration of the study(ies);
2. The information to be disclosed;
3. A requirement that the receiving organization uses the personally identifiable information from the educational records only for the purpose(s) of the study as stated in the agreement;
4. A requirement that the receiving organization conducts the study in a manner that does not permit personal identification of students and parents by anyone other than representatives of the organization with legitimate interests; and
5. A requirement that the receiving organization destroys or returns all personally identifiable information when the information is no longer needed for the purposes for which the study was conducted and that specified the time period in which the information must be returned or destroyed.

Education records may be released without consent under FERPA if all personally identifiable information has been removed including:

1. Students' names and other direct identifiers, such as students' Social Security Numbers or student numbers;
2. Indirect identifiers, such as the name of students' parents or other family members, the students' or families addresses, and personal characteristics or other information that would make the students' identities easily traceable, and dates and places of birth and mothers' maiden names;
3. Biometric records, including measurable biological or behavioral characteristics that can be used for automated recognition of an individual, including fingerprints, retina and iris patterns, voiceprints, DNA sequence, facial characteristics, and handwriting; and
4. Other information that, alone, or in combination, is linked or linkable to a student that would allow a reasonable person in the school community, who does not have personal knowledge of the relevant circumstances, to identify to student with reasonable certainty.

25.10. ICH-GCP E6

When SJH/SPHP commits to comply with International Conference on Harmonization (ICH)-GCP E6 as a term of a grant or contract, investigators and the IRB take on additional responsibilities. Investigators are responsible for clearly indicating within their IRB application materials that proposed research is subject to ICH-GCP E6 and for attesting to compliance with ICH-GCP E6 requirements. The SJH/SPHP IRB will evaluate compliance by consulting the current ICH-GCP E6 guidance posted by the FDA on it's website and in IRBManager. SJH/SPHP does not require or evaluate compliance with ICH-GCP E6 requirements that are not consistent with FDA regulations (for example, requiring the reporting to the IRB of all adverse drug reactions that are both serious and unexpected instead of requiring the reporting of unanticipated problems involving risks to subjects or others).

25.10.1. IRB Responsibilities

In addition to the IRB responsibilities, functions, and procedures outlined elsewhere in this manual, ICH-GCP E6 specifically requires that:

1. An IRB should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects;
2. The IRB/IEC should obtain the following documents:
    a. Trial protocol(s)/amendment(s);
    b. Written informed consent form(s) and consent form updates that the investigator proposes for use in the trial;
    c. Subject recruitment procedures (e.g., advertisements);
    d. Written information to be provided to subjects;
    e. Investigator's Brochure (IB) and available safety information;
    f. Information about payments and compensation available to subjects;
    g. The investigator's current curriculum vitae and/or other documentation evidencing qualifications; and
    h. Any other documents that the IRB/IEC may need to fulfil its responsibilities.
3. The IRB should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates that actions were taken;
4. The IRB should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB requests;
5. The IRB should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year;
6. The IRB may request more information than is required by regulation or the ICH-GCP E6 guidance be given to subjects when, in the judgment of the IRB, the additional information would add meaningfully to the protection of the rights, safety, and/or well-being of the subjects;
7. When a nontherapeutic trial is to be carried out with the consent of the subject's LAR, the IRB should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials;
8. Where the protocol indicates that prior consent of the trial subject or the subject's LAR is not possible, the IRB should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e., in emergency situations);
9. The IRB should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject; and
10. The IRB should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

25.10.2. Investigator Responsibilities

In addition to the investigator responsibilities outlined elsewhere in this manual, ICH-GCP E6 specifically requires that:

