



Human Research Protection Program &
Institutional Review Board
(HRPP/IRB)
Standard Operating Procedures

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1 Human Research Protection Program

Allina Health fosters a research environment that promotes the respect for the rights and welfare of individuals recruited for, or participating in, research conducted by or under the auspices of Allina Health. The review and conduct of research, and actions by Allina Health will be guided by the principles (i.e., respect for persons, beneficence, and justice) set forth in the ***Ethical Principles and Guidelines for the Protection of Human Subjects of Research*** (referred to as the *Belmont Report*). The actions of Allina Health will also conform to all applicable federal, state, and local laws and regulations. Allina Health has established a Human Research Protection Program (HRPP). The Allina Health 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. The research may be externally funded, funded from internal sources, or conducted without direct funding.

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 review and oversight of human research projects; and
- To facilitate excellence in the conduct of human subjects research.

1.2 Definitions

The following definitions will be applied when Allina Health IRB reviews research subject to the revised Common Rule, and for exempt determinations and evaluations regarding whether a proposed activity is human subjects research when the research (or activity) is conducted or supported by a Common Rule agency. Likewise, the definitions will be applied, as applicable, to the conduct of the research, investigator responsibilities, and organizational responsibilities.

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

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.

Department or agency head means the head of any Federal department or agency, for example, the Secretary of HHS, and any other officer or employee of any Federal department or agency to whom the authority provided by these regulations to the department or agency head has been delegated.

Federal department or agency refers to a federal department or agency (the department or agency itself rather than its bureaus, offices or divisions) that takes appropriate administrative action to make this policy applicable to the research involving human subjects it conducts, supports, or otherwise regulates (e.g., the U.S. Department of Health and Human Services, the U.S. Department of Defense, or the Central Intelligence Agency).

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.

Human subject means a living individual about whom an investigator (whether professional or student) conducting research:

- (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii)
- Obtains, uses, studies, analyzes, or generates identifiable private information.

Intervention means both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes.

Interaction means communication or interpersonal contact between investigator and subject.

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).

Identifiable private information means information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information).

For research covered by FDA regulations, 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 may be in normal health or may have a medical condition or disease. In the case of a medical device, a human subject also includes any individual on whose specimen or an investigational device is used or tested or used as a control.

An **identifiable biospecimen** is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

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.

Minimal risk means that 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.

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.

Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities. For purposes of this rule, the following activities are deemed not to be research:

- (i) 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.
- (ii) 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).
- (iii) 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.
- (iv) Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

- (v) **Written, or in writing**, refers to writing on a tangible medium (e.g., paper) or in an electronic format.

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.

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 Food and Drug Administration 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 Food and Drug Administration 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 Food and Drug Administration 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 of the Food and Drug Administration 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\(c\)](#)]

Research with nonidentified newborn dried blood spots. Similar to other research with nonidentified biospecimens, is not considered research with human subjects under both the 2018 and pre-2018 Requirements, and thus, is not subject to 45 CFR part 46.

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:

- a) **Human drugs** – The primary intended use of a drug is achieved through chemical action or by being metabolized by the body. 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.)

<http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm>

- b) **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."

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051512.htm>

- c) **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 cutting-edge technologies. 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.

<http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm>

- d) **Food Additives** - A food additive is defined in Section 201(s) of the FD&C Act as any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristic of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use); if such substance is not Generally Recognized As Safe (GRAS) or sanctioned prior to 1958 or otherwise excluded from the definition of food *additives*.

<http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm>

- e) **Color Additives** - A color additive is any dye, pigment or substance which when added or applied to a food, drug or cosmetic, or to the human body, is capable (alone or through reactions with other substances) of imparting color. Color additives for use in food, drugs, and cosmetics require premarket approval. Color additives for use in or on a medical device are subject to premarket approval, if the color additive comes in direct

contact with the body for a significant period of time. <http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm>

- f) **Foods** - Foods include dietary supplements that bear a nutrient content claim or a health claim.
- g) **Infant Formulas** – Infant formulas are liquid foods intended for infants which substitute for mother’s milk.
- h) **Electronic Products** - The FDA regulates certain classes of electronic products including radiation-emitting electronic products such as microwaves and x-rays.

1.3 Ethical Principles

Allina Health is committed to conducting research with the highest regard for the welfare of human subjects. Allina Health 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 (1979). These principles are:

- 1) **Respect for Persons**, which involves obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations.
- 2) **Beneficence**, which involves ensuring that possible benefits are maximized and possible risks are minimized to all human subjects.
- 3) **Justice**, which involves the equitable selection of subjects.

Allina Health, 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.

1.4 Regulatory Compliance

The HRPP is responsible for ensuring compliance with federal regulations, state law and organizational policies. Human subjects research at Allina Health 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 revised [Common Rule](#) is reviewed and conducted in accordance with the revised Common Rule. 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 revised Common Rule will cite the DHHS regulations.

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](#).

Research conducted or supported by the U.S. **Department of Education (ED)** is subject to the Common Rule with regulations published at [34 CFR 97](#). In addition to the Common Rule, human subjects research involving education records conducted at institutions receiving ED funding must comply with additional requirements, including the Family Educational Rights and Privacy Act ([FERPA](#)) (34 CFR 99) and the Protection of Pupil Rights Amendment ([PPRA](#)) (34 CFR 98). Investigators should consult these regulations and [resources provided by ED](#) when developing their research protocol. The IRB will evaluate the research in accordance with these regulations when applicable.

Research supported by the **Department of Defense (DoD)** is reviewed and conducted in compliance with [32 CFR 219](#), [10 USC 980](#), applicable parts of title [21 CFR](#) (50, 56, 312, 600, 812), [DoD Instruction 3216.02](#), [DoD Directive 3210.07](#), and applicable additional requirements from respective DoD component(s). See Section 26.6 for more information on requirements for DoD research.

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

Allina Health applies the International Conference on Harmonization (“ICH”) Good Clinical Practices (“GCP”) Guidelines (sometimes referred to as “ICH-GCP” or “E6”) to clinical trials when required by a sponsor or funding agency. In general, Allina Health applies the ICH-GCP guidelines only to the extent that they are compatible with FDA and DHHS regulations.

1.6 Federalwide Assurance (FWA) and IRB Registration

The federal regulations require that federally-funded human subject research only be conducted at facilities covered by a Federalwide Assurance (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. In its FWA, Allina Health has opted to limit the application of the FWA to non-exempt human subject research conducted or supported by DHHS or federal agencies that have adopted the Common Rule.

Likewise, federal regulations require IRBs to register with HHS if they will review FDA-regulated studies or human subjects research conducted or supported by HHS under FWA.

The [HHS registration system database](#) can be used to verify the status of Allina Health’s FWA, IORG, and IRB registration.

Allina Health Federal Registration Numbers	
FWA	FWA00002425
IORG	IORG0001001
Internal IRB registration	IRB00001381

1.7 HRPP Scope and Authority

The Allina Health HRPP is charged with ensuring the protection of human subjects in research conducted under the auspices of Allina Health. Research under the auspices or jurisdiction of Allina Health includes research conducted at or using any property or facility of Allina Health, conducted by or under the direction of any employee or agent of Allina Health (including students) in connection with their Allina Health position or responsibilities, and research involving the use of Allina Health's non-public information (e.g., medical records) to identify, contact, or study human subjects.

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, and volunteers, among others, regardless of whether the individual is receiving compensation.

1.8 Written Procedures

These Standard Operating Procedures (SOPs) for Human Research Protection detail the procedures, standards, and regulations governing research with human subjects under the auspices of Allina Health and the requirements for submitting research proposals for review by the Allina Health IRB. The SOPs are reviewed at a minimum of annually and revised by the HRPP Director with the assistance of others as needed. The Institutional Official (IO) approves all revisions of the SOPs.

The HRPP 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 through materials on its website, in its electronic system, email communications, and other forums. Changes to the SOPs are communicated to investigators and research staff, and IRB members and IRB staff by email, standing meetings, and other forums, as appropriate.

In the event of an emergency or disaster (e.g., public health or weather-related), the procedures in these SOPs may be modified as appropriate for the situation. Such modifications may include alternative meeting procedures, alternative procedures for the submission and review of modifications, alternative procedures for prompt reporting, and any other changes necessary to ensure appropriate ongoing oversight and conduct of research. Because procedural modifications may vary based on the nature of the event, these cannot be anticipated and described in these SOPs. Instead, such procedural modifications will be recorded in an addendum to the SOPs, note-to-file, or other appropriate means of documentation and communicated to the research community. This documentation will be maintained in accordance with applicable record retention requirements.

1.9 HRPP Structure

The HRPP consists of individuals, departments and committees with responsibilities for human research protections such as the Institutional Official, the Director of the HRPP, the Medical Director of the HRPP, the IRB(s), Compliance, Research Administration, legal counsel (or their designee) (“Counsel” or ‘Legal”), the IRB Executive Advisory Council, the Institutional Biosafety Committee (IBC), Radiation Safety Committee (RSC), Research Conflict of Interest Committee, HRPP and IRB staff, investigators, research staff, and others. The objective of this system is to assist the organization 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:

1.9.1 Institutional Official

The ultimate responsibility of the HRPP resides with the **Institutional Official (IO)** of the program. The IO is legally authorized to represent Allina Health. The IO is the signatory of the FWA and assumes the obligations of the FWA. At Allina Health, the IO is a corporate senior leader appointed by the CEO. The IO’s responsibilities include:

- Serving as signatory for Allina Health's Federal-Wide Assurance
- Ensuring compliance with applicable regulations, statute, and institutional policies and procedures
- Designating one or more Institutional Review Boards (IRBs) that review human subjects research conducted under the auspices of Allina Health
- Providing sufficient resources, space, and staff to support the IRB's review and record keeping duties
- Establishing HRPP and IRB policies and procedures
- Providing training and educational opportunities for the IRB and investigators
- Ensuring effective institution-wide communication and guidance on human subjects research
- Setting the "tone" for an institutional culture of respect for human subjects
- Ensuring that investigators fulfill their responsibilities
- Encouraging that all staff engaged in the conduct or oversight of human subject research participate in education activities
- Serving as a knowledgeable point of contact for OHRP, FDA, and other regulatory agencies or delegating this responsibility to another appropriate individual

The IO has the authority to suspend, terminate, or disapprove research or take other actions, such as sanctions or restrictions of research privilege or uses of research data, as necessary, to ensure the proper conduct of research, the protection of human

subjects, the autonomy and authority of the IRB, compliance with regulation or policy, or to protect the interests of Allina Health. However, the IO may not approve research that has been disapproved (or not yet approved) by the IRB.

The IO also has the authority to delegate the performance of certain oversight and operational duties to one or more individuals if such delegation is documented in writing and is not contrary to HRPP policies and procedures.

The IO completes the CITI Institutional/Signatory Official: Human Subjects Research Course. HRPP staff support the IO by providing information and updates to the IO on topics related to human research protections.

1.9.2 Director of the HRPP

The Director of the HRPP (Director) reports to the Chief Compliance Officer and IO and is responsible for:

- Developing, implementing, and refining policies and procedures that ensure compliance with state and federal regulations governing research and Allina Health policies. This includes monitoring changes in regulations and policies that relate to human research protection
- Advising the IO on key matters regarding human subjects research
- Overseeing the administration of the IRB(s)
- Managing and implementing IRB reliance agreements
- Submitting, implementing and maintaining an approved FWA through the IO and the Department of Health and Human Services Office of Human Research Protection (OHRP)
- Managing the finances of the HRPP and IRB
- Assisting the IRB(s) in their efforts to review research and ensure the protection of human subjects
- Assisting investigators in their efforts to carry out the organization's research mission
- Serving as an expert resource on matters of human subject protections
- 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 investigators, IRB members and research staff, and ensuring that training is completed on a timely basis
- Serving as the primary contact at Allina Health for the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services, the Food & Drug Administration (FDA) and other federal regulatory agencies
- Day-to-day operation of the HRPP office, including supervising HRPP and IRB staff.

1.9.3 Medical Director of the HRPP

The Medical Director of the HRPP (Medical Director) is a member of the medical staff and has extensive knowledge and experience in the area of human subjects protection. The Medical Director works collaboratively with the HRPP Director and is responsible for assisting with implementation of the HRPP, including:

- Serving as the physician liaison for the HRPP
- Serving as a resource to investigators in their efforts to carry out Allina's research mission
- Assisting in the development of HRPP policies and procedures
- Reviewing findings from the research QA/QI program
- Providing consultation and support to the IRB and HRPP Director, as needed
- Making recommendations regarding the development of education and training requirements for investigators, IRB members and research staff
- Fostering communication among the IRB and other Allina offices or committees as appropriate to enhance a cohesive approach to research involving human subjects
- Consulting on the institution's reports to sponsors and federal regulatory agencies
- Other mutually agreed upon services.

1.9.4 Institutional Review Boards (IRBs)

Allina Health has one internal IRB, appointed by the Institutional Official (IO). The internal IRB is referred to as IRB, Internal IRB, and Allina IRB. The IRB prospectively reviews and makes decisions concerning all human research conducted at Allina Health facilities, by its employees or agents, or under its auspices unless an external IRB has been designated to do so. The IRB is responsible for the protection of rights and welfare of human research subjects at Allina Health, 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. (See Section 4 for a detailed discussion of the IRB.)

The IRB functions independently of, but in coordination with, other organizational committees and officials. The IRB, however, makes its independent determination whether to approve or disapprove a research plan 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.

Allina Health also uses the services of external IRBs. External IRBs are primarily relied upon for the review and oversight of industry-sponsored clinical trials, however, at the discretion of the IO, Allina Health may enter into reliance agreements for other reasons, for example, when required as a term or condition of a grant.

1.9.5 IRB Executive Advisory Council

The role of the IRB Executive Advisory Council is to provide input on matters related to the Allina Health IRB. The IRB-related matters on which the IRB Executive Advisory Council may be asked to provide input will vary. For example, the IRB Executive Advisory Council may be asked to provide input on the interpretation and application of compliance requirements and standards, the development and revision of IRB-related policies and procedures, guidelines for engagement of external IRBs, and the IRB's provision of IRB services for third parties. The IRB Executive Advisory Council meets on an ad hoc basis at the request of an Executive Council member.

The Council is comprised of the Chair and Vice Chair of the Allina Health IRB or his or her designee, the Institutional Official, the Research Integrity Director, the HRPP Medical Director, the IRB Manager, a representative from the Allina Health Legal Department, a Chief Compliance Officer and other members as deemed appropriate. The Chair and Vice Chair of the IRB Executive Advisory Council must be a member of the Allina IRB.

1.9.6 Legal Counsel

The actions of Allina Health conform to all applicable federal, state, and local laws and regulations. As needed, Allina Health conducts preemption analysis to resolve conflicts between federal or state and other applicable laws. The HRPP may, as needed, request legal counsel from Allina Health Legal Department (or their designee) ("Counsel" or "Legal") for issues, including issues pertaining to research involving human subjects. Issues such as acceptable language for informed consent documents, determinations regarding whether a consent document contains exculpatory language, interpretation of local and state laws, laws of other jurisdictions, federal regulations and guidance, including the Privacy Rule (HIPAA), and interpretation of Allina policy are among the topics for which counsel may be requested.

1.9.7 Research Compliance

The HRPP may consult with members of the Integrity and Compliance Department, including without limitation the Chief Compliance Officer, the Chief Privacy Officer, and the Director of Research Compliance, regarding research compliance issues, quality monitoring, and policy development, interpretation and implementation.

1.9.8 Research Conflict of Interest Committee

The Research Conflict of Interest Committee oversees and implements the Outside Interests and Conflicts Management Policy (SYS-COMPLIANCE-909), procedures and guidelines governing the identification, assessment, management, and monitoring of conflicts of interest in research, including federally sponsored projects. As further described in Section 23, the IRB may either affirm or request changes to strengthen any management proposed by the Research Conflict of Interest Committee.

1.9.9 Clinical Service Line and other Organizational Leaders

Clinical Service Line (CSL) and other organizational leaders are responsible for ensuring that the investigator is qualified by training and experience to conduct the proposed research. For each study submitted to the IRB for review, the CSL or other appropriate leader signs a memo attesting to the scientific merit and relevance of the proposal, and that the PI is appropriately qualified and has the time and resources to conduct the project.

1.9.10 Principal Investigators

The Principal Investigator (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 that incorporates 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 required training as well as training for their responsibilities in any given specific research study. When investigational drugs or devices are used, the investigator is responsible for ensuring an appropriate plan for storage, security, dispensing, accounting, and disposal.

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

With limited exceptions, the Principal Investigator for research under Allina Health's jurisdiction generally must be employed by or have privileges at an Allina entity. Students and residents may serve as the PI but must include an Allina Health employee or member of the medical staff that supervises the project on their IRB project application, typically as a Sub-Investigator. Fellows may serve as PI but mentorship by an appropriate leader is encouraged.

In limited situations, the HRPP Director may conduct a special review and allow someone to serve as PI who is not employed by Allina and who does not have privileges at an Allina Health entity. The Director will take the following into consideration:

- The basis for the request
- The credentials of the proposed PI
- The expertise and experience of the proposed PI
- The ability of the proposed PI to fulfill the responsibility to personally conduct or supervise the research and other PI responsibilities
- Pertinent compliance information including the results of any prior audits or inspections

Investigators approved to serve as PI under a special review may be asked to sign an Investigator Agreement or Assurance. HRPP Director will work with Counsel to determine any other agreement necessary.

Persons 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.

Persons with a history of compliance issues related to the conduct of research (e.g., recipients of a FDA Warning Letter; investigators whose research approval has been suspended or terminated by an IRB for serious or continuing noncompliance) will be considered on a case-by-case basis. Factors to consider include whether corrective actions have been accepted by the FDA as adequate, whether information from an audit or quality review indicate that the issues have been resolved, and similar considerations.

1.9.11 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:

- Facilities where research activities will occur
- Pharmacy
- Radiology/Imaging
- Pathology/laboratory services
- Nursing
- Office of Sponsored Programs
- Institutional Biosafety Committee
- Radiation Safety Committee
- Research Conflict of Interest Committee

Documentation of permission or approval may be required as a component of the IRB application. The IRB may request review or consultation with any of the above or other organizational committees or components even when such review or consultation is not technically required by policy.