1. The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB, and/or the regulatory authorities;
2. The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information, and in other information sources provided by the sponsor.
3. The investigator should be aware of and should comply with GCP and applicable regulatory requirements.
4. The investigator should permit monitoring and auditing by the sponsor, and inspection by appropriate regulatory authorities.
5. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.
6. The investigator must have adequate resources to conduct the trial, including:
    a. Being able to demonstrate (e.g., based on retrospective data) the potential for recruiting the required number of subjects within the agreed upon recruitment period.
    b. Sufficient time to properly conduct and complete the trial within the agreed trial period.
    c. Adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely; and
    d. Ensuring that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.
7. The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.
8. If the investigator retains the services of any individual or party to perform trial-related duties and functions, the investigator should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated;
9. A qualified physician (or dentist, when appropriate), who is an investigator or sub-investigator on the trial, should be responsible for all trial-related medical (or dental) decisions.
10. During and following a subject's participation in a trial, the investigator should ensure that adequate medical care is provided for any adverse events, including clinically significant laboratory values, related to the trial. The investigator should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.
11. The investigator should inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and agrees to the primary physician being informed.
12. Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.
13. Before initiating a trial, the investigator must have written and dated approval/favorable opinion from the IRB for the trial protocol, written informed consent form, consent form updates, subject recruitment

procedures (e.g., advertisements), and any other written information to be provided to subjects;

14. As part of the investigator's application to the IRB, the investigator should provide the IRB with a current copy of the Investigator's Brochure (IB). If the IB is updated during the trial, the investigator should supply a copy of the updated IB to the IRB.
15. During the trial the investigator should provide to the IRB all documents subject to review.
16. The investigator should sign the protocol, or an alternative contract, to confirm their agreement to comply with the approved protocol.
17. The investigator may not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to trial subjects.
18. In addition to reporting to the IRB, when the investigator implements a deviation from or change in the protocol to eliminate an immediate hazard(s) to subject(s) without prior approval, this must be reported as soon as possible to the sponsor.
19. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.
20. The investigator is ultimately responsible for investigational product accountability and for all of the responsibilities for investigational product outlined in section 4.6 of ICH-GCP E6.
21. The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor (and IRB) any premature unblinding.
22. Additional requirements for Informed Consent -
    a. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB's approval in advance of use. The subject or the subject's LAR should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.
    b. The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's LAR.
    c. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's LAR ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's LAR.
    d. Neither the investigator, nor the trial staff, may coerce or unduly influence a subject to participate or to continue to participate in a trial.
    e. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's LAR, and by the person who conducted the informed consent discussion.
    f. Prior to participation in the trial, the subject or the subject's LAR should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's LAR

should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

g. If a subject is unable to read or if a LAR is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject's LAR, and after the subject or the subject's LAR has orally consented to the subject's participation in the trial, and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's LAR and that informed consent was freely given by the subject or the subject's LAR.
h. Consent for non-therapeutic trials (i.e., a trial in which there is no anticipated direct clinical benefit to the subject) must be obtained from subjects who personally give consent and who sign and date the written informed consent form unless the IRB has expressly approved, in writing, that consent from a LAR is permitted;
i. The consent discussion and written informed consent form should include the following additional elements:
    i. An explanation of the trial treatment(s) and the probability for random assignment to each treatment.
    ii. An explanation of the subject's responsibilities (avoiding any language that appears to restrict subject's rights).
    iii. An explanation that the monitor(s), auditor(s), the IRB, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or LAR is authorizing such access;
    iv. An explanation of the anticipated prorated payment, if any, to the subject for participating in the trial.
    v. An explanation of the reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
    vi. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
    vii. An explanation that, to the extent permitted by applicable laws or regulations, records identifying the subject will not be made publicly available, and, if the results of the trial are published, the subject's identity will remain confidential; and
    viii. A statement that the trial has the approval of the IRB.

23. Investigators must comply with the requirements for records and reports outlined in section 4.9 and 8 of ICH-GCP E6.

24. Investigators must comply with the requirements for safety reporting outlined in Section 4.11 of ICH-GCP E6 including the redaction of personally identifying information; and

25. Investigators must comply with the requirements for premature termination or suspension of a trial outlined in section 4.12 of ICH-GCP E6 including the requirements for sponsor and IRB reporting.

25.11. International Research

The SJH/SPHP IRB reviews international research involving human subjects to ensure that adequate provisions are in place to protect the rights and welfare of the subjects. All policies and procedures that are applied to research conducted domestically should be applied to research conducted in other countries, as appropriate. Approval of research is permitted if *"the procedures prescribed by the foreign institution afford protections that are at least equivalent to those provided in 45 CFR 46."*

For SJH/SPHP researchers involved in federally conducted or supported international research, approval of research for foreign institutions or sites "engaged" in research is only permitted if the foreign institution or site holds a FWA with OHRP and local IRB review and approval is obtained.

Approval of research for foreign institutions or sites "not engaged" in research is only permitted if one or more of the following circumstances exist:

- When the foreign institution or site has an established IRB/EC, the investigator must obtain approval to conduct the research at the "not engaged" site from the site's

  IRB/IEC or provide documentation that the local site's IRB/EC has determined that approval is not necessary for the investigator to conduct the proposed research at the site.
- When the foreign institution or site does not have an established IRB/IEC, a letter of cooperation must be obtained demonstrating that the appropriate institutional or oversight officials permit the research to be conducted at the performance site.
- IRB approval to conduct research at the foreign institution or site is contingent upon receiving documentation of the performance site's IRB/EC determination, or letter of cooperation, as applicable.

For international research, the SJH/SPHP IRB seeks sufficient knowledge of the local research context by requesting approval for the project from local IRBs or ethics committees (which may or may not be OHRP-registered) and/or local letters of support. The source of this information will depend on the nature of the study, on the country, and on the resources available to the investigator. Where there is a local IRB/EC, SJH/SPHP IRB must receive and review the foreign institution or site's IRB/EC review and approval of each study prior to beginning the research at the foreign institution or site.

In settings where there are no IRBs/ECs, the SJH/SPHP IRB may require additional verification and information from people outside the particular research project who are familiar with the customs, practices, or standards of care where the research will be taking place, including other IRBs or committees with experience reviewing research in the region, other SJH/SPHP investigators with knowledge of the region, or a consultant who is an expert on the region, prior to approval. These individuals may either provide a written review of the research protocol or attend an IRB meeting to provide the SJH/SPHP IRB with recommendations based on his or her expertise.

The SJH/SPHP PI should review any cited provisions provided in the current International Compilation of

Human Subject Research Protections available through OHRP at http://www.hhs.gov/ohrp/international/index.html.

25.11.1. Responsibilities

1. It is the responsibility of the SJH/SPHP investigator and the foreign institution or site to assure that the resources and facilities are appropriate for the nature of the research.
2. It is the responsibility of the SJH/SPHP investigator and the foreign institution or site to confirm the qualifications of the investigators and research staff for conducting research in that country(ies).
3. It is the responsibility of the SJH/SPHP investigator and the foreign institution or site to ensure that the following activities will occur:
   a) Initial review, continuing review (as required), and review of modification;
   b) Post-approval monitoring;
   c) Handling of complaints, non-compliance and unanticipated problems involving risk to subjects or others; and
   d) The IRB will not rely on a local ethics committee that does not have policies and procedures for the activities listed above.
4. It is the responsibility of the SJH/SPHP investigator and the foreign institution or site to notify the IRB promptly if a change in research activities alters the performance site's engagement in the research (e.g., performance site "not engaged" begins consenting research subjects, etc.).
5. The SJH/SPHP PI should review any cited provisions provided in current International Compilation of Human Subject Research Protections available through OHRP at http://www.hhs.gov/ohrp/international/index.html.

25.11.2. Consent Documents

The informed consent documents must be appropriate for and in a language understandable to the proposed subjects. The IRB will review the proposed document and a back translation of the exact content contained in the foreign language informed consent document, with the credentials of the translator detailed in the Study Protocol or Modification Request form. All documents, including verification of the back translation, are maintained in the IRB file.