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

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

1.10 Multi-site and Collaborative Research Projects

When engaged in multi-site research, research involving collaborators from external organizations or that is otherwise under the jurisdiction of more than one IRB, Allina Health acknowledges that each organization is responsible for safeguarding the rights and welfare of human subjects and for complying with applicable federal regulations. Allina Health may choose to review the research in its entirety, only those components or activities of research Allina Health is engaged in, rely on the review of another qualified IRB, or make other arrangements for avoiding duplication of effort.

When relying upon another IRB or when serving as the reviewing IRB for an outside organization or external investigator, a formal relationship must be established between Allina Health and the other organization or investigator through an Institutional Agreement, Investigator Agreement, a Memorandum of Understanding, or other such written agreement. This relationship must be formalized before Allina Health will accept any human research proposals from the other organization or investigator or rely on the review of the other organization. Without such an agreement, before a multi-site or collaborative study can begin, it must be approved by the IRBs for each participating organization.

When the Allina Health IRB reviews research conducted in whole or in part at another organization, the characteristics of each organization's local research context must be considered, through knowledge of the local research context by the IRB or through consultation.

PIs are responsible for identifying all organizations and investigators participating in collaborative research, the responsible IRB(s), and the procedures for dissemination of study information (e.g., IRB initial and continuing approvals, reports of unanticipated problems, study modifications, interim reports) between participating organizations and investigators.

When the Allina Health PI is the lead investigator or Allina Health is the coordinating center for multi-site research, the investigator must document how the research plan and issues relevant to the protection of human subjects will be communicated among the other participating organizations and investigators. The lead PI or coordinating center is responsible for serving as the liaison with regulatory and funding agencies, and with other participating organizations and investigators. The lead PI or coordinating center is responsible for ensuring that all participating investigators obtain review and approval from their IRB of record prior to initiating the research, maintain approval, and obtain IRB approval for modifications to the research. When Allina IRB is the IRB of record for the lead investigator or coordinating center, the research team must submit the Collaborative Research Supplement to the IRB for review at the time of initial review, continuing review or 2-year status report, and study closure.

2 Quality Assurance

Allina Health performs Quality Assurance and Improvement activities for the purposes of monitoring the safety of ongoing studies and measuring and improving human research protection effectiveness, quality, and compliance with organizational policies and procedures and applicable federal, state, and local laws.

2.1 External Monitoring, Audit, and Inspection Reports

The HRPP and Research Compliance should be notified in advance, whenever possible, of upcoming audits or inspections of research whether the study is reviewed by the internal IRB or an external IRB on Allina's behalf. Representatives of Allina Health, such as HRPP or Research Compliance staff, may participate in entrance and exit interviews and otherwise observe or support the audit or inspection. Likewise, Allina Health representatives may assist in the development of any responses to audits or inspections.

When research is reviewed by the Allina Health 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 non-compliance. If such issues are identified, the report will be forwarded to the convened IRB to determine what additional actions are necessary.

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

2.2 Investigator Compliance Reviews

Allina Health may engage internal or external staff to conduct directed ("for cause") and periodic (not "for cause") compliance reviews of research under the auspices of Allina Health. Additionally, 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 review. The subcommittee may be composed of IRB members and staff from within, and/or individuals from outside of the organization.

Compliance reviews are conducted to assess investigator compliance with federal, state, and local law, and Allina Health policies, to identify strengths and areas for improvement, and to provide recommendations based on existing policies and procedures. The results of compliance reviews will be reported to the HRPP Director, the investigator, the Internal IRB (when the Internal IRB is the IRB of record), and other Allina Health leadership, as appropriate. Any noncompliance will be handled as follows: for research conducted under the Internal IRB, according to the procedures in Section 16; for research conducted under an External IRB, according to the procedures of the External IRB.

If it is identified that subjects in a research project have been exposed to unexpected

serious harm, the reviewer will promptly report such findings to the HRPP Director and the IRB of record.

If issues are identified that indicate possible misconduct in research, the procedures in *SYS-ADMIN-RA-002 Research Misconduct* will be initiated.

Compliance reviews may include:

- Requesting progress reports from investigators
- Examining investigator-held research records
- Reviewing consent materials and the documentation of consent
- Observing the consent process and other research activities
- Reviewing advertisements and other recruiting materials
- Interviewing investigators and research staff
- 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 deemed appropriate by the HRPP or IRB.

2.3 IRB Compliance Reviews

The HRPP Quality Specialist or, on occasion, other internal or external staff, 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 determine that adequate documentation of the meeting discussion and any required determinations has occurred and that quorum was met and maintained
- Reviewing IRB files to determine that adequate documentation of exemptions, expedited reviews, and other outside of committee reviews has occurred
- Reviewing consent forms to ensure that all required elements are included
- Reviewing the IRB database to assure all required fields are completed accurately
- Verifying IRB approvals for collaborating institutions or external performance sites
- Reviewing the metrics (for example, time from submission to first review) to evaluate the quality, efficiency, and effectiveness of the IRB review process
- Reviewing the workload of the IRB and IRB staff
- Other review activities as appropriate

The HRPP Director and Medical Director will review the results of IRB compliance reviews and engage other parties as appropriate such as the Director of Research Compliance and the IRB

Manager. If substantive deficiencies are identified in the review, a corrective action plan will be developed by the Directors and approved by the Institutional Official. The HRPP Director will have responsibility for implementing and reporting progress on the corrective action plan, the results of which will be evaluated by the Institutional Official.

2.4 HRPP Quality Assessment and Improvement

At least annually, the HRPP Director, the HRPP Quality Specialists, and the Director of Research Compliance will develop a HRPP QA/QI plan with defined goals and objectives for evaluating and supporting the quality and effectiveness of the HRPP.

The HRPP Director, Quality Specialists, and the Director of Research Compliance will meet regularly throughout the year to review progress and the results of any reviews conducted under, or in addition to, the plan. When substantive or concerning issues or trends are identified, the HRPP Director, Director of Research Compliance and other relevant parties such as the HRPP Medical Director, the IRB Chair and Vice Chairs, and the IRB Manager will collaborate in the development and implementation of a corrective and preventative action plan. The IO may utilize designees, but is ultimately responsible for addressing such issues.

The HRPP Quality Specialists are responsible for tracking and reporting internal data and metrics that are informative when considering HRPP and IRB effectiveness, workload and resources.

3 Education & Training

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

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

3.1.1 Orientation

New IRB members, including alternate members, will meet with the HRPP Director, IRB Manager, or HRPP Quality Specialist for an orientation session. At the session, IRB processes, resources, and regulations will be reviewed and the new member will be provided with a copy of the IRB Member Handbook.

New members are required to complete the Initial Education requirement for IRB members before their appointment becomes effective.

3.1.2 Initial Education

IRB members and HRPP and IRB staff must complete the required modules in the CITI Course in the Protection of Human Research Subjects (IRB member, biomedical, or social behavioral), or other training determined to be equivalent by the HRPP Director.

3.1.3 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, Allina Health also uses the following activities as a means for offering continuing education to IRB members and HRPP and IRB staff:

- In-service training at IRB meetings
- Training workshops
- Webinars
- Email distribution of articles, announcements, presentations, and other materials relevant to human subject protections

IRB members and HRPP and IRB staff are also required to complete CITI basic or refresher training every 3 years or other training determined to be equivalent by the HRPP Director.

The activities for continuing education vary on a yearly basis depending on areas of need, as determined by the HRPP Director. Whenever possible, the HRPP provides support for staff and members to attend PRIM&R, OHRP, and other relevant conferences focused on human subject protections.

3.2 Training / Ongoing Education of Investigators and Research Team

As stated previously, a vital component of a comprehensive human research protection program is an education program for all individuals involved with research subjects. Allina Health is committed to providing training and an on-going education for investigators and research staff on human subject protections and other relevant topics.

3.2.1 Initial Education

Investigators and research staff who interact or intervene with subjects, or who have access to subjects' identifiable information for the purposes of research, must complete Allina Health CITI Courses relevant to the type of research being conducted and the investigator or staff member's responsibilities. An information sheet detailing Allina Health's CITI training requirements is available in Allina's electronic IRB system.

All investigators and research staff must complete the required coursework before assuming any human subject responsibilities.

If individuals can provide documentation verifying that they have successfully completed human subject research training equivalent to that required by Allina Health, they may request a waiver of Allina Health's specific requirements. The HRPP Director or IRB staff will review the documentation and determine if it satisfies organizational standards.

3.2.2 Continuing Education

Initial training is considered current for a period of three years at which time investigators and staff must complete basic or refresher CITI training or provide evidence of equivalent training for consideration as described above. There is no exception to this requirement. Acceptable alternative training includes attendance at approved PRIM&R, OHRP, or FDA seminars and conferences. Other training may also be acceptable.

Training will be verified at the time of initial application, continuing review, and applications to add study personnel. If training has not been completed or has 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, Allina Health 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 via in-service, workshops, webinars, e-Learning, or through the distribution of articles, presentations, and other materials. Investigators and staff may request training or offer training suggestions by contacting the HRPP Director or Quality Specialist.

4 Institutional Review Board

Allina Health has established an Institutional Review Board (IRB) to ensure the protection of human subjects in research conducted under its auspices. All non-exempt human subject research conducted under the auspices of Allina Health must be reviewed and approved by the Allina Health IRB or an Allina-designated IRB prior to the initiation of the research unless it has been determined that Allina is not engaged in the research. (See Section 5 for information regarding engagement and Section 7 for information on exempt research.)

Allina Health also uses the services of external IRBs. External IRBs that serve as the IRB-of-record for Allina Health have the same authority as the internal IRB and all determinations of the external IRBs are equally binding. For more information on procedures for the use of external IRBs, see Section 8.

4.1 IRB Authority

Under the federal regulations, IRBs have the authority:

1. To approve, require modifications to secure approval, or disapprove human subjects research
2. To require that informed consent be obtained and documented in accordance with regulatory requirements unless the criteria for the waiver or alteration of such requirements has been satisfied and approved by the IRB. The IRB may require that information, in addition to that specifically mentioned in the regulations, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects;
3. To conduct continuing review of research at intervals appropriate to the degree of risk of the research, but not less than once per year;
4. To suspend or terminate approval of research not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to participants;
5. To observe, or have a third party observe, the consent process; and
6. To observe, or have a third party observe, the conduct of the research.

The IRB functions independently. Attempts to coerce or otherwise unduly influence the actions of the IRB are forbidden by policy, and are to be reported as described in Section 4.6. Likewise, the IRB must remain free from the influence of financial and other organizational interests. No individual with responsibility for the business and financial interests of the organization may serve on the IRB.

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 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 ancillary committee. 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 reviews/approvals.

4.2 Roles and Responsibilities

4.2.1 Chair of the IRB

The IO, in consultation with the HRPP Director, appoints a Chair and Vice Chair of the IRB to serve for renewable 2-year terms. Any change in appointment, including reappointment or removal, requires written notification.

The IRB Chair 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 has the same duties of an IRB member, but the Chair is also responsible for conducting the meetings, conducting expedited reviews and 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 information is presented regarding subject safety 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.

The IRB Chair advises the Institutional Official and the HRPP Director about IRB member performance and competence.

If the Chair is not acting in accordance with the IRB's mission, or following policies and procedures, has an undue number of absences, or not fulfilling the responsibilities of the Chair, he/she may be removed by the IO.

4.2.2 Vice Chair of the IRB

The Vice Chair serves as the Chair of the IRB in the absence of the Chair and has the same qualifications, authority, and duties as the Chair.

If the Vice Chair is not acting in accordance with the IRB's mission, or following policies and procedures, has an undue number of absences, or not fulfilling the responsibilities of the Vice Chair, he/she may be removed by the IO.

4.2.3 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 of assigned research in a timely fashion
- Attending IRB meetings as scheduled
- Recusing self from final deliberations and vote when s/he has a conflict of interest (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 IRB staff.

If an IRB member is to be absent for an extended period of time, he or she must notify the IRB office as far in advance as possible so that an appropriate alternate/replacement can be obtained. If the member has a designated alternate, the alternate can serve during the primary member's absence.

IRB Members who are not acting in accordance with the IRB's mission, or following policies and procedures, have an undue number of absences, or otherwise are not fulfilling the responsibilities of membership, may be removed by the IO.

4.2.4 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 when the regular member is unavailable to attend a convened meeting. 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 received or 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. The alternate member will not be counted toward meeting quorum as a voting member unless the primary member is absent. The IRB minutes will document when an alternate member replaces a primary member.

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

4.2.5 Subcommittees of the IRB

The IRB Chair, in consultation with the HRPP Director or IRB Manager, may appoint one or more IRB members to a subcommittee of the IRB to review issues and to make recommendations to the IRB (e.g., to supplement the IRB's initial review or review of reports of unanticipated problems or of serious or continuing non-compliance). 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 at a convened IRB meeting.

4.3 IRB Membership

The structure and composition of the Allina Health IRB is appropriate to the amount and nature of the research that is reviewed. Every effort is made to have member representation knowledgeable about the areas of specialty that encompass most of the research performed at or by Allina Health.

The IRB will include members who are knowledgeable about and/or experienced working with vulnerable populations that typically participate in Allina Health research.

The IRB must promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects and possess the professional competence necessary to review specific research activities. A member of the IRB may fill multiple membership position requirements for the IRB.

Individuals from Allina Health Office of Sponsored Programs and individuals whose responsibilities are primarily related to the financial interests of the organization may not serve as members of the IRB or carry out day-to-day operations of the review process. Individuals from these offices may provide information to the IRB and attend IRB meetings as invited guests.

4.4 Composition of the IRB

1. 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.
2. The IRB will be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.
3. In addition to possessing the professional competence necessary to review specific research activities, the IRB will be able to ascertain the acceptability of proposed research in terms of organizational commitments (*including policies and resources*) and regulations, applicable law, and standards of professional conduct and practice. The IRB will therefore include persons knowledgeable in these areas.

4. If the IRB regularly reviews research that involves a vulnerable category of subjects (e.g., children, prisoners, pregnant women, or handicapped or mentally disabled persons), consideration will be given to the inclusion of one or more individuals on the IRB, who are knowledgeable about and/or experienced in working with these subjects.
5. 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 shall not consist entirely of members of one profession.
6. 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.
7. 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.
8. *No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.*
9. *An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB. [§__.107]*
10. When reviewing nursing research from a Magnet facility, the IRB will include at least one nurse representative.
11. One member may satisfy more than one membership category.

At the discretion of the IO and HRPP Director, IRB staff may be appointed as members or alternates of the IRB.

4.4.1 Appointment of Members to the IRB

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

When the need for a new member or alternate is identified, the HRPP Director seeks out qualified candidates and makes recommendations to the IO. The final decision in selecting a new member is made by the IO.

IRB members are appointed by the IO for renewable 2-year terms. Any change in appointment, including reappointment or removal before the end of a member's term, requires written notification. Members may resign by written notification to the Chair, Manager or Director.

4.4.2 IRB Registration Updates

Changes to the Allina Health IRB will be reported to FDA and OHRP as follows:

1. An Allina Health decision to disband a registered IRB will be reported within 30 days after permanent cessation of the IRB's review of DHHS-conducted or supported research.
2. If an IRB that reviews FDA-regulated research decides to review additional types of FDA-regulated products (e.g., to review device studies if it only reviewed drug studies previously) or to discontinue reviewing clinical investigations regulated by FDA, it must report this within 30 days of the change.
3. Within 90 days after changes to the IRB Chair or the contact person responsible for IRB registration.
4. To register any additional IRB before it is designated under an FWA and reviews research conducted or supported by DHHS or regulated by FDA.
5. Within 90 days of a change in the membership roster if that IRB is designated under an FWA.
6. Within 90 days of any other changes.

4.5 Use of Consultants

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

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

The consultant's findings will be presented to the IRB for consideration either in person or in writing. If in attendance, consultants may provide information and assist in the IRB's deliberations, but may not participate in the vote.

Written statements or reviews from consultants will be kept in the IRB records. Information provided by consultants at 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 investigator's confidentiality and that complies with the IRB conflict of interest policy.

4.6 Reporting and Investigation of Allegations of Undue Influence

If an 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 Director 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 Chief Compliance Officer for investigation and any necessary action.

Undue influence means attempting to interfere with a normal functioning and decision making of the IRB or to influence an IRB member of staff, 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.

5 Engagement Determinations

Determining when research involving human subjects is under the jurisdiction of the Allina IRB depends on whether the research is under the auspices of Allina Health (See Section 1.7) and whether Allina Health is “engaged” in the research.

Per DHHS: *“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 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 Allina Health facilities or by Allina Health Principal or Sub-Investigators (as defined on the FDA 1572 or equivalent, or the delegation of responsibilities log) requires review by an Allina Health-designated IRB. Exceptions to this requirement may be granted on a case-by-case basis (e.g., when Allina Health’s involvement in the research is limited to the provision of a common diagnostic procedure and associated reading or analysis).

When external organizations and researchers wish to conduct research within Allina facilities, involving Allina patients or employees, using Allina’s privately held information, or otherwise under the auspices of the Allina Health HRPP, and Allina’s engagement in the research is uncertain (e.g., Allina’s involvement is limited to facilitating recruitment, providing data to external researchers, or providing a low-risk service (phlebotomy, routine labs, ECGs)), the external organization or researchers must consult with Allina Health HRPP or IRB staff prior to initiating any research activities at or involving Allina Health. Based upon the information provided, the HRPP or IRB staff may advise the researcher to proceed with an “engagement determination” submission or to proceed with an IRB submission.

Requests to determine engagement are submitted via the IRB electronic system. Instructions for such submissions are also available in the system or from the HRPP or IRB staff.

An IRB Chair or Vice Chair (or such delegate as permitted by this provision), with the assistance of staff and Counsel as needed, will determine whether Allina Health is engaged in a particular research study. As appropriate, the IRB Chair may delegate to the HRPP Director the ability to determine whether Allina Health is engaged in a particular research study. Investigators and other institutions **may not** independently determine whether Allina Health is engaged in a particular research study.

When Allina Health is engaged in research, the Institutional Official may choose to enter into an agreement to cede review to an external IRB.

For additional information on determining engagement please refer to OHRP's Guidance on Engagement of Institutions in Human Subjects Research:
<http://www.hhs.gov/ohrp/policy/engage08.html>.

6 “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 in the Common Rule and FDA regulations, respectively. Consultation with the HRPP or IRB staff is encouraged. Guidance to help evaluate whether quality assessment or improvement activities, program evaluation activities, and healthcare innovation are research is available in the IRB's electronic system. Because the analysis can be complex, persons with any questions regarding the applicability of the guidance to their activities are urged to request a confirmation that an activity does not involve research. Such confirmation should be submitted through an application requesting a "Human Subjects Research Determination" via the IRB electronic system.

Similarly, the responsibility for the initial determination of whether research involves “human subjects” rests with the investigator. Under the Common Rule, data is considered identifiable, and thus involving human subjects, when the identity of the subject is (known) 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 “identifiability” in the evaluation of whether an activity is a clinical investigation 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 under FDA regulations. Investigators are urged to submit for a determination whenever they are uncertain if the research involves “human subjects” as defined by the Common Rule or FDA.

Research under the auspices of Allina Health that includes the use of coded private information or specimens **must** be submitted for a “Human Subjects Research Determination” via the IRB electronic system. The only exception to this policy is when the coded private information or specimens are to be obtained from an IRB-approved repository and the rules of that repository 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.

Human Subjects Research Determinations must be submitted, and determined, prospectively (i.e., before the activity or research begins). Conducting human subjects research without IRB approval or exemption is noncompliance and will be managed as described in Section 16.

An IRB Chair or Vice Chair (or such delegate as permitted by this provision), with the assistance of staff and Counsel as needed, will determine whether the proposed project is Human Subjects Research. As appropriate, the IRB Chair may delegate to the HRPP Director the ability to determine whether the proposed project is Human Subjects Research. Investigators **may not** rely upon determinations made by other organizations or through the use of other tools.

7 Exempt Determinations and Limited IRB Review

All research using human subjects must be approved by Allina Health. Although certain categories of human subject research are exempt from IRB oversight, at Allina Health the determination of exempt status must be made by the Allina Health IRB Chair or Vice Chairs or a Chair – designated member of the IRB. Determinations of exempt status for industry-sponsored research may also be made by an Allina-designated external IRB. This policy and procedure section applies to exempt reviews by the Allina Health IRB Chairs and Vice Chairs or a Chair – designated member of the IRB. Allina’s designated external IRBs follow their own procedures.

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 conflict of interest.

Exemptions are determined or granted, rather than approved. Exempt studies are exempt from the revised Common Rule [\[45 CFR 46\]](#) (i.e., FWA, IRB approval and full research consent are not required). They do require a determination/confirmation of exemption status. Although exempt research is not covered by the federal regulations, this 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.)

When the research requires limited IRB review or a HIPAA determination (i.e., waivers or alterations of the requirement for HIPAA authorization), the review will be conducted by the IRB Chair or a Chair-designated member of the IRB and may be conducted using expedited review procedures. 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. [§46.109(a)]

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 7 business days). [§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. [§46.109(f)(ii), §46.115(a)(3)]

7.1 Limitations on Exemptions

Children: Exemption #2(i) and (ii) for research involving survey or interview procedures or observations of public behavior does NOT apply to research in children, except for research involving observations of public behavior when the investigator does not participate in the activities being observed. Exemption #2(iii), where identifiable information is obtained and the IRB conducts a limited IRB review, is NOT applicable to research in children. Exemption #3 does NOT apply to research involving children. [§46.104(b)(3)]

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

7.2 Categories of Exempt Research [§46.104(d)]

Unless otherwise required by law or a federal agency or department, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from the additional requirements of the revised Common Rule, except as specified.

Note: Other than exempt category 6, these categories do not apply to research that is also FDA-regulated.

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:
 - (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 §46.111(a)(7): *"When appropriate, there*

are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.”

3. Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:
 - (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 §46.111(a)(7): *“When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.”*

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.

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 ['HIPAA'], 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 nonresearch 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.

Note: Exempt categories 7 & 8 always require limited IRB review and are only available when broad consent will be (or has been) obtained. *Allina Health made the decision to not implement broad consent at this time, therefore Exempt categories 7 & 8 will not be used.*

7.3 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 14.8 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\(d\)\]](#)

7.4 Procedures for Exempt Determination

To request an exempt determination, investigators submit the following materials via The IRB electronic system:

1. IRB Application 1
2. IRB Application 2 – Request for Exempt Determination (or IRB Application 2 – Chart Reviews, when applicable)
3. The study protocol
4. Any subject materials such as recruitment materials, information sheets, consents, scripts, and questionnaires or surveys
5. Memo of Acknowledgment
6. Certification of current CITI training for all members of the research team
7. Curriculum Vitae, Bio sketch, or Resume, for the PI.

An IRB Chair, Vice Chair or a Chair – designated member of the IRB reviews all requests for exemptions and determines whether the request meets the criteria for exempt research. The

reviewer's determinations are documented on Application 2 – Request for Exempt Determination (or the Chart Reviews Checklist) and uploaded into The IRB electronic system.

Although exempt research is not covered by the federal regulations, this research is not exempt from the ethical guidelines of the Belmont Report. The individual making the determination of exemption will determine whether to require additional protections for subjects in keeping with the guidelines of the Belmont Report.

The IRB staff will publish a letter documenting the outcome of the review in The IRB electronic system. The exempt application, 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 not have an expiration date. Investigators must report to the IRB any proposed modifications to the research during the course of the exempt study for a determination of whether the modified activity still qualifies for exemption. Investigators must also submit proposed changes to study personnel so that training can be verified and COI evaluated.

8 External IRB Policies and Procedures and Reliance Agreements for Multi-Site Research

8.1 External IRB Review

Regardless of which IRB is designated to review a research project, Allina Health is responsible for research under its auspices or jurisdiction. Research reviewed by external IRBs remains subject to review, approval, and oversight by Allina Health and must adhere to all applicable policies, procedures, and requirements, including those of the HRPP.

Investigators must submit basic information about proposed research to the Allina Health IRB Office via The IRB electronic system for review to gain approval to move forward with a submission to an external IRB.

Investigators seeking IRB review for industry-sponsored clinical trials may apply to one of the accredited external IRBs with which Allina Health has a master agreement. Guidance documents, fact sheets, and other materials describing the processes and requirements for submissions to an external IRB are available in The IRB electronic system.

Allina Health relies upon the IRBs designated by the Metro-Minnesota Community Oncology Research Consortium (MMCORC) for the MMCORC studies it participates in. Procedures for these studies are developed by the consortium, and the procedures in this section do not apply.

On a study-specific, case-by-case basis, Allina Health may also choose to enter into an agreement to rely on other commercial or institutional External IRBs, most commonly when required as a condition of a grant or contract. Investigators should submit reliance requests as early in the grant/contract process as possible by emailing irb@allina.com.

When considering a request to rely upon an External IRB, the following factors, and others as appropriate, are evaluated:

- 1) The AAHRPP accreditation status of the proposed IRB;
- 2) The compliance history of the IRB (e.g., outcomes of prior audits or inspections, corrective actions);
- 3) Prior experience with the IRB;
- 4) The federal IRB registration and organizational FWA, as applicable;
- 5) The expertise and experience of the proposed IRB (e.g., with reviewing the type of research, research procedures, and subject population(s));
- 6) The research activities that will be conducted at or by Allina Health;
- 7) The risks and complexities of the proposed research;
- 8) The proposed reliance terms and procedures including the procedures for collaborative management of matters such as conflicts of interest, noncompliance, unanticipated problems, and federal reports;

9) The plan for review and allowance of the incorporation of site-specific consent language; and

10) The plan for incorporation of other relevant local requirements or context information in the review process.

When reliance on a non-AAHRPP-accredited IRB is proposed, the evaluation may also take into consideration one or more of the following based upon the risks of the research, the research activities that Allina Health will be involved in, and Allina Health's familiarity with the IRB:

1) When the research is minimal risk (or the activities that Allina Health is involved with are minimal risk), a statement of assurance from the proposed IRB that its review will be consistent with applicable ethical and regulatory standards, and that it will report any regulatory investigations, citations, or actions taken regarding the reviewing IRB, and, when applicable, the organization's FWA;

2) An attestation about, or summary of, any quality assessment of the reviewing IRB such as evaluation by an external consultant or internal evaluation of compliance using the FDA's self-evaluation checklist or AAHRPP's self-evaluation instrument;

3) The willingness of the External IRB to accommodate requests for relevant minutes and other records of the proposed study and/or to copy Allina Health's HRPP office on correspondence such as determination letters and notices of suspensions or terminations of IRB approval;

4) The willingness of the External IRB to accommodate a request for someone from the relying organization to serve as a consultant to the IRB or to observe the review of the proposed study; and/or

5) An assessment of the External IRB's policies and procedures.

8.1.1 Internal Reporting Responsibilities: Post External IRB Approval

Investigators approved through external IRB review must still report local unanticipated problems, complaints, any serious or continuing non-compliance to the Allina Health HRPP/IRB Office via The IRB electronic system, in addition to any external IRB reporting requirements. Investigators may also need to submit other non-local reportable events when requested by the IRB Office. Copies of the report submitted to the external IRB are generally acceptable but additional information may be requested on an as needed basis. Investigators must also submit copies of continuing review reports and study closures. Changes in study personnel must be submitted to the IRB office via The IRB electronic system prior to the personnel assuming any study responsibilities.

Notices about and reports of audits or inspections must be provided to the HRPP as described in Section 2.1 of this manual.

Investigators are reminded that other Allina Health reporting requirements, such as to Compliance, Privacy, and Risk Management, remain applicable regardless of IRB reporting.

8.2 Allina IRB Serving as the Reviewing IRB/sIRB for Other Sites

Allina Health IRB may serve as the reviewing IRB or single IRB (sIRB) for multi-site or collaborative research studies. This includes non-exempt, federally-funded Common Rule agency multi-site research, including research subject to sIRB under NIH Policy and/or federal regulations as well as other industry, foundation, or other government-sponsored research and unfunded research. The Allina Health IRB Office should be notified in advance of the request to serve as the reviewing IRB for another site to determine whether the Allina IRB agrees to serve as the reviewing IRB or sIRB.

Before another institution can rely on the Allina Health IRB for the oversight of a study, the institutions must document the reliance arrangement through the execution of a reliance agreement. The reliance agreement documents the respective authorities, roles, and responsibilities between Allina Health and the other institution. Allina Health will primarily use SMART IRB (section 8.2.1) for establishing reliance agreements with other institutions.

While there may be local context requirements, including institutional and state laws that are unique to a participating site, it is the expectation that participating sites will follow all policies and procedures agreed upon in the reliance agreement. If the participating site cannot follow the Allina Health IRB requirements, the participating site cannot rely upon Allina Health for IRB review.

In consultation with the Institutional Official and HRPP Director, there are several factors that the IRB Office assesses on a study-by-study basis when determining whether to recommend serving as the reviewing IRB/sIRB. Allina Health IRB may serve as the reviewing/sIRB only when Allina is engaged in the research and/or has an agreement in place with the external organization and when:

- Allina is the main grantee for a multi-site project requiring use of a single IRB (e.g., NIH or other Common Rule Agency funding) and all participating sites are willing to rely on Allina (Exception: Allina IRB does not serve as the reviewing IRB for international sites); or
- The overall study PI is employed by Allina Health or a member of the medical staff; or
- The Allina Health IRB Office evaluates other key factors and study-by-study circumstances, including those listed in 8.2.2, and recommends serving as the reviewing IRB.

When the Allina IRB serves as the reviewing/sIRB for another organization, the requirements and procedures outlined in the sections below apply unless an alternative procedure has been agreed upon in the reliance agreement or in a companion document.

8.2.1 Reliance using SMART IRB

When Allina IRB is serving as the reviewing/sIRB, the SMART IRB agreement or other existing master agreement is the preferred mechanism for site reliance. In collaboration with the other participating organizations, the IRB Office will determine on a study-by-study basis whether the SMART IRB SOPs or alternative procedures will be used to implement the reliance.

8.2.2 Reliance on Allina Health IRB

When the SMART IRB or another existing master agreement is not being utilized, the HRPP Director, IRB Manager, and IRB staff will ensure the agreement is appropriate and aligned with the reviewing and relying IRBs' responsibilities.

When considering a request to serve as the reviewing/sIRB, the following factors, and others as appropriate, are evaluated:

- 1) The terms of the external organization's FWA;
- 2) Prior experience with the organization and investigators;
- 3) The AAHRPP accreditation status of the external organization's HRPP;
- 4) The compliance history of the organization and investigators (e.g., outcomes of prior audits or inspections, corrective actions);
- 5) The research activities conducted by or at the external organization;
- 6) The willingness of the external organization to accept the proposed terms of the reliance agreements and procedures;
- 7) The ability of the organizations to collaboratively provide meaningful oversight of the proposed research, taking into account factors such as:
 - a. The risks and procedures of the research;
 - b. The resources available at each organization and ability to accommodate or collaborate with each other in observing the consent process, performing compliance reviews, investigations of potential noncompliance, and similar matters;
 - c. The expertise and experience of the Allina Health IRB with the proposed research, subject population, and applicable regulations;
 - d. The familiarity of the Allina Health IRB with the relevant local context considerations of the external organization; and/or
 - e. The willingness or ability of the external organization to provide information and respond to questions regarding investigator qualifications, conflicts of interest, organizational requirements, local context, and other matters that may inform the IRB review.

8.2.3 Initial Submission and Review Process for Adding a Relying Site

Guidance documents and templates for establishing a multi-site or collaborative study with Allina IRB as the reviewing IRB may be found in the electronic system's Forms and Templates Library. The local site will complete and attach the Collaborative Research Supplement located in the Forms and Templates Library to identify sites relying on Allina IRB if the IRB Office has confirmed that Allina IRB agrees to serve as the relying IRB. IRB approval of the study protocol and Allina local consent documents should be obtained prior to the addition of any other relying sites. Relying sites and site-specific documents may be added to the study via amendment in the electronic submission system after reliance has been established and the relying site has completed any local administrative review. Amendments to add sites may be reviewed by expedited review or referred to the full board. The following should be submitted in the amendment to add each site, as applicable, and unless reliance terms have been agreed upon otherwise:

- Fully-executed reliance agreement or acknowledgment of existing agreement;
- Allina Health Relying Site Local Context Form, which includes:
 - Any conflict management plans for potential conflict of interest relevant to the study. It is the responsibility of the external site relying on Allina Health to review and report any relevant COIs;
 - Attestation that all relying site study team members have completed their institution's training and education requirements. The relying site is responsible for reviewing and documenting their own team's training and educational requirements.
 - Local context information, consent, and HIPAA requirements for the relying institution.
 - Any local changes of protocol (Only implement changes of protocol, including local variations, after the Allina IRB has approved them, except in cases where a change is required to avoid an apparent immediate hazard to participants).
- All site-specific advertising materials, subject-facing materials, and data collection tools;
- Tracked and clean copies of the consent with site-specific changes:
 - The relying institution may perform their own Local Context review and include site-specific language (e.g., the availability of treatment and compensation for research-related injury, payment/reimbursement of costs incurred by subjects for participation, confidentiality, and Relying Site Investigator contact information).

8.2.4 Communications Requirements

IRB correspondence and determinations will be published in the electronic submission system as is done with all IRB determinations. The Allina Health PI is responsible for ensuring that the

relying site(s) PI(s) have received the most current versions of all the protocol documents and IRB determination letters, including site-specific determinations for relying sites.

Standard Operating Procedures are posted on the Allina Health webpage and are available for public viewing. The Allina Health PI is responsible for communicating changes to relevant procedures and policies when they are updated. The relying institutions may also communicate directly with the Allina Health IRB by e-mailing irb@allina.com with any questions. All relevant IRB records, including meeting minutes, are made available to the relying organization upon request.

8.2.5 Post-Approval Requirements

As the reviewing IRB, Allina IRB is responsible for the continuing oversight and review of amendments and continuations for each of the relying sites that have ceded review. It is the Allina Health PI's responsibility to submit all modifications, continuing reviews, study or site closure reports, unanticipated problems involving risks to subjects or others, other reportable events (e.g., noncompliance), subject complaints, and deviations that occur at Allina Health or any relying site to the Allina IRB in accordance with these standard operating procedures. It is the responsibility of the Allina Health PI to communicate all determinations with the relying sites.

Each relying site maintains responsibility for approving key personnel changes and authorizing any changes related to local context (e.g., local context consent language, HIPAA Authorization changes). The relying site's documentation should be submitted to the Allina IRB as an expedited amendment with the exception of non-PI key personnel changes. Continuing review submissions must include an update for progress at each relying site as part of the overall progress updated for the study.

Allina Health has the authority to request an audit of research under their review at local and relying sites.

9 IRB Review Process

The IRB will review and ensure that research involving human subjects meets all required ethical and regulatory criteria for initial and continuing review and any modifications of approved research. The IRB may conduct reviews using one of the following review methods:

- Expedited Review
- Review by Convened IRB

In addition, the IRB Office staff may administratively review a response package to verify that specific conditions of approval requested by the IRB have been fulfilled. The IRB or reviewer will indicate during the IRB meeting or on the reviewer worksheet if the IRB Office staff may administratively review the conditions.

The following describe the procedures required for the review of research by the Allina Health IRB. External IRBs follow their own procedures.

9.1 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:

- The level of risk to subjects
- The research design or methodology
- The subject population
- Qualifications of the research team
- The facilities available to support the safe conduct of the research
- Any other factor that would warrant review of the proposed changes by the convened IRB

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.

Suspension of IRB approval. A suspension of IRB approval is a directive of the IRB to temporarily stop some or all previously approved research activities. Suspended research studies remain open and require continuing review.

Termination of IRB approval. A termination of IRB approval is a directive of the convened IRB to permanently stop all activities in a previously IRB approved research study. Terminated research studies are closed and no longer require continuing review.