25.11.3. Monitoring of Approved International Research

The IRB is responsible for the ongoing review of international research conducted under its jurisdiction through the continuing review process in accordance with all applicable federal regulations. When the IRB and a local ethics committee are both involved in the review of research, the PI will be responsible for ensuring coordination and communication with the local IRB/IECs.

The IRB may require documentation of regular correspondence between the SJH/SPHP investigator and the foreign institution or site and may require verification from sources other than the SJH/SPHP investigator that there have been no changes made to the research since its last review.

25.12. Individual Research Projects Conducted by Students

When students conduct or participate as a research team member in human subject research they must follow the standard procedures for research described throughout this manual, as applicable to the

research. As described in Section 1.10.6, SJH/SPHP-College of Nursing (CON) student projects, Medical Education resident projects, and Doctor of Pharmacy resident projects, a SJH/SPHP faculty/preceptor (resident director for pharmacy, or designee) must be listed as the secondary (Co-) investigator / advisor. An unaffiliated person may not be listed as the secondary investigator / advisor. For unaffiliated student projects conducted on SJH/SPHP-properties, a SJH/SPHP-affiliate must be listed as a secondary investigator / advisor. If the SJH/SPHP-colleague is unfamiliar with the SJH/SPHP-research and IRB processes, a SJH/SPHP employee-colleague, research liaison must be listed as advisor.

When employees of SJH/SPHP are students at an outside institution and plan to conduct research outside of SJH/SPHP, they must contact the SJH/SPHP HRPP/IRB office to determine if SJH/SPHP is engaged in the research and if review by the SJH/SPHP IRB is required, or if a reliance agreement is needed, prior to engaging in the activity. It is important to keep in mind that any human subject research activity that will ultimately contribute to part or all of a thesis, dissertation, or other type of publication or presentation must go through the IRB review process prior to enrolling subjects and collecting data. IRB review/approval cannot occur after a study has begun.

Students and advisors should contact the IRB Office with any questions.

DOCUMENT CONTROL TRACKING FILE

Title: St. Joseph's Hospital Health Center Human Research Protection Program /Institutional Review Board Standard Operating Procedures	
Standard: NIAHO:_____ CMS:_____ ISO:_____	
Document Owner: Chief Medical Officer	Forms #:
Reviewed by the following:	
SJH/SPHP Institutional Official (Chief Medical Officer)	Date: 4/20, 4/22
Research Integrity Compliance and Operations (RICO) Committee	Date: 4/20
SJH/SPHP-Institutional Review Board / Research Committee	Date: 4/20, 4/22
CCOIC (Corporate Compliance and Organizational Integrity Committee)	Date: 4/20
Clinical Trials Oversite Committee (CTOC)	Date: 4/22
	Date:
Administrative Approvals:	

Philip Falcone, MD RN, NEA-BC Chief Medical Officer Additional Approvals:	Jamie M. Kabanuk, DNP, MSN, Chief Nursing Officer
Education: IRB Coordinator education: April 1-30, 2020 Monthly Policy / Procedure Update: 5/20, 4/22 Additional:	
Revisions: 4/22 Minor format corrections, Review for content and new sign-off.	
References: SUNY Upstate Medical University. (2019*). Standard Operating Procedures (SOPs): Human Research Protections Program/IRB* Syracuse, NY: Author. U.S. Dept. of Health and Human Services (HHS), OHRP, *Title 45 CFR §46 (pre-2018 version [1991; 2009]; 2018 version [2018; 2019])*. Rockville, MD: Author. U.S. Dept. of Health and Human Services, Office of Human Research Protections. (2018, May). *IRB written procedures*. Rockville, MD: Author. U.S. Food & Drug Administration. (1981; 2017). *Code of federal regulations Title 21 §50 and §56; Title 21 §800-§900*. Silver Spring, MD: Author.	
Original Date: 5/20	Reviewed/Revision Dates: 4/22