9.2 Expedited Review

An 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 and found by the reviewer(s) to involve no more than minimal risk.
- Minor changes in previously approved research during the period (of one year or less) for which approval is authorized.
- Studies requiring limited IRB review.

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.

9.2.1 Categories of Research Eligible for Expedited Review

The Allina Health IRB 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 activities listed below should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

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

Research Categories one (1) through seven (7) may be used for both initial and continuing IRB review:

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

(a) Research on drugs for which an investigational new drug application ([21 CFR Part 312](#)) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(b) Research on medical devices for which (i) an investigational device exemption application ([21 CFR Part 812](#)) is not required; or (ii) the medical device is cleared/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 nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46 101(b)(2) and b(3). This listing refers only to research that is not exempt.)

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

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior); or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

Categories 8 and 9 apply only to continuing review.

(8) Continuing review of research previously approved by the convened IRB as follows:

(a) Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects (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 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 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.)

(9) Continuing review of research previously approved by the IRB at a convened meeting that meets the following conditions:

- The research is not conducted under an investigational new drug application (IND) or an investigational device exemption (IDE);
- Expedited review categories (2) through (8) do not apply to the research;
- 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
- 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 IRB’s most recent prior review.)

9.2.2 Expedited Review Procedures

Under an expedited review procedure, the review may be carried out by the IRB Chair or by one or more reviewers designated by the Chair from among members of the IRB.

The Chair will designate a list of IRB members eligible to conduct expedited review. The designees must be experienced (having served on an IRB for at least one year or other equivalent IRB administrative experience) voting members or alternate members of the IRB. The IRB Staff will select expedited reviewers from that list. Selected reviewers will have the qualifications, experience and knowledge in types of research to be reviewed, as well as be knowledgeable of the requirements to approve research under expedited review. IRB members with a conflict of interest in the research (see Section 23.2) will not be selected.

When reviewing research under an expedited review procedure, the IRB Chair, or designated IRB member(s), will receive and review all documentation that would normally be submitted for a full-board review. This requirement applies to all categories of submissions including initial reviews, continuing reviews, and modifications. The reviewer will determine and document the regulatory criteria allowing use of the expedited review procedure by using the appropriate reviewer checklist.

If the research meets the criteria allowing review using the expedited procedure, the reviewer(s) conducting initial or continuing review will complete the appropriate reviewer checklist to determine whether the research meets the regulatory criteria for approval. The same criteria of approval apply to reviews conducted via expedited review as to those conducted by the convened board. If the research does not meet the criteria for expedited review, then the reviewer will indicate that the research requires full review by the IRB and the research study will be placed on the next available agenda for an IRB meeting.

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

In the event that expedited review is carried out by more than one IRB member and the reviewers disagree, the IRB Chair may make a final determination or the study will be referred to the convened IRB for review.

The limited IRB review that is required for certain exempt research (See Section 3) may be conducted using expedited review procedures [§ __.110(b)(1)(iii)]

Continuing review of research is not required for research that qualifies for expedited review unless the IRB determines that it is required and documents the rationale within the IRB record.

The IRB staff will produce a letter for the investigators documenting the outcome of the review.

9.2.3 Informing the IRB

All members of the IRB will be apprised of expedited reviews by means of a list in The electronic system and prior to each scheduled meeting. Any IRB member can request to review the materials for any study by contacting the IRB Office.

9.3 Convened IRB Meetings

Except when an expedited review procedure is used, the IRB will conduct initial and continuing reviews of all non-exempt research at convened meetings at which a quorum of the members is present.

9.3.1 IRB Meeting Schedule

The IRB meets on a regular basis throughout the year (usually once per month). The schedule for the IRB may vary due to holidays, lack of quorum, or other reasons. The schedule for IRB meetings is posted on the IRB website and in The IRB electronic system. Special meetings may be called as needed by the Chair, IRB Manager or the HRPP Director.

9.3.2 Preliminary Review

IRB Staff will perform a preliminary review of all submissions for determination of completeness and accuracy, including an elements of consent checklist, when applicable. Only complete submissions will be placed on the IRB agenda for review. The investigator will be informed via The IRB electronic system or by e-mail of missing materials and any needed changes. If an investigator is submitting for the first time or is not well-versed in the submission procedures, consultations can be arranged with HRPP or IRB staff.

9.3.3 Primary and Secondary Reviewers

After it has been determined that the submission is complete, IRB staff, with the assistance of the IRB Chair as needed, will assign submissions for review paying close attention to the subject matter of the research, the potential reviewer's area/s of expertise and representation for any vulnerable populations involved in the research. A "primary reviewer" will be assigned to each

submission and receive and review the full submission materials. A reviewer may be assigned several submissions or other items for review. When the IRB is presented with a research study which may be outside of the knowledge base or representative capacity of the IRB members, an outside consultant will be sought (See Section 4.5). Research studies for which appropriate expertise cannot be obtained for a given meeting will be deferred to another meeting when appropriate expertise is available.

Primary reviewers are responsible for:

1. Having a thorough knowledge of all of the details of the proposed research.
2. Performing an in-depth review of the proposed research.
3. Beginning the discussion of the proposed research at the convened meeting, by summarizing the proposed research and leading the IRB through the criteria for approval (See Section 9.4).
4. Making suggestions for changes to the proposed research, where applicable.
5. Completing all applicable IRB reviewer forms.

One or more “secondary” reviewers may be assigned in addition to the primary reviewer. A secondary reviewer may be assigned to review the full submission materials or may be asked to pay special attention to specified sections of the submission (e.g., subject materials).

All IRB members receive and are expected to review all studies, not just those assigned as primary or secondary reviewer.

When it can be anticipated that the primary reviewer may be absent from the meeting, a new primary reviewer may be assigned, provided that they have sufficient time to review the materials in advance of the meeting. Absent reviewers can submit their written comments for presentation and consideration at the convened meeting. If an absent reviewer submits comments, those can indicate a recommendation regarding approval, but such recommendation will not be counted as a vote.

9.3.4 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 IRB staff in consultation with the Chair or HRPP Director as needed. All IRB members receive the IRB agenda, prior meeting minutes, applicable business items, continuing education materials and research submission materials at least 5 business days before the scheduled meeting to allow sufficient time for the review process. On occasion, a time sensitive item may be added to the agenda less than 5 business days in advance if circumstances warrant and the IRB staff have contacted the IRB members and verified that they will have sufficient time to review.

Each IRB member receives and reviews all submission materials for all studies on the agenda, these may include:

- A Protocol/Research Plan
- The Application Forms
- Proposed Consent / Parental Permission / Assent Form(s), when applicable
- Recruitment materials including advertisements intended to be seen or heard by potential subjects
- Any other subject materials (e.g., questionnaires, diaries, etc.)

The materials provided to the primary reviewer are available to all members in The IRB electronic system.

If an IRB member requires additional information to complete the review, they may contact the investigator directly or may contact the IRB Office to make the request of the investigator.

Primary reviewers will complete the applicable reviewer checklist to summarize their review and recommendations for other IRB members.

9.3.5 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 from a Magnet facility 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 IRB staff, will confirm that a quorum is present before calling the meeting to order. The IRB Chair, with the assistance of the IRB staff, 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, the IRB cannot take further actions or vote on submissions until quorum is restored.

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 reviews research that involves a vulnerable category of subjects, such as children, pregnant women, or persons with impaired decision-making capacity, one or more individuals (e.g., IRB members, alternate members, or consultants) who are knowledgeable about and/or experienced with those 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 permit 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 the quorum for convened meetings.

9.3.6 Meeting Procedures

The IRB Chair will call the meeting to order, once it has been determined that a quorum is in place. The Chair will remind IRB members to recuse themselves from discussion and votes by leaving the room when they have a conflict. 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 Chair or Vice Chair outside of the meeting.

The IRB reviews all submissions for initial and continuing review, as well as requests for modifications and other business items. The Primary Reviewer presents an overview of the research and assists the Chair in leading the IRB through the evaluation of the regulatory criteria for approval. For the research to be approved, it must receive the approval of a majority of those voting members present at the meeting.

The IRB staff are responsible for taking minutes at each IRB meeting.

9.3.7 Guests

Investigators and research staff may be invited to the IRB meeting, at the discretion of the IRB, to make a brief presentation or to answer questions about proposed or ongoing research. The investigator/research staff may not be present for the deliberations or voting portion of the review.

The HRPP Director and HRPP/IRB staff regularly attend IRB meetings and may participate in the IRB discussion and deliberations, but may not vote unless attending as a member or alternate.

Other guests may be permitted to attend IRB meetings at the discretion of the IRB Chair and the IRB Manager. Such guests may be asked to sign a confidentiality agreement and do not participate in discussion unless requested by the IRB; under no circumstances may they vote.

9.4 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 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 vulnerable populations such as children, prisoners, pregnant women, mentally disable persons, or economically or educationally disadvantaged persons.
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 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.
8. 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. While pregnant women are no longer described as vulnerable within the above criteria, the IRB shall continue to apply Subpart B “Additional Protections for Pregnant Women, Human Fetuses and Neonates” as described in the Allina Health HRPP/IRB SOP Manual. The revised Common Rule does not eliminate or modify Subpart B.
9. For exempt research subject to limited IRB review, the following criteria shall be applied:
 - i. For exempt categories 2(iii) and 3(iii) (See Section 3.2), the IRB may approve the research when it determines that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

9.4.1 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 even if not participating in 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 to be gained;

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. When evaluating risks, the IRB should consider the adequacy of the settings or facilities to execute the protocol requirements where the research will take place.

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.

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”).

9.4.1.1 Scientific or Scholarly Review

In order to assess the risks and benefits of the proposed research, the IRB must determine that:

- The research uses procedures consistent with sound research design; and
- The research design is sound enough to reasonably expect the research to answer its proposed question.

In making this determination, the IRB may draw on its own knowledge and expertise, or the IRB may draw on the knowledge and expertise of others, such as reviews by a funding agency, or

departmental review. When scientific or scholarly review is conducted by an individual or entity external to the IRB, documentation of the review must be provided to the IRB for review and consideration.

9.4.2 Equitable Selection of Subjects

The IRB determines by reviewing the application, protocol/research plan and other materials that the selection of subjects is equitable with respect to gender, age, class, etc. 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 vulnerable populations such as children, prisoners, pregnant women, mentally disabled persons, 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.

At the time of the continuing review the IRB evaluates whether subject selection has been equitable.

9.4.2.1 Recruitment of Subjects

The investigator will provide the IRB with a plan for recruitment of all 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 9.5.8 for a discussion of IRB review of advertisements and Section 9.5.9 for a discussion of IRB review of payments.

9.4.3 Informed Consent

The IRB will ensure that 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 [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 protocol/research plan. See Section 12 for detailed discussion of informed consent.

9.4.4 Data and Safety Monitoring

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 transmitting the DSM results to the IRB. This description should include information regarding an independent Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), if one exists, or an explanation why an independent data safety monitor is not necessary.

The IRB reviews the safety monitoring plan and determines if it makes adequate provision for monitoring the reactions of subjects and the collection of data to ensure the safety of subjects and address 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 DSM plan may vary depending on the potential risks, complexity, and nature of the research study.

The factors the IRB will consider in determining whether the safety monitoring plan is adequate for the research are as follows:

1. Monitoring is commensurate with the nature, complexity, size and risk involved.
2. Monitoring is timely. Frequency should be commensurate with risk. Conclusions are reported to the IRB.
3. For low risk studies, continuous, close monitoring by the study investigator or an independent individual may be an adequate and appropriate format for monitoring, with prompt reporting of problems to the IRB, sponsor and regulatory bodies as appropriate.
4. Data and Safety Monitoring plans should specify:
 - a. 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
 - b. The safety information that will be collected and monitored, including serious adverse events and unanticipated problems
 - c. The frequency or periodicity of review of safety data
 - d. The procedures for analysis and interpretation of the data
 - e. The procedures for review of scientific literature and data from other sources that may inform the safety or conduct of the study
 - f. The conditions that trigger a suspension or termination of the research (i.e., stopping rules), if applicable
 - g. The procedures for reporting to the IRB, including a summary description of what information, or the types of information, that will be provided
 - h. For a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), the plan should also describe the composition of the board or

committee. Generally, a DSMB 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.

In general, it is desirable for a DSMB or DMC to be established by the study sponsor for research that is blinded, involves multiple sites, involves vulnerable subjects, or employs high-risk interventions. The National Institutes of Health (NIH) requires the establishment of DSMBs for multi-site clinical trials involving interventions that entail potential risk to the participants. The IRB has the authority to require a DSMB or DMC as a condition for approval of research where it determines that such monitoring is needed. When DSMBs or DMCs are used, IRBs conducting continuing review of research may rely on a current statement, or the most recent report, from the DSMB or DMC which indicates that it has and will continue to review study-wide adverse events, study-wide interim findings, and any recent literature that may be relevant to the research in lieu of requiring that this information be submitted directly to the IRB.

9.4.5 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**.

9.4.5.1 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 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.

9.4.5.2 Privacy

The IRB must determine whether the activities in the research appropriately protect the privacy of potential and actual 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. Investigators must have appropriate authorization to access the subjects or the subjects' information.

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

1. Methods used to identify and contact potential participants
2. Settings in which an individual will be interacting with an investigator
3. Appropriateness of all personnel present for research activities
4. Methods used to obtain information about participants, and the nature of the requested information including minimizing the information obtained to achieve the aims of the research
5. Information that is obtained about individuals other than the "target subjects," (e.g., a subject provides information about a family member for a survey) and whether such individuals meet the regulatory definition of "human subject"

9.4.5.3 Confidentiality

The IRB must determine if appropriate protections are in place to minimize the likelihood that information about subjects will be inappropriately 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. Additionally, the investigator will provide information regarding information security procedures and plans to address the protection of paper documents, other physical media (e.g., audio or videotapes), and electronic data and information including the use, maintenance, storage, and transmission of information. The IRB will review all 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 be obtained to additionally protect research data (See Section 26.2).

In reviewing confidentiality protections, the IRB shall consider whether the data or other information accessed or gathered for research purposes is sensitive and the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. It shall evaluate the effectiveness of proposed de-identification techniques, coding systems, encryption methods, methods of transmission,

storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections. In reviewing confidentiality protections, the IRB shall also consider regulations and organizational requirements and policies regarding the use of information and information security.

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](#).

9.4.6 Vulnerable Populations

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

For an extensive discussion about the IRB's review and approval process for individual populations of vulnerable subjects, please refer to Section 13.

9.5 Additional Considerations

9.5.1 Determination of Risk

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 convened IRB's determination regarding risk levels; expedited reviewers will document the determination of risk level on the reviewer's checklist.

9.5.2 Period of Approval

At the time of initial review and at continuing review, the IRB will make a determination regarding the period of approval. All studies will be reviewed by the IRB at intervals appropriate to the degree of risk. All FDA-regulated studies, any studies approved prior to January 21, 2019, and any greater than minimal risk studies reviewed by the full IRB require review no less than once per year. Studies qualifying for expedited review and any study closed to enrollment but analysis of identifiable/coded information and/or accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care continues do not require an approval period unless justified by the IRB or reviewer.. In some circumstances, a shorter review interval (e.g., semi-annually, quarterly, or after accrual of a specific number of

participants) may be required (see below). The meeting minutes will reflect the convened IRB's determination regarding review frequency; expedited reviewers will document the determination of risk level on the reviewer's checklist.

IRB approval is considered to have lapsed at the end of the day of the expiration date noted on IRB approval letters (i.e., the expiration date is the last day research can be conducted). For a new study reviewed by the 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 or expedited reviewer approves the research **or** the date (the "effective date") when it has been verified that the requirements of the IRB have been satisfied following an action of "Approval with Conditions". The expiration date of the initial approval period, which is the date by which the first continuing review must occur, may be as late as one year after the effective date of initial IRB approval.

The use of the effective date of IRB approval to determine the latest permissible date for continuing review *only applies to the first continuing review*. For all subsequent continuing reviews of a research study subject to convened board review, the date the convened IRB or the date that the expedited reviewer conducts continuing review and approves the study (with or without conditions) determines the latest permissible date of the next continuing review.

The approval date and approval expiration date are clearly noted on IRB determination letters and must be strictly adhered to. Investigators must allow sufficient time for development and review of continuing review submissions. As a courtesy, the electronic system sends reminders to the investigator prior to the study's expiration date, notifying him or her that the study is due for a continuing review or when approval has expired.

IRB review of a proposed modification to research ordinarily does not alter the date by which continuing review must occur. This is because continuing review is review of the full research project, not simply a change to it.

The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of research must occur before midnight of the date when IRB approval expires. If the IRB performs continuing review within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must occur.

9.5.3 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 likely medical/psychological/social/legal/educational condition of the proposed subjects.
3. The overall qualifications of the investigator and other members of the research team.
4. The specific experience of the investigator and other members of the research team in conducting similar research.

5. The nature and frequency of adverse events observed in similar research at this and other institutions.
6. The novelty of the research making unanticipated adverse events/unanticipated problems more likely.
7. The involvement of especially vulnerable populations likely to be subject to undue influence or coercion (e.g., terminally ill).
8. A history of serious or continuing non-compliance on the part of the investigator.
9. 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 subjects either studied or enrolled. If a maximum number of subjects studied or enrolled is used to define the approval period, it is understood that the approval period in no case can exceed one year and that the number of subjects studied or enrolled determines the approval period only when that number of subjects is studied or enrolled in less than one year. If an approval period of less than one year is specified by the IRB, the reason for more frequent review is documented in the minutes or the expedited reviewer's checklist.

9.5.4 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 occurred during the IRB-designated approval period.

In support of this requirement, the Allina IRB requires the submission of all 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 will 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.
3. The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed.
4. Concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources.
5. Investigators who have previously failed to comply with federal regulations and/or the requirements or determinations of the IRB.
6. Research without a routine monitoring plan.

7. Any other factors where the IRB deems verification from outside sources is relevant.

In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period, or may require such verification at the time of continuing review, review of modification requests and/or unanticipated problems.

If any material changes have occurred without IRB review and approval, the IRB will decide whether corrective actions need to be taken (see Section 16 on Noncompliance).

9.5.5 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. Studies involving study staff with minimal experience in administering consent to potential study participants; or
5. Other situations when the IRB has concerns that consent process may not be being conducted appropriately (e.g., prior investigator non-compliance, 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 HRPP Director, HRPP Quality Specialists, and others to develop an appropriate plan. The consent monitoring may be conducted by HRPP or IRB staff, IRB members, or another appropriate designee. The investigator will be notified of the IRB's 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 observing the consent process, the monitor will evaluate:

- Whether the informed consent process was appropriately conducted and documented;
- Whether the participant had sufficient time to consider study participation;
- Whether the consent process involved coercion or undue influence;
- Whether the information was accurate and conveyed in understandable language; and

- Whether 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.

9.5.6 Investigator Qualifications

The IRB reviews credentials, curriculum vitae, resumes, or other relevant materials to determine whether investigators and members of the research team are appropriately qualified to conduct the research. The IRB may rely upon other Allina Health processes (e.g., credentialing) to inform this determination.

9.5.7 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 subjects' rights and welfare. 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. The IRB may also require that former subjects be provided with the new information, e.g., if it impacts their rights or welfare.

9.5.8 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:

1. The information contained in the advertisement.
2. The mode/method of its communication.
3. The final copy of printed advertisements.
4. The proposed script and final audio/video taped advertisements.

This information must be submitted to the IRB with the initial application or, if recruitment is 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 on the subject to participate. This includes but is not limited to:

1. Statements implying a certainty of favorable outcome or other benefits beyond what was outlined in the consent document and the research plan.

2. Claims, either explicitly or implicitly, that the test article (drug, biologic or device) is safe or effective for the purposes under investigation.
3. Claims, either explicitly or implicitly, that the test article was known to be equivalent or superior to any other drug, biologic or device.
4. Using terms like “new treatment,” “new medication,” or “new drug” without explaining that the test article was investigational.
5. Promising “free medical treatment” when the intent was only to say participants will not be charged for taking part in the investigation.
6. Emphasis on payment or the amount to be paid, such as bold type or larger font on printed media.
7. Offers for a coupon good for a discount on the purchase price of an investigational product once it has been approved for marketing.
8. The inclusion of exculpatory language.

Recruitment materials should be limited to the information the 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 this is research and not treatment.
7. A brief list of potential benefits (e.g., no-cost health exam).

Once approved by the IRB, an advertisement cannot be altered or manipulated in any way without prior IRB approval.

Directory listings of research such as [ClinicalTrials.Gov](https://www.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, research plan summary, 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 assure that the screening procedures adequately protect the rights and welfare of the prospective subjects.

9.5.9 Payments to Research Subjects

Payment to research subjects may be an incentive for participation or a way to reimburse a subject for travel and other experiences incurred due to participation. However, payment for participation is not considered a research benefit. Regardless of the form of remuneration, investigators must take care to avoid unduly influencing subjects. The amount of compensation must be proportional to the time and inconveniences posed by participation in the study.

Investigators who wish to pay research subjects must submit to the IRB the amount and schedule of all payments. Investigators should indicate in their application the justification for such payment. Such justification should substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject and do not constitute (or appear to constitute) undue pressure on the potential subject to volunteer for the research study.

The IRB must review both the amount of payment and the proposed method and timing of disbursement to assure that neither entails problems of coercion or undue influence.

When research involves multiple visits or interactions, payment should be prorated and not be contingent upon the participant completing the entire study. The IRB does not allow the entire payment to be contingent upon completion of the entire study. Further, any amount paid as 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.

Allina has policy in place to address how information is collected and reported for subjects who receive the amount required to be reported by the Internal Revenue Service. Please see *SYS-ADMIN-RA-006* "[1099 Reporting for Payments to Research Subjects](#)" policy for additional information. Where such reporting will take place, this should be disclosed in the consent form.

9.5.10 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 or tokens of appreciation, such as totes, books, toys, or other such materials, the approximate retail value must be described to the IRB and the IRB will be provided with a description, photo, or sample product to review.

The IRB will review all gifts and incentives being particularly sensitive to the influence of power or authority, whether perceived or actual, over free decision-making. Overt coercion (e.g., threatening loss of credit or access to services or programs to which the potential subjects are otherwise entitled) is never appropriate. Moreover, it must be clear that choosing to not

participate will not adversely affect an individual's relationship with the organization or its staff or the provision of services in any way (e.g., loss of credit or access to programs).

Investigators must carefully structure incentives and methods of disbursement so that while the incentives may serve as a factor in a subject's decision to participate, they have not served to unduly influence or coerce participation.

9.5.11 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 Counsel for the interpretation and application of Minnesota law and the laws of any other jurisdiction where research is conducted as they apply to human subjects research. The IRB will ensure that consent forms are consistent with applicable state and local laws.

9.6 Possible IRB Actions

Approval. The research, proposed modification to previously approved research, or other item is approved. The IRB has made all of the determinations required for approval (i.e., approval criteria and any applicable special determinations (e.g., waivers, alterations, vulnerable population determinations, etc.)). No further action is needed.

Approval with Conditions. The research, proposed modification to the previously approved research, or other item is approved but conditions must be satisfied before the approval becomes effective.

The IRB may approve research with conditions if, given the scope and nature of the conditions, the IRB is able, based on the assumption that the conditions are satisfied, to make all of the determinations required for approval (i.e., approval criteria and any applicable special determinations (e.g., waivers, alterations, vulnerable population determinations, etc.)). Any time the IRB cannot make one or more of the determinations required for approval, the IRB may not approve the study with conditions.

The IRB may require the following as conditions of approval of research:

- Confirmation of specific assumptions or understandings on the part of the IRB regarding how the research will be conducted (e.g., confirmation that the research excludes children);
- Submission of additional documentation (e.g., certificate of training);
- Precise language changes to the study, consent, or other study documents; or
- Substantive changes to the study, consent, or other study documents along with clearly stated parameters that the changes must satisfy.

When the IRB approves research with conditions, the conditions will be documented in the IRB minutes for research reviewed at a convened meeting or in the applicable reviewer checklist for research reviewed under an expedited review procedure.

When the convened IRB approves research with conditions, the IRB may designate the IRB Chair (and/or other qualified individual(s)) to review responsive materials from the investigator and determine that the conditions have been satisfied. If the conditions have not been satisfied, or are only partially satisfied, the responsive materials must be referred to the convened IRB for review. When an expedited reviewer approves research with conditions, the original expedited reviewer (and/or other qualified individual(s)) will receive the response materials.

After verification, the following will be documented in IRB records and written communication to the investigator:

- The date when verification was made that all IRB conditions have been satisfied (i.e., the “effective date”);
- For initial approval, the date when approval becomes effective (i.e., the date on which the investigator’s response has been accepted as satisfactory), and;
- The date by which continuing review must occur.

The IRB will be informed of the outcome of the review of the investigator’s response in the agenda of the next meeting.

Deferred. 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 with the information provided).

The deferral and the basis for the deferral is documented in the IRB minutes (for convened review) or reviewer checklist (for expedited review) 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. When an expedited reviewer defers approval, the original expedited reviewer will review the response materials whenever possible. In the event that the original expedited reviewer is unavailable, the response will be reviewed by the IRB Chair or other qualified IRB member who has been designated to conduct expedited review.

Disapproved. The IRB may determine that the proposed research cannot be conducted at Allina Health or by employees or agents of Allina Health or otherwise under the auspices of Allina Health. Disapproval can only be decided at the convened IRB meeting. An expedited reviewer cannot disapprove a study.

Approval in Principle. As per federal regulations, [[45 CFR 46.118](#)], there are circumstances in which a sponsoring agency may require certification of IRB approval as a condition of submitting for or releasing funds but before definitive plans for the involvement of human subjects have been developed (e.g., certain training grants or grants in which the procedures involving human subjects are dependent on the completion of animal studies or instrument development). In these circumstances, the IRB may grant “approval in principle” without

having reviewed the as of yet undeveloped procedures or materials. The IRB Chair or designee will review the available information (i.e., the grant or proposal and any supplemental information provided by the investigator) and, if appropriate, will provide certification of IRB approval in principal. Any approvals in principle will note that IRB approval must be obtained before any activities involving human subjects may commence.

In addition to the above actions, the IRB may **acknowledge** reports and other items that don't involve prospective changes to already approved research. For example, the IRB may acknowledge the report of a protocol deviation but approve, require modifications in, or disapprove any associated corrective action plan. Further, the IRB may approve an item but include **comments** noting certain requirements, restrictions, or understandings. For example, with collaborative research, the IRB may note that approval must also be obtained from another IRB with jurisdiction and that the letter documenting that approval must submitted to the Allina IRB.

9.7 Continuing Review

The IRB will conduct a continuing review of ongoing research at intervals that are appropriate to the level of risk for each research plan. The date by which continuing review must occur will be recorded in the IRB electronic system and on initial and continuing review approval letters. Continuing review must occur as long as the research remains active including when the remaining research activities are limited to the use, study, or analysis of private identifiable information.

The revised Common Rule modifies when continuing review is required. Unless Allina Health IRB determines otherwise, continuing review of research is not required for research subject to the revised Common Rule in the following circumstances:

1. Research eligible for expedited review in accordance with §__.110;
2. Research reviewed by the IRB in accordance with limited IRB review as described in Section 3;
3. 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:
 - a. Data analysis, including analysis of identifiable private information or identifiable biospecimens, **or**
 - b. Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care

When continuing review is not required for non-exempt research, researchers are required to provide a study status update to the IRB Office every two years to confirm the research is still ongoing. If the research is still ongoing, current CITI training documentation for all study personnel with human subjects responsibilities must be attached or linked to a submission in the electronic system. The IRB Office staff administratively review the CITI training documentation for compliance, acknowledge the submission upon completion of requirements,

and update the two-year status report date. The research team must submit a Closure Report Form if the study is no longer active at the time of the two-year status update.

Allina Health 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's 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 Allina Health 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

9.7.1 Continuing Review Process

As a courtesy to investigators, the IRB electronic system will send out reminder notices to investigators in advance of the expiration date; however, it is the investigator's responsibility to ensure that the continuing review of ongoing research is approved prior to the expiration date. By federal regulation, no extension to that date can be granted.

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

- The Continuing Review Report
- The current consent, information sheet, or script if study is open to enrollment (or if sponsor requires re-approval)
- The current protocol
- The current Investigator's Brochure
- Any previously un-submitted publication(s)/presentations resulting from the research
- Any previously un-submitted reports identified while completing the continuing review report
- The most recent DSMB or DMC report
- For investigator held INDs or IDEs, a copy of the most recent annual report to the FDA

- CITI training certificates for each member of the research team with human subjects responsibilities that are not linked through their IRBNet user profile

Continuing review materials and historical documents are made available to members via the IRB electronic system. In addition, a Conflict of Interest review will be completed at the time of continuing review. COI Smart disclosures and CITI COI training must be current for all members of the research team.

9.7.2 Approval Considerations

In order to re-approve research at the time of continuing review, the IRB must determine that the regulatory criteria for approval continue to be satisfied. Because the research was previously found to satisfy the criteria for approval, the IRB focuses its considerations at the time of continuing review on whether any new information is available that would affect the IRB's prior determination that the criteria for approval are satisfied. The IRB pays particular attention to four aspects of the research:

1. Risk assessment and monitoring;
2. Adequacy of the informed consent process;
3. Local investigator and organizational issues; and
4. Research progress.

9.7.3 Convened Board Review

In conducting continuing review of research not eligible for expedited review, all IRB members receive and are responsible for reviewing all of the materials listed in Section 9.7.1. The Primary Reviewer conducts an in-depth review and completes a reviewer checklist to facilitate the review and discussion at the meeting. At the meeting, the Primary Reviewer (and Secondary when assigned) assists the Chair by providing a summary of the research, their evaluation of the research and continuing review materials, and recommendations.

9.7.4 Expedited Review

In conducting continuing review under expedited procedures, the designated reviewer receives all of the previously noted materials. The reviewer(s) complete the continuing review checklist to determine and document 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, except in limited circumstances described by expedited review categories (8) and (9) (see Expedited Review Categories in Section 9.2.1). It is also possible that research activities that previously qualified

for expedited review, have changed or will change, such that expedited IRB review would no longer be permitted for continuing review.

9.7.5 Possible IRB Actions after Continuing Review

As with Initial Review, at the time of Continuing Review, the Convened IRB or IRB Member(s) conducting expedited review may take any of the following actions (see Section 9.6 for a detailed description of these actions):

- Approval
- Approval with Conditions
- Deferred

The convened IRB may also vote to disapprove the study. If an IRB member conducting expedited review believes that the study should be disapproved, it will be referred to the convened board for review. If the IRB has significant concerns, the IRB may vote to suspend or terminate the research (See Section 10 for a detailed discussion of suspensions and terminations).

If a research study receives Approval with Conditions at the time of the Continuing Review, the IRB will specify whether any conditions need to be satisfied before an investigator can continue particular research activities related to those conditions or requirements that must be adhered to until the conditions of approval have been satisfied. For example, if at the time of continuing review, the IRB requires the investigator to change the research protocol to include a specific new procedure for screening prospective subjects, the IRB could approve the research with the following condition: research activities involving currently enrolled subjects may continue, but no new subjects may be enrolled until a designated IRB member reviews a revised protocol and verifies that the protocol includes the new screening procedure. Additionally, the IRB may specify a time period, such as 1, 2, or 3 months, for the condition/s to be satisfied as long as the activity with conditions is not begun/restarted until approval is granted.

9.7.6 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 re-approval does not occur within the time set by the IRB, all research activities must stop, including recruitment (media advertisements must be withdrawn), enrollment, consent, interventions, interactions, and data collection. **This will occur even if the investigator has provided the continuing information before the expiration date. Therefore, investigators must submit their continuing review materials enough in advance of expiration to allow sufficient time for IRB review before the expiration date.**

When the IRB approves research with conditions at the time of continuing review before the expiration date of the preceding IRB approval period, IRB approval does not lapse if the investigator needs additional time – beyond the date on which the preceding IRB approval would have expired – to satisfy some or all of the IRB’s conditions. However, the investigator

and the IRB should make every effort to resolve any conditions and finalize approval in as timely a manner as possible.

In the event that study approval does expire, the IRB electronic system sends a notification to the investigator noting the expiration of approval and instructions that all research activities must stop.

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 non-compliance 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. The IRB must report to FDA/OHRP any instance of serious or continuing non-compliance with FDA regulations or IRB requirements or determinations.

9.7.6.1 Management of Enrolled Subjects During Lapse

While enrollment of new subjects cannot occur after the expiration of IRB approval, the IRB recognizes that temporarily continuing participation of already enrolled subjects may be necessary or appropriate, for example, when the research interventions hold out the prospect of direct benefit to the subjects, or when withholding those interventions or safety monitoring procedures, would place subjects at increased risk. In these instances, the investigator must, at the earliest opportunity, contact the IRB office and submit a request to continue those research activities that are in the best interests of subjects. Such a request should specifically list the research activities that should continue, provide justification, and indicate whether the request applies to all or only certain subjects. The IRB Chair or designee will review the request and provide a determination regarding what activities, if any, may continue during the lapse. Such a determination may include a time limit or other conditions or restrictions. If the IRB decides that already enrolled subjects should continue to receive the interventions that were being administered to subjects under the research project, data collection (especially safety information) should also continue for such subjects.

When there is insufficient time to obtain an IRB determination (e.g., the study regimen includes daily administration of an investigational agent), the investigator may make an initial determination, in consultation with the subjects' treating physician, if appropriate. In such cases, the investigator must, as soon as possible, contact the IRB office and submit a request for confirmation that the IRB agrees with the determination. The IRB Chair or designee will review the request and provide a determination. In the event that the IRB does not agree with the investigator's determination, or only agrees in part (e.g., agrees that some but not all of the activities are in the best interests of subjects), the IRB will notify the investigator who must then comply with the IRB's requirements or request a re-review of the determination by providing additional justification or information that the IRB may not have considered.

9.8 Modification of an Approved Protocol

Investigators may wish to modify or amend their approved applications. **Investigators must seek IRB approval before making any changes, no matter how minor, in approved research** - even though the changes are planned for the period for which IRB approval has already been given - unless the change is necessary to eliminate an apparent immediate hazard 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 will typically require a new study application rather than allow such changes to be made through a modification to the existing research plan.

This requirement applies to all research approved by the Allina Health IRB, including any aspects of exempt research subject to limited IRB review, and research for which continuing review is not required.

9.8.1 Procedures

Investigators proposing to modify a study must submit a Modification Request Form and all supporting documents identified in the form via The IRB electronic system for review. 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.

IRB Office staff will review the submission and make an initial determination whether the proposed changes may be approved through an expedited review process (i.e., changes to expedited research that do not alter the eligibility of the research for expedited review or minor changes to convened board studies), or whether the modification warrants convened board review. The IRB reviewer(s) using the expedited procedure has the ultimate responsibility to determine that the proposed changes may be approved through the expedited review procedure and, if not, must refer the research study for convened board review.

9.8.2 Convened Board Review of Modifications

When a proposed change in a convened board research study is not minor, then 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 research subjects. In such a case, the IRB must be promptly informed of the change following its implementation and should review the change to determine that it is consistent with ensuring the subjects' continued welfare.

All IRB members scheduled to attend the meeting are provided access to and review all documents provided by the investigator. The Primary Reviewer completes a worksheet to facilitate the review process and discussion at the meeting.

At the meeting, the Primary Reviewer presents an overview of the proposed modifications and assists the IRB Chair in leading 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 participants' welfare or willingness to continue to take part in the research and if so, whether to provide that information to future, current, or past participants.

9.8.3 Expedited Review of Modifications

An IRB may use expedited review procedures to review changes to expedited research that do not impact the study's eligibility for expedited review and minor changes to studies normally subject to convened IRB review. An expedited review may be carried out by the IRB Chair and/or experienced designee(s) among the IRB members.

Expedited reviewer(s) complete a reviewer checklist to determine whether the modifications meet the criteria allowing review using the expedited procedure, and if so, whether the research with the proposed modifications continues to meet the regulatory criteria for approval. The reviewer(s) will also evaluate whether the modification alters any previous determinations (e.g., a Subpart determination), or necessitates any additional determinations (e.g., for vulnerable populations).

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

9.8.4 Possible IRB Actions after Modification Review

As with Initial Review, at the time of Continuing Review, the Convened IRB or IRB Member(s) conducting expedited review may take any of the following actions (see Section 9.6 for a detailed description of these actions):

- Approval
- Approval with Conditions
- Deferral

Additionally, the convened IRB may vote to disapprove the proposed changes. If an IRB member conducting expedited review believes that the proposed modifications should be disapproved, they will refer the proposed modification to the convened board for review. If the proposed changes raise significant concerns on the part of the IRB, the IRB may vote to suspend or terminate the research (See Section 10 for a detailed discussion of suspensions and terminations).

9.8.5 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 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. In order to be approved under expedited review, the research must be eligible for expedited review or, for convened board research, the proposed exception must not increase risk or decrease benefit, negatively alter or change the risk/benefit analysis, negatively affect the participant's rights, safety, welfare, or negatively affect the integrity of the resultant data.

Procedures for exceptions must be submitted using the "Protocol Deviation/Exception Report Form". The investigator must submit this form along with any revised documentation to be presented to the subject(s) and documentation of sponsor approval, if applicable.

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

9.9 Closure of Research Studies

The completion or early termination of the 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 Allina Health and any sites for which the Allina IRB is 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 coordinating center is still receiving, studying, using, or analyzing identifiable private information from other sites (even if local interventions, interactions, observations, and data gathering are complete).

Investigators may submit study closures to the IRB on a Study Closure Report.

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 identifiable 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 IRB will review study closure reports, typically by expedited review, and either approve the closure of the study or request additional information or confirmation of facts from the investigator.

9.10 Reporting IRB Actions

All IRB actions are communicated to the investigator, and/or designated contact person for the research study, via the publication of a letter in The IRB electronic system within ten (10) working days, whenever possible, of the review. When applicable, a stamped copy of the approved consent form, parental permission form, and/or assent form will also be published. For approval with conditions or deferral, the notification will include a listing of the conditions or requirements that must be satisfied or responded to. For a disapproval, termination or suspension, the notification will include the basis for the action and will offer the investigator an opportunity to respond in person or in writing.

The IRB reports its findings and actions to the organization in the form of its minutes, which are distributed by IRB staff to the IO.

9.11 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 within 60 days (or less if the IRB determines that the information must be submitted earlier to ensure protection of the research subjects) 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. At its discretion, the IRB may grant an extension beyond 60 days if the investigator contacts the IRB Office prior to the deadline and presents sufficient cause for delay.

9.12 Appeal of IRB Decisions

When the IRB suspends, terminates, or disapproves research, the IRB letter communicating the decision will include the basis for the action and will offer the investigator the opportunity to respond in person or in writing. 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 supportive materials via The IRB electronic system. The investigator may be invited to attend the IRB meeting to discuss the request and provide information, but will be asked to leave prior to the IRB's final deliberations and vote.

9.13

10 Study Suspension, Termination and Investigator Hold

10.1 Suspension/Termination

IRB approval may be suspended or terminated if research is not being conducted in accordance with IRB or regulatory requirements or has been associated with unexpected problems or serious harm to subjects. (See Section 15 for a discussion of unanticipated problems and Section 16 for a discussion of non-compliance.)

The IO has the authority to suspend, in part or in full, or terminate institutional approval for research. Such actions will be promptly reported to the IRB so that the IRB can review the circumstances and take any necessary actions relevant to IRB review and oversight.

Suspension of IRB approval is a directive of the convened IRB or IRB Chair to temporarily stop some or all previously approved research activities. The IRB Chair may temporarily suspend IRB approval, in part or in full, when the available information suggests that actions must be taken to protect human subjects or the integrity of the research, prior to the next convened meeting of the IRB. Temporary suspensions by the Chair will be reported to the convened IRB at the next scheduled meeting at which time the convened IRB will determine if the suspension should continue, be lifted, or be modified. Suspended research studies remain open and require continuing review. Investigators must continue to provide reports to both the IRB and sponsors 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).

When approval of some or all research activities is suspended by the IRB, the IRB will consider whether subjects should be notified and any actions necessary to ensure that the rights, safety, and welfare of subjects are appropriately protected.

The IRB shall notify the investigator in writing of suspensions and shall include a statement of the reasons for the IRB's action and any requirements or conditions associated with the suspension (e.g., notification of subjects). The investigator shall be provided with an opportunity to respond in person or in writing.

Suspensions of IRB approval must be reported promptly to the IO, sponsors including federal department or agency heads, and federal oversight agencies as applicable. See Section 20 for a detailed discussion of reporting procedures.

Termination of IRB approval is a directive of the convened IRB to permanently stop all activities in a previously approved research study. Terminated research studies are closed and no longer require continuing review. Terminations of IRB approval of research studies must be made by the convened IRB.

When study approval is terminated by the IRB, in addition to stopping all research activities, the IRB will consider notification of subjects and any actions necessary to ensure that the rights, safety, and welfare of subjects are appropriately protected.

The IRB shall notify the investigator in writing of a study termination and shall include a statement of the reasons for the IRB's actions and any requirements associated with the

termination (e.g., notification of subjects). The investigator shall be provided with an opportunity to respond in person or in writing.

Terminations of IRB approval must be reported promptly to the IO, sponsors including federal department or agency heads, and federal oversight agencies according to applicable federal and organizational requirements. See Section 20 for a detailed discussion of reporting procedures.

10.2 Investigator Hold

An investigator may request an investigator hold when the investigator wishes to temporarily or permanently stop some or all approved research activities. Such a hold is initiated by an investigator, but must be immediately reported to the IRB so that the IRB can consider whether any additional actions are necessary to protect subjects. Investigator holds are not equivalent to IRB suspensions or terminations.

10.2.1 Procedures

1. Investigators must submit a memo and any supporting materials via The IRB electronic system to inform the IRB of the hold. The memo and materials should include:
 - a. A statement that the investigator is voluntarily placing a study on hold
 - b. The reason(s) for the hold
 - c. A description of the research activities that will be stopped
 - d. Proposed actions to be taken to protect current participants
 - e. Any actions that will be taken prior to IRB approval of proposed changes in order to eliminate apparent immediate risk of harm
2. Upon receipt, IRB staff notify the Chair and places the research on the next available agenda for review.
3. The IRB Chair or designee, in consultation with the investigator, determines whether any additional procedures need to be followed to protect the rights and welfare of current participants as described in Section 10.3.
4. The IRB Chair or designee, in consultation with the investigator, determines whether and how currently enrolled participants will be notified of the hold.
5. Prior to lifting the hold, the investigator must seek approval from the IRB so that the IRB may consider whether subjects are appropriately protected and the research remains approvable.

10.3 Protection of Currently Enrolled Participants

Before a study hold, termination, or suspension is put into effect, the IRB Chair or convened IRB considers whether any additional procedures need to be followed to protect the rights and welfare of current participants. Such procedures might include:

- Transferring participants to another investigator/site
- Making arrangements for clinical care outside the research
- Allowing continuation of some research activities
- Allowing continuation of some research activities under the supervision of an independent monitor
- Requiring or permitting follow-up of participants for safety reasons
- Requiring adverse events or outcomes to be reported to the IRB and the sponsor
- Notification of current participants
- Notification of former participants

11 Documentation and Records

Allina Health 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, and other authorized parties at reasonable times and in a reasonable manner.

11.1 IRB Records

IRB records include, but are not limited to:

1. Written operating procedures
2. IRB membership rosters
3. IRB member files including documentation of appointments, experience, education/training and expertise
4. IRB correspondence including reports to regulatory agencies
5. IRB Protocol Files
6. Documentation of exemptions including exemptions related to emergency uses
7. Convened IRB meeting minutes
8. Documentation of review by another institution's IRB, when appropriate
9. Documentation of IRB reliance and cooperative review agreements
10. Federal Wide Assurances
11. Federal IRB Registrations
12. Documentation of complaints and any related findings and/or resolution

11.2 IRB Protocol Files

The IRB maintains a separate file for each protocol (including expanded access), HUD, emergency use, or report it receives for review in the IRB electronic system under a unique identification number assigned by the system. Protocol files include, but are not limited to:

1. The initial application and all associated documents and materials.
2. Modification requests and all associated documents and materials.
3. Continuing review/progress reports and all associated documents and materials.
4. Closure reports and all associated documents and materials.
5. Reports submitted after study or HUD approval including reports of significant new findings, data and safety monitoring reports, protocol violation reports, complaints, non-compliance, 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, as applicable.
7. DHHS-approved sample consent form document and grant application/protocol, as applicable.
8. IRB reviewer forms and checklists.
9. Documentation of scientific or scholarly review (if available).
10. Documentation of type of IRB review. For exempt determinations and expedited review, this will include the category under which the review is allowed.
11. 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, and research involving children. For research reviewed by the convened board, these findings and determinations are recorded in the minutes.
12. For expedited review, documentation of the risk determination and the rationale for conducting continuing review of research that otherwise would not require continuing review. For research reviewed by the convened board these determinations are recorded in the minutes.
 - a. The rationale for a determination that research appearing on the expedited review list published in the Federal Register is more than minimal risk
13. Documentation of all IRB review actions.
14. Notification of expiration of IRB approval to the investigator.
15. Notification of suspension or termination of research.
16. Letters to investigators informing them of IRB review outcomes.
17. IRB correspondence to and from investigators related to the protocol.
18. All other IRB correspondence related to the research.
19. For studies evaluating the safety or effectiveness of medical devices, documentation of device determinations (exempt, non-significant risk, significant risk).
20. Reports of unanticipated problems involving risk to subjects or others.
21. Any statements of significant new findings provided to subjects

11.3 The IRB Minutes

Draft minutes of IRB meeting proceedings are written and available for review by the next regularly scheduled IRB meeting. Once reviewed and accepted by the members, a copy is sent to the IO. Changes may not be made to finalized minutes without re-review by the IRB to verify accuracy.

Minutes of IRB meetings must contain sufficient detail to show:

1. Attendance

- a. Names of members or alternates present
- b. Names of members or alternate members who are participating through videoconference or teleconference and documentation that those attending remotely received all pertinent material prior to the meeting and were able to actively and equally participate in all discussions
- c. Names of alternates attending in lieu of specified (named) absent members. (Alternates may substitute for specific absent members or categories of members only as designated on the official IRB membership roster)
- d. Names of any consultants present
- e. Names of any investigators present
- f. Names of any guests present

Note: The minutes will indicate, by name, those members who enter or leave the meeting. The vote on each action will reflect the numbers of members present for the vote on that item.

7. The presence of a quorum throughout the meeting, including the presence of one member whose primary concern is in a non-scientific area.
8. Business Items discussed and any education provided.
9. Actions taken, including separate deliberations, actions, and votes for each submission undergoing review by the convened IRB.
10. Vote counts on these actions (Total Number Voting; Number voting for; Number voting against; Number abstaining; Number of those recused). When a member is recused due to conflict of interest, the name of the member and reason for the recusal will be noted.
11. Basis or justification for actions disapproving or requiring changes in research
12. Summary of controverted issues and their resolution
13. Approval period for initial and continuing reviews, including identification of research that warrants review more often than annually and the basis for that determination
14. Risk determination for initial and continuing reviews, and modifications when the modification alters the prior risk determination
15. Justification for deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document.
16. Study-specific findings supporting that the research meets each of the required criteria 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

17. Study-specific findings supporting that the research meets each of the required criteria when the requirements for documentation of consent are waived
18. Study-specific findings supporting that the research meets each of the criteria for approval for vulnerable populations under any applicable Subparts.
19. Exempt/significant risk/non-significant risk device determinations and the basis for those determinations.
20. Determinations related to conflicts of interest and acceptance or modification of conflict management plans
21. 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.
22. Review and determinations related to interim reports, e.g., unanticipated problems or safety reports, serious or continuing non-compliance, suspensions or terminations, etc.
23. A list of research approved under expedited review procedures since the time of the last such report.
24. An indication that, when an IRB member or alternate has a conflicting interest (see Section 23.2) with the research under review, the IRB member or alternate was not present during the final deliberations or voting.
25. Key information provided by consultants will be documented in the minutes or in a report provided by the consultant.

11.4 IRB Membership Roster

A membership list of IRB members will be maintained; it will identify members sufficiently to describe each member's chief anticipated contributions to IRB deliberations. The list will contain the following information about members:

1. Name.
2. Earned degrees.
3. Employment or other relationship between each member and the organization (i.e., affiliated or non-affiliated). To be categorized as non-affiliated, neither the member nor an immediate family member of the member may be affiliated with Allina Health.
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, while 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, such as board certifications, licenses, and areas of practice sufficient to describe each member's chief anticipated contributions to IRB deliberations.
6. Representative capacities of each IRB member; including which IRB members are knowledgeable about and/or experienced in working with children, pregnant women, cognitively impaired individuals, and other vulnerable populations commonly involved in Allina Health research.
7. Role on the IRB (Chair, Vice-Chair, etc.)
8. Voting status
9. For alternate members, the primary member or class of members for whom the member could substitute

The IRB office must keep the IRB membership list current. Changes in IRB membership are reported to OHRP and FDA on the federal IRB registration within 90 days of the change.

11.5 Documentation of Exemptions

Documentation of verified exemptions consists of the reviewer's citation of a specific exemption category and written concurrence that the activity described in the investigator's request for satisfies the conditions of the cited exemption category as detailed in Section 7.

11.6 Documentation of Expedited Reviews

IRB records for initial and continuing review by the expedited procedure must include: the reviewer's verification that the study qualifies for expedited review including the specific permissible category, documentation that the activity satisfies the criteria for approval, the period of approval, and any determinations required by the regulations including study-specific findings justifying the following determinations:

1. Approving a procedure which waives or alters the informed consent process;
2. Approving a procedure which waives the requirement for documentation of consent;
3. Approving research involving pregnant women, human fetuses, or neonates;
4. Approving research involving children.

11.7 Access to IRB Records

IRB protocol files are secured in the IRB electronic system 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 Allina Health's servers, locked filing cabinets or locked storage rooms.

Ordinarily, access to IRB records is limited to the IO, HRPP Director, HRPP Medical Director, HRPP and IRB staff, IRB members, authorized organizational officials, and officials of federal and

state regulatory agencies (e.g., OHRP and FDA). Research investigators are provided reasonable access to files related to their research. Appropriate accreditation bodies are provided access.

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

IRB member rosters are only provided to regulatory agencies, accreditation bodies, and persons or offices within Allina Health with a legitimate need (e.g., Compliance, Legal, Internal Audit). A memorandum documenting compliance with pertinent federal rules and regulations, IRB membership requirements, and with Allina Health's Federalwide Assurance is available and will be provided to sponsors and others upon request.

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

11.8 Record Retention

IRB records are retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research.

IRB records for research cancelled without participant enrollment will be retained for at least 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 3 years.

12 Obtaining Informed Consent from Research Subjects

No investigator conducting research under the auspices of Allina Health 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 12.10, 12.11, and 12.12 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 participants.

The following procedures describe the requirements for obtaining consent from participants in research conducted under the auspices of Allina Health.

In addition to the requirements for obtaining informed consent and the consent process described in the Allina Health HRPP/IRB SOP Manual, the following specific requirements for consent, whether written or oral, apply to research subject to the revised Common Rule:

1. 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 (*new requirement*)
2. Except for broad consent (See Section 8.3):
 - a. 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 (*new requirement*)
 - b. 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 (*new requirement*)

12.1 Basic 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 Allina Health HRPP. Investigators are required to obtain legally effective informed consent from a subject or the subject's LAR unless the requirement has been waived by the IRB. When informed consent is required, it must be sought prospectively, and properly documented.

[Minnesota Statute 144.651](#), known as the Health Care Bill of Rights, provides patients and residents of health care facilities with certain rights that a health care facility cannot require to be waived as a condition of admission. “Patients” and “residents” are statutorily defined terms. Among those rights is the right to refuse experimental research: *“Written, informed consent must be obtained prior to a patient’s or resident’s participation in experimental research. Patients and residents have the right to refuse participation. Both consent and refusal shall be documented in the individual care record.”* “Experimental research” is not defined. As noted in the statute, there are certain, limited federal exceptions that allow for emergency research to be performed without informed consent. See Section 12.12 for further discussion of planned emergency research.

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 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 of 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.

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 to be able to answer questions about the study including those regarding risks, procedures, and alternatives. The Allina IRB application solicits information regarding who will obtain consent; proposed changes to the personnel authorized to obtain consent must be submitted to the Allina IRB for approval.

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

These informed consent requirements are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed for informed consent to be legally effective.

12.2 Informed Consent Process

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 process provides the prospective subject (or LAR/guardian) with sufficient opportunity to read the consent document, when applicable.
3. The informed consent process provides the prospective subject (or LAR/guardian) with the opportunity to ask questions and have them answered.
4. The informed consent process shall be sought under circumstances that provide the subject (or LAR/guardian) with sufficient opportunity to consider whether to participate.
5. The informed consent process shall be sought under circumstances that minimize the possibility of coercion or undue influence.
6. 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.
7. For subjects who are not fluent in English, informed consent must be obtained in a language that is understandable to the subject (or LAR/guardian). In accordance with this policy, the 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.
8. The informed consent process may not include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights or through which any entity (including the investigator, the sponsor, Allina Health or its employees or agents) is released from liability for negligence or appears to be so released.
9. The investigator is responsible for ensuring that each prospective subject is adequately informed about all aspects of the research and understands the information provided.

12.3 Legally Authorized Representatives (LAR)

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."*

Who may serve as LAR is determined by state law. Minnesota law does not specifically address informed consent by LARs of incapacitated persons for participation in clinical research. Thus,

the applicable guidelines for determining the most appropriate LAR for research are based upon the guidelines that apply in the clinical setting.

For legally incompetent adults who are unable to make medical decisions, a legal representative (court appointed guardian) or durable power of attorney for health care must provide informed consent for non-emergent medical treatment. The legal guardian must be authorized by the court to make decisions regarding the types of activities, procedures, or treatments called for in the research to serve as LAR. If the patient does not have a guardian or durable power of attorney, consent should be obtained from one of the following, in order of priority: spouse, parents, adult children, or adult siblings.

Substitute decision-makers, as defined in Allina Health's clinical informed consent policy (*SYS-PC-RMC-001*), may serve as LAR for research involving clinical procedures or treatments when a court appointed guardian or durable power of attorney for health care are not in place.

Minnesota has two specific limitations on the consent authority of legally authorized representatives. First, under Minn. Stat. § 524.5-313(c)(4)(i), guardians appointed by the court have the power to give consent for necessary medical treatment, "except that no guardian may give consent for psychosurgery, electroshock, sterilization, or **experimental treatment of any kind**" (emphasis added) without first obtaining a court order. Second, under Minn. Stat. 253B.095, persons under a civil commitment order may not give consent to participate in a psychiatric clinical drug trial unless the court approves the specific drug trial. "Experimental treatment" is not defined.

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 13.8.

12.4 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. For **FDA-regulated studies**, a statement that notes the possibility that the Food and Drug Administration may inspect the records;
10. For ["applicable" FDA-regulated clinical trials](#), the following statement must be included verbatim:
 - a. "A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."
11. 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.

12.5 Additional elements of informed consent to be applied, as applicable:

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.
7. Additional Elements (must be included when appropriate) [§__.116(c)]
 - a. 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;
 - b. A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions;
 - c. 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).

12.6 Allina Health Requirements

In addition to the federal elements of consent described above, Allina Health has defined specific additional information that must be included in consent documents when applicable to the research (e.g., a billing error statement). A list of these requirements is maintained in the IRB electronic system for investigator and IRB reviewer reference.

12.7 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 plans and consent documents.

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

- 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.
- 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 subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

12.8 Documentation of Informed Consent

Except as provided in Section 12.10, 12.11, and 12.12 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 and dated by the subject or the subject's legally authorized representative at the time of consent.
2. For research conducted in accordance with ICH-GCP E6 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 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.
4. The consent form may be either of the following:

- a. A written consent document that embodies the basic and required additional elements of informed consent. The consent form may be read to the subject or the subject's legally authorized representative, but the subject or representative must be given adequate opportunity to read it before it is signed; or
- b. A short form written consent document stating that the elements of informed consent have been presented orally to the subject or the subject's legally authorized representative.

When this method is used:

- i. The oral presentation and the short form written document should be in a language understandable to the subject; and
- ii. There must be a witness to the oral presentation; and
- iii. 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
- iv. The short form document is signed by the subject;
- v. The witness must sign both the short form and a copy of the summary; and
- vi. The person actually obtaining consent must sign a copy of the summary; and
- vii. 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, or read, English, or have limited proficiency in oral or written English, (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; and (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, the full English language informed consent document, and the English version of the short form document have already been approved by the convened IRB.

12.9 Special Consent Circumstances

12.9.1 Enrollment of persons with limited English-language proficiency

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 and/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. To ensure that translated documents are accurate, the IRB may choose to require a certified translation, to have an independent back-translation or to have a review of the translated documents by an IRB member or other person who is fluent in that language. When non-English speaking subjects enroll, they and a witness sign the translated consent document. The subjects are given a copy of the signed translated consent document.

- 2. Unexpected enrollment:** If a person who does not speak or read, or has limited proficiency in, English 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, and therefore, not effective.

If an investigator decides to enroll a subject into a study for which there is not an extant 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 in as described in Section 12.8.

- 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 script, 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.

12.9.2 Braille consent

For blind subjects who read Braille, the IRB may approve a consent document prepared in Braille. In order to assure itself 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 oral consent will be obtained, witnessed and documented as described under "Oral Consent" (see Section 12.9.4).

12.9.3 Consenting in American Sign Language (ASL)

For deaf subjects who are fluent in 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 a certified 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 12.8.

12.9.4 Oral Consent

When subjects are unable to read a written consent form (such as blind or illiterate subjects), the IRB may approve an oral 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 orally and (2) is able to indicate approval or disapproval to study entry.

For minimal risk research, documentation of consent may be waived according to the criteria in Section 12.11.

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 oral consent. The person obtaining consent and a witness will sign the written study consent form with a statement that documents that an oral process was used and, if necessary, that the subject gave oral consent. 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.

12.10 Waiver or Alteration of Informed Consent

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

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

In addition, an IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent; or waive the requirements to obtain informed consent, provided the IRB finds and documents that:

1. The research or demonstration project is to be conducted by or is 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.

FDA regulations do not provide for waivers of informed consent except in certain emergency situations..

When reviewing research subject to the revised Common Rule, the Allina Health IRB will evaluate requests for waivers or alterations of informed consent in accordance with the requirements and criteria specified in the revised rule and summarized below. The IRB's determination will be documented in the IRB record and communicated to the investigator.

In order to approve a request from an investigator to waive the requirement for informed consent, or to omit or alter one or more basic or additional element of consent (an "Alteration"), under this provision the Allina Health IRB must determine and document that the below criteria are satisfied.

1. The research involves no more than minimal risk to the subjects;
2. The research could not practicably be carried out without the 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 or LARs will be provided with additional pertinent information after participation.

Investigators may be asked to provide justification, or additional information or documentation, to support that the above criteria are satisfied.

Restrictions:

1. Alterations –
 - a. An IRB may not approve a request to alter or omit any of the general requirements for informed consent described in Section 8.1

12.11 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 either that the:

1. Only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality;

Note 1: Subjects must be asked whether they want documentation linking them with the research, and their wishes must govern. (Example: domestic violence research where the primary risk is discovery by the abuser that the subject is talking to investigators.)

Note 2: In order to waive written documentation of consent where the only record linking the participant and the research would be the consent document, the IRB has to determine that the research was not FDA-regulated.

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 when conducted by non-investigators (e.g., marketing surveys, telemarketing).

Note: The FDA does permit a waiver of documentation of consent if this condition is satisfied. This is most commonly applied in the context of minimal risk screening activities that are necessary to determine eligibility for enrollment in the full trial.

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.

12.12 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 non-FDA-regulated research.

The FDA exception from informed consent requirements for emergency research under FDA regulations, 21 CFR 50.24, 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 11.12.2.1 and 11.12.2.2. The DHHS waiver is not applicable to research involving prisoners, pregnant women, fetuses, or in vitro fertilization.

12.12.1 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.

12.12.2 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 paragraph (7)(v) 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.

12.12.2.1 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 12.12.2 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 investigations under this section 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 12.12.2 and in 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\(b\)](#).

12.12.2.2 Planned Emergency Research Not Subject to FDA Regulations

The IRB responsible for the review, approval, and continuing review of the research has approved both the research and a waiver of informed consent and has (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 Section 12.12.2 have been met relative to the research.

12.13 10. Posting of Clinical Trial Consent Forms [§__.116(h)]

The revised Common Rule includes a requirement for the posting of one IRB-approved consent form to a publicly available Federal website for each clinical trial conducted or supported by a Common Rule department or agency after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject. This requirement may be satisfied by either the awardee or the Federal department or agency. 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 website (e.g., confidential commercial information), the department or agency may permit or require redactions to the information posted.

Federal guidance or instructions regarding the implementation of this requirement was not available at the time this SOP went into effect. Until federal guidance or instructions are available, when Allina Health is the prime awardee, investigators should consult with the grant officer regarding how to satisfy this requirement.

13 Vulnerable Subjects in Research

When participants in research conducted under the auspices of Allina Health 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 vulnerable subjects are met and that appropriate additional protections for vulnerable subjects are in place.

13.1 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.

According to Minnesota law, minors are persons under the age of eighteen. However, under Minnesota law, minors may provide consent for their own medical treatment for “Confidential Minor Services”. While no formal system exists in Minnesota for a judge to legally emancipate a minor, a minor living separately from parents or guardians, and managing his/her own financial affairs, may seek any medical treatment without the consent of a parent or guardian. This exception applies to a minor regardless of whether the minor’s parents have consented to the minor living apart, or regardless of the extent or source of the minor’s income. Minnesota law also allows minors who have been married or have given birth to seek treatment without the consent of parent or guardian for their own medical, mental, dental, or other health services or for services for the minor’s child.

[Minnesota statute 144.343](#) addresses requirements for parental notification before a minor may undergo an abortion.

Because Minnesota law does not specifically address when minors may provide consent for research, the Allina Health IRB applies the above standards to research involving medical care of treatment. When research does not involve medical care or treatment, the Allina Health IRB defines children as persons who are under the age of eighteen and, unless specified otherwise, allows “emancipated” minors and minors who have been married or given birth to provide consent for their own participation, or their child’s participation, in research not involving medical treatment. **NOTE:** For research conducted in jurisdictions other than Minnesota, the research must comply with the laws regarding the legal age of consent in the relevant jurisdictions. Legal will be consulted as needed with regard to the laws in other jurisdictions.

Confidential Medical Services. Confidential Medical Services are those services for which a minor can give consent and the consent of a parent or other person is not required, including care related to pregnancy (including birth control), STDs, drug or alcohol dependency, hepatitis B vaccination, and admission of a 16 or 17-year-old for treatment of a mental illness.

Guardian. A guardianship is a legal relationship created when a person is assigned by the court to take care or make decisions for an individual of any age. In many cases, a legal guardian has the authority to make health care decisions for the protected person (ward).

Minnesota Law provides that a court appointed guardian for an incapacitated person cannot give the necessary consent to enable the ward to partake in experimental treatment of any kind unless the procedure is first approved by order of the court Minnesota Statute 524.5-313 and 524.5-207. Minnesota Statute 524.5-313 also provides that a court appointed guardian for an incapacitated person cannot consent to any medical care which violates “known, conscientious, religious, or moral belief of the ward.”

Fetus. A fetus means the product of conception from implantation until delivery.

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

Delivery. A delivery is a complete separation of the fetus from the woman by expulsion or extraction or any other means.

Neonate. A neonate is a newborn.

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.

Nonviable neonate. A nonviable neonate means a neonate after delivery that, although living, is not viable.

Pregnancy. A 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.

Prisoner. A prisoner is 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.

13.2 Involvement of Vulnerable Populations

If 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. The IRB may include one or more individuals who are knowledgeable about and/or experienced in working with individuals from these populations or it may seek such expertise through the use of consultants.

45 CFR 46 has additional subparts designed to provide extra protections for 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

DHHS-conducted or supported research that involves any of these populations must comply with the requirements of the relevant subparts. Research funded by other federal agencies may or may not be covered by the subparts.

In its FWA, Allina Health limits its commitment to apply Subparts B, C, and D to non-exempt human subjects research conducted or supported by DHHS or any other federal agency that requires compliance with the Subpart(s) (B, C, or D) applicable to the research.

The following policies and procedures apply to all research regardless of funding. The individual sections describe how the subparts apply specifically to DHHS-supported research.

13.3 Responsibilities

1. The investigator is responsible for identifying the potential for enrolling vulnerable subjects in the research proposal, including the possible inclusion of subjects who are at risk for impaired decisional capacity, and who are being asked to participate in a research study with greater than minimal risk.
2. The IRB shall include representation, either as members or through the use of consultants, of individual(s) who are knowledgeable about and/or experienced working with the vulnerable populations involved in the research proposal under review.
3. The IRB reviews the investigator's justifications for including vulnerable populations in the research to assess appropriateness for inclusion in the research proposal.
4. The IRB must ensure that appropriate additional safeguards have been included in each study to protect the rights and welfare of vulnerable subjects at the time of initial review of the research proposal.
5. Information reviewed as part of the continuing review process should include the number of participants considered to be members of specific vulnerable populations.

13.4 Procedures

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. The IRB evaluates the proposed safeguards, including, if applicable, the proposed plan for obtaining consent from legally authorized representatives and the plans for assent of children and adults unable to provide consent.
4. The IRB evaluates the research to determine the need for additional protections and considers, if appropriate, the use of a data and safety monitoring board, consent monitor, or research subject advocate.

Continuing Review and Monitoring. At Continuing Review the investigator should identify the number and categories of vulnerable subjects enrolled and any problems that arose relevant to their rights and welfare.

13.5 Research Involving Pregnant Women, Human Fetuses and Neonates

The following applies to all research involving pregnant women, human fetuses, and neonates reviewed by the Allina Health 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.

13.5.1 Research Involving Pregnant Women or Fetuses

13.5.1.1 Research Not Conducted or Supported by DHHS

For research not supported by DHHS where the risk to the pregnant women and fetus is no more than minimal, no additional safeguards are required and there are no restrictions on the involvement of pregnant women in research.

Pregnant women or fetuses may be involved in research not supported 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 13.1) who are pregnant, assent and permission are obtained in accord with the requirements of state law and the IRB;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. 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 initiating research activities. 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.

13.5.1.2 Research Conducted or Supported by DHHS

For research conducted or supported by DHHS, 45 CFR 46 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 13.1) who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in Section 13.7.2;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

13.5.2 Research involving Neonates of Uncertain Viability or Nonviable Neonates

13.5.2.1 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 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. 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 beginning 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 in this section) 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 legally authorized representative is obtained in accord with the provisions of permission and assent, except that the consent of the father or his legally authorized representative 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 legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph.

13.5.2.2 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 in this section) 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 biomedical 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 legally authorized representative is obtained in accord with the provisions of permission and assent, except that the consent of the father or his legally authorized representative 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 legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph.

13.5.3 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 regulations and Allina Health research policies).

13.5.4 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.

13.5.5 Research Not Otherwise Approvable

13.5.5.1 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 above provisions, then 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 provisions for informed consent and other applicable sections of this manual.

13.5.5.2 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.

13.6 Research Involving Prisoners

The Allina Health IRB does not currently review research involving prisoners. If this were to change, procedures consistent with the requirements of [Subpart C](#) of 45 CFR 46 will be developed.

If a subject were to become incarcerated while participating in a study that has not been approved for inclusion of prisoners, 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.

Research involving prisoners that is under the oversight of an external IRB must comply with the requirements of that IRB and applicable policies and law.

13.7 Research Involving Children

The following applies to all 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.

13.7.1 Allowable Categories

In addition to the IRB's normal duties, 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 13.7.2.
- 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 13.7.2.
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 13.7.2.
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 in this category that is not DHHS conducted or supported and is 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 13.7.2.

13.7.2 Parental Permission and Assent

13.7.2.1 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 Sections 12.4, 12.5, 12.6, and 12.7.

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 in the reviewer's notes 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.

Permission from both parents is also required for research involving care or treatment to a child in connection with an abortion.

For research not covered by the FDA regulation, 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 12.10; or
2. 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.

Parental permission may not be waived for research covered by the FDA regulations.

Permission from parents or legal guardians must be documented in accordance with and to the extent required by Section 12.8.

13.7.2.2 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 when 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.

13.7.2.3 Documentation of Assent

When the IRB determines that assent is required, it also 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.

13.7.2.4 Children Who are Wards

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 13.7.1), **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.

No consent may be given for experimental treatment of such a child or children unless it is first approved by an order of the court as set forth in Minnesota Statute 524.5-207.

13.8 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 with impaired, fluctuating, or diminishing decision-making capacity are particularly vulnerable. Researchers 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 guidelines in this section were developed to assist Allina Health researchers and the IRB with the development and review of research proposals.

13.8.1 What is 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 or not to participate (or continue participating) in a study.

13.8.2 What is “Decision-Making Capacity”?

“Decision-making capacity” refers to a potential subject’s ability to make a rationale and meaningful decision about whether or not to participate in a research study. This ability is generally thought to include at least the following four elements:

1. Understanding, i.e., the ability to comprehend the disclosed information about the nature and purpose of the study, the procedures involved, the risks and benefits of participating versus not participating, and the voluntary nature of participating;
2. Appreciation, i.e., the ability to appreciate the significance of the disclosed information and the potential risks and benefits for one’s own situation and condition;
3. Reasoning, i.e., the ability to engage in a reasoning process about the risks and benefits of participating versus alternatives, and;
4. Choice, i.e., the ability to express a choice about whether or not to participate.

“Decision-making capacity” should not be confused with the legal concept of “competence.” While the court may consider information about a person’s decision-making capacity in making a competency determination, the terms are not synonymous. Incompetence is a legal determination made by a court of law. For example, someone who is judged legally incompetent to manage their financial affairs may retain sufficient decision-making capacity to make meaningful decisions about participating in a particular research protocol. As well, persons who have normal cognitive functioning and are considered legally competent may be put into circumstances where their decision-making capacity is temporarily impaired by a physical or mental condition or by alcohol or drugs.

Decision-making capacity is protocol-specific and situation-specific. Thus, a subject may have capacity to consent to a low-risk research protocol in usual circumstances, but not have the capacity to consent to a high-risk protocol or when he or she is confused or under duress.

13.8.3 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.

Investigators must disclose to the IRB both plans and justification for including individuals with impaired, fluctuating, or diminishing capacity in a given study. If persons with questionable, impaired, 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 may be required to request designation of a future LAR at the time of the initial consent process and written documentation of the subject’s wishes regarding the study. When the study includes subjects likely to regain capacity to consent, the investigator should include future provisions to inform them of their participation and seek consent for ongoing participation, if applicable. For research involving subjects who may have fluctuating or

declining decision-making capacity, the IRB may require periodic re-evaluation of capacity and/or periodic re-consent.

Plans for evaluation of capacity should be tailored to the subject population and the risks and nature of the research. In some instances, assessment by the investigator may be appropriate. However, an independent, qualified assessor other than the investigator should evaluate subjects' capacity when the risks of the research are more than a minor increase over minimal or the investigator is in a position of authority over a prospective subject. In all cases, the person(s) evaluating capacity must be qualified to do so and use appropriate, validated tools and methods (e.g., University of California, San Diego Brief Assessment of Capacity to Consent [UBACC], MacArthur Competence Assessment Tool for Clinical Research [MacCAT-CR]). Assessments of capacity should be documented in the research record, and when appropriate, in the medical record.

Under some circumstances, individuals with decisional impairment may be able to make voluntary and informed decisions to consent or refuse participation in research. In these cases, investigators use an array of methods to optimize the prospective subjects' ability to comprehend study procedures, risks, and benefits such as presenting the information multiple times or on multiple occasions and use of audiovisual presentations (e.g., audio or video recordings). In addition, investigators use a variety of methods to evaluate prospective subjects' comprehension before proceeding to obtain informed consent such as second opinions, use of independent consent observers, interpreter for hearing-impaired subjects, allowing a waiting period before enrollment, or involvement of a trusted family member or friend in the disclosure and decision making process. Audio or videotapes, computer video presentations, or written materials used to promote understanding must be provided to the IRB for review. Third party consent monitors may be used during the recruitment and consenting process, or waiting periods may be required to allow more time for the subject to consider the information that has been presented.

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 12.3). Under these circumstances, the prospective subject should still be informed about the trial in a manner compatible with the subjects' likely understanding and if possible, be asked to assent to participate. 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 persons 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, but a research subject becomes unable to provide consent or impaired in decision-making capacity after

enrollment, the investigator is responsible for notifying the IRB. The investigator 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.

13.8.4 IRB Review

The IRB review process will include at least one member, or a consultant, who is experienced with and/or otherwise knowledgeable about the population when the research involves greater than minimal risk and the proposed subject population includes adults who cannot provide consent, may have impaired capacity to provide consent, or whose capacity can be expected to fluctuate over time.

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 subjects unable to provide informed consent or with diminished capacity to do so, the IRB should consider whether any components of the research involve risks that are greater for participants with diminished capacity. For example, the population 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.

As appropriate to the research, the IRB will consider the following in evaluating research involving adults unable to consent or with impaired decision-making capacity:

1. Whether the aims of the research cannot reasonably be achieved without inclusion of the population
2. Whether the research is likely to improve the understanding of the condition, disease, or issue affecting the subject population
3. Whether any experimental procedure or interventions have undergone pre-clinical testing or human testing on other populations and whether the data from that testing supports its use in the proposed research
4. Whether the procedures or interventions that the subject will undergo in the research place them at increased risk and if appropriate mechanisms are in place to minimize risks, when possible
5. Whether the data and safety monitoring plan, including any stopping rules, is appropriate given the risks of the research and the vulnerability of the population
6. Whether the procedures for withdrawing individual subjects from the research are appropriate
7. Whether the recruitment procedures, consent process, and any plans for financial compensation support voluntariness and minimize the likelihood of undue influence or coercion

8. Whether the subjects will be exposed to financial or other risks that they might not consider acceptable if they had the capacity to provide consent, and whether appropriate mechanisms have been put into place to minimize these risks
9. Whether the procedures for determining capacity to provide consent, and for evaluating capacity on an ongoing basis, if applicable, are appropriate
10. Whether the procedures for informing subjects who regain capacity about their involvement in the research, and for obtaining consent for on-going participation, if applicable, are appropriate
11. Whether assent should be required when possible, and, if so, if the proposed procedures to obtain and document assent are appropriate
12. Whether a research subject advocate or consent monitor should be required, for some or all subjects

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.

In addition, the IRB applies the following risk/benefit guidelines:

1. Studies with minimal risk

- a. Research involving interventions or procedures that are considered **minimal risk** and present the **prospect of direct benefit** to the individual subject. The IRB may approve such studies if the risks are reasonable in relation to the prospective benefits.
- b. Research involving interventions or procedures that are considered **minimal risk** and have **no prospect of direct benefit** to the individual subject, but are **likely to yield generalizable knowledge** about the subject's disorder or condition. The IRB may approve such studies if important to advance the scientific knowledge of a condition that affects the research population, and if the risks are reasonable in relation to such importance. For research in this category, the disorder, condition or factor that prevents the individual from having capacity to consent must be an intrinsic characteristic of the research population such that the research could not otherwise be conducted on subjects who have capacity.

2. Studies with a minor increase over minimal risk

- a. Research involving interventions or procedures that are considered a **minor increase over minimal risk** but present **the prospect of direct benefit** to the individual subject. The IRB may approve such studies only if the risks are reasonable in relation to the prospective benefits, if the potential benefits are similar to those available in the standard clinical or treatment setting, and if the risk-benefit ratio is favorable to participants.

- b. Research involving interventions or procedures that are considered a **minor increase over minimal risk** and have **no prospect of direct benefit** to the individual subject, but are **likely to yield generalizable knowledge** about the subject's disorder or condition. The IRB may approve such studies if vitally important to advance to the scientific knowledge of a condition that affects the research population, and if the risks are reasonable in relation to such vital importance. For research in this category, the disorder, condition or factor that prevents the individual from having capacity to consent must be an intrinsic characteristic of the research population such that the research could not otherwise be conducted on subjects who have capacity.

3. Studies with more than a minor increase over minimal risk

- a. Research involving interventions or procedures that are considered a **more than a minor increase over minimal risk** but present **the prospect of direct benefit** to the individual subject. The IRB may approve such studies only if the risks are reasonable in relation to the prospective benefits, if the potential benefits are similar to those available in the standard clinical or treatment setting, and if the risk-benefit ratio is favorable to participants. Such ratios are less favorable when the risk is substantially more than a minor increase over minimal risk. Such ratios are more favorable when the prospect of direct benefit is more certain, or the benefit is expected to be more frequent or more significant.
- b. Research involving interventions or procedures that are considered **more than a minor increase over minimal risk** and **do not present a prospect of direct benefit** to the individual subject nor are likely to yield generalizable knowledge. The IRB **will not** approve such studies.

13.9 Studies Involving Employees as Subjects

When employees of Allina Health are being recruited as potential subjects, investigators must ensure that there are additional safeguards for these subjects. It is important to take steps to reduce possible sources of undue influence and ensure participant privacy. Employees' performance ratings, employment, and workplace relationships, particularly relationships with leaders, should be unaffected by their choice whether to participate. Below are suggestions for minimizing risks specific to employees:

- Promote voluntary participation by creating recruitment postings, flyers and email messages that require interested employees to contact the researcher.
- Encourage distribution of recruitment materials by those who do not directly supervise or oversee the employees as a way of minimizing pressure to participate.
- Remind employees' leaders that, when employees are the subjects of research, employees have the right to accept or decline participation and to have their decision so kept private. Whenever possible, have a qualified member of the research team meet with the interested individual privately about participation. Informing employees of research opportunities may be fine for a group setting like a team meeting, but

separating recruitment from group settings will reduce pressure felt by being observed by coworkers and supervisors.

- When possible, arrange for research activities to take place off-site and/or outside of regular work hours. This will protect the privacy of participating employees who may not want their peers to know or ask about research participation. Any resulting travel costs such as parking fees can be described in the consent form.
- When workplace activities are the topic of research, clearly list and describe the difference between the normal or standard workplace activities and the optional or altered research activities. This will allow participants to decline research activities they are uncomfortable performing without concerns for job performance.
- Minimize informational risks. When research results or data may be shared with the employer or persons of authority, take steps to avoid identification of individual participants. Informational risks, and the steps being taken to minimize those risks, should be disclosed in the consent process.
- When research activities include any risk of physical injury, inform research participants of employer policies for reporting workplace injuries. Any accidents or injuries resulting from participation in research must be shared with the investigator for study-related reporting. Include these instructions and contact information in the consent form.
- Compensation for employee participation in research requires consultation with Human Resources regarding wage and employment policies and laws. Participation incentives such as pre-paid gift cards may minimize confusion with wages or bonuses.
- Include all the details in the study protocol and consent form that would be included for a non-employee. Do not omit study information that all employees may be assumed to know.
- Consider how to protect subjects from accidental identification if quotes, names of facilities, or other potentially identifying information are used in a publication. Describe a plan for masking identities when sensitive and personal information is disclosed for research through surveys, focus groups and interviews. This plan should be included in the study protocol and disclosed in the consent process along with any associated risks.

When reviewing research involving employees as subjects, the IRB will consider the above guidelines and other steps, when appropriate, to ensure participation is voluntary, free from undue influence or coercion to participate or continue to participate, and to ensure that the privacy interests of employees are appropriately safeguarded. Researchers seeking to take an approach that appears inconsistent with the above guidelines should provide justification within their submission and propose an alternate approach to ensure employee protections.

13.10 Persons undergoing In-Patient Mental Health Treatment or under Involuntary Holds or Commitment Proceedings

Patients undergoing mental health evaluation or treatment are particularly vulnerable and should only be included in research when the aims of the research cannot reasonably be achieved without their participation and with extreme care and caution to protect their rights, safety, and welfare. Investigators must disclose plans to recruit or enroll such subjects in their research and explain why inclusion is necessary, how potential subjects will be identified and recruited, the circumstances under which consent will be sought, the consent process, and how subjects will be protected throughout their involvement.

When reviewed by the Allina Health IRB, the IRB review process will include at least one member, or a consultant, who is experienced with or otherwise knowledgeable about the population when the research involves greater than minimal risk. When appropriate, the IRB review may apply the guidelines described in the section of this manual for research involving subjects with impaired decision-making capacity (Section 13.8.3).

Minnesota has established law with specific protections for persons undergoing in-patient mental health treatment and persons under involuntary holds or commitment proceedings. Investigators must adhere to these requirements.

13.10.1 Clinical Drug Trials

Per Minnesota Statute 253B.05, a patient cannot participate in, or consent to participate in, a clinical drug trial during an emergency admission or hold (e.g., (72-hour emergency admission hold, peace officer transport hold, or court apprehend and hold order). Consent given during a period of an emergency admission or hold is void and unenforceable. This statute does not prohibit a patient from continuing participation in a clinical drug trial if the patient was participating in the drug trial at the time of the emergency admission or hold.

13.10.2 Psychiatric Clinical Drug Trials

Per Minnesota Statute 253B.095, Subd. 1, a person who has had a commitment hearing and is released by the court before a commitment order is issued cannot be enrolled or participate in a psychiatric clinical drug trial during the period of a stay of commitment unless the court specifically authorizes the participation. The statute states:

[D]uring the period of a stay of commitment, the court may allow the patient to give consent to participate in a specific psychiatric clinical drug trial if the treating psychiatrist testifies or submits an affidavit that the patient may benefit from participating in the trial because, after providing other treatment options for a reasonable period of time, those options have been ineffective. The treating psychiatrist must not be the psychiatrist conducting the psychiatric clinical drug trial. The court must determine that, under the circumstances of the case, the patient is competent to choose to participate in the trial, that the patient is freely choosing to participate in the trial, that the compulsion of the stayed commitment is not being used to coerce the person to

participate in the clinical trial, and that a reasonable person may choose to participate in the clinical trial.

13.10.3 Other Relevant Protections

Minnesota Statute 524.313(c)(4)(i) provides that a court appointed guardian for an incapacitated person cannot provide consent to enable the ward to partake in “experimental treatment of any kind unless the procedure is first approved by order of the court[.]” The statute also provides that the guardian cannot consent “to any medical care for the ward which violates the known, conscientious, religious, or moral belief of the ward.” In keeping with these statutes, in Minnesota, investigators may not enroll subjects under the care of a guardian in research involving experimental treatment without the necessary court order and must seek the assent of wards for participation in research which involves medical care, whenever the potential subject is capable of providing assent.

Additional protections apply to the use or disclosure of certain medical records regarding mental health and to the use or disclosure of psychotherapy notes. See Section 24 for a discussion of these protections.

Investigators conducting research in other jurisdictions must comply with the rules of that state and locality.

14 FDA-Regulated Research, Humanitarian Use Devices, Expanded Access, and Emergency Use

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](#).

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.

Industry-sponsored clinical trials are reviewed by Allina's designated external IRBs. The following procedures describe the review of FDA-regulated research by the Allina Health IRB.

14.1 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. See section 201(ff) of the FD&C Act [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\(d\)](#)]

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 Part 812](#).

In Vitro Diagnostic Product (IVD). In vitro diagnostic 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 non-significant risk device is an investigational device that does not meet the definition of a significant risk device.

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.

Test Article. Test article means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n). [[21 CFR 50.3\(j\)](#)]

14.2 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\(d\)](#)]

14.3 Investigator Responsibilities

The investigator holds additional responsibilities when conducting a clinical trial evaluating FDA-regulated drugs, devices, and other articles. 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 obtained 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 Allina Health IRB, the investigator proposing the clinical investigation will be required to provide a plan – to be evaluated by the IRB - that includes storage, security, and dispensing of the test article.
 - a. The investigator is responsible for investigational drug accountability that includes storage, security, dispensing, administration, return, disposition, and records of accountability. Such details will be provided in the IRB submission and reviewed by the IRB for acceptability.
 - b. The investigator may delegate in writing, as part of the IRB submission, the responsibility detailed in 'a' above to the Pharmacy Service.
 - c. Investigational drugs and devices must be labeled in accordance with federal and state standards.
 - d. 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.

14.4 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 Data and Safety Monitoring must be included.

14.5 Clinical Investigations of Items Regulated as Drugs or Devices

14.5.1 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.
4. Other document and/or communication verifying the IND/IDE.

For investigational devices, the study may be exempt from IDE requirements 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 exempt or NSR, then the investigator should include documentation with the submission providing the basis for exempt or NSR categorization. If the FDA has determined that the study is 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 exempt or NSR, or, (3) if neither of the above, whether an IND is necessary, or that a device study is exempt or NSR, 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.

14.5.1.1 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 of unapproved drugs 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].

14.5.1.2 IDE Exemptions

For clinical investigations of 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 “501k” 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.

14.5.1.3 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:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- 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;
- 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
- 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 14.5.1. The FDA's determination 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):

- (i) Labels the device in accordance with [812.5](#);
- (ii) 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;
- (iii) 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 documentation is waived by an IRB under [56.109\(c\)](#).
- (iv) Complies with the requirements of [812.46](#) with respect to monitoring investigations;
- (v) 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 \(10\)](#);
- (vi) 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
- (vii) 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.

14.6 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 IRBs 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.

14.6.1 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.

14.6.2 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.

14.6.3 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 seeking approval for diagnostic or treatment use of a HUD at Allina Health 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, institutional policies, and the requirements of the IRB.

Health care providers seeking initial IRB approval for diagnostic or treatment use of a HUD submit the following materials to the IRB via the IRB electronic system:

1. IRB Application 1
2. IRB Application 2 – Humanitarian Use Devices (non-research uses)
3. A copy of the HDE approval letter from the FDA
4. A description of the device, such as a device brochure
5. The patient information packet for the HUD
6. The proposed clinical consent process and written consent form
7. Other relevant materials (e.g., training certificates) as identified in the Application Form

If the provider is proposing off-label use of the HUD, the provider should include justification for the proposed off-label use and summarize any available information regarding risks associated with the off-label use. The consent form must clearly indicate that the use is off-label and describe what this means.

The IRB will review the proposal at a convened meeting ensuring that appropriate expertise is available either within the membership in attendance or via the use of consultants. 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. While federal regulations governing the use of HUDs may not require signed written consent, the Allina IRB requires the use of a signed written consent form for all HUD uses, unless a request to waive this requirement is made to the IRB at the time of the application submission and the IRB agrees to waive the use of a written consent for individual HUDs. A consent form template specific for HUD use will be posted within the IRB's electronic system to assist providers in creating consent forms that cover the Allina-required elements of consent for these studies.

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 mediate an apparent immediate risk to a patient. Proposed changes may be submitted using the Modification Request Form and must 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 prior to expiration. Materials to be submitted include:

1. The Continuing Review Report – Humanitarian Use Devices (non-research uses)
2. Any safety reports or summaries provided by the HDE holder that had not previously been submitted
3. The current patient information packet, if applicable

4. The current consent, if applicable
5. Other materials as identified on the Continuing Review Report
6. Any other new relevant information or materials

The IRB may conduct continuing review using expedited review procedures or review by the convened IRB.

14.6.4 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 Allina IRB including the identification of the patient involved, the date of the use, and the reason for the use.

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.

14.7 Expanded Access to Investigational Drugs, Biologics, and Devices ('Compassionate Use')

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 access to investigational medical products outside of a clinical trial, where the intent is treatment, rather than research. Because the investigational 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 representative and to monitor for safety.

Charging for expanded access use of investigational products is discussed in Section 14.8.4.

14.7.1 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, and approved drugs with limited availability under a risk evaluation and mitigation strategy (REMS), for patients with serious or immediately life-threatening diseases or conditions who lack other therapeutic options and may benefit from the investigational diagnostic or therapy.

Under the FDA's expanded access rule, access to investigational drugs for treatment purposes will be available to:

- Individual patients, including in emergencies [[21 CFR 312.310](#)]
- Intermediate-size patient populations [[21 CFR 312.315](#)]
- Larger populations under a treatment protocol or treatment IND [[21 CFR 312.320](#)]

Expanded access submissions are categorized by FDA as either "Access Protocols", which involve a protocol amendment to an existing IND, or "Access INDs", which are managed separately from any existing INDs.

Investigators, when seeking access to drugs under the expanded access provisions, should work closely with the sponsor or manufacturer, the FDA, and the Allina Health HRPP, to determine the appropriate access mechanism and ensure that proper regulatory procedures are followed.

Prospective IRB review and approval is required for all expanded access uses, including clinical patient use. This requires, among other things, that the IRB review the expanded access use at a convened meeting at which a majority of IRB members are present. There are two exceptions when prospective review and approval of the convened IRB for expanded access use of a drug or biologic are not required:

- The conditions that permit an emergency use exemption (see Section 14.8) are satisfied, or
- A physician submitting an individual patient expanded access IND selects the appropriate box on Form FDA 3926 to request a waiver of full IRB review or includes a separate IRB review waiver request with the application when using Form FDA 1571. The physician must obtain concurrence by the IRB chairperson or another designated IRB member before treatment use begins. If the physician has submitted this request, they should notify the Allina IRB Office and create a package in IRBNet for concurrence by the IRB Chair. The IRB Office or IRB Chair may determine that prospective review of the convened IRB is required for the individual patient expanded access IND.

When an expanded access protocol is already opened through a central IRB, or the expanded access use is time-sensitive but does not satisfy the emergency use exemption criteria, and the Allina Health IRB may not be able to convene within sufficient time to meet the needs of the patient(s), the investigator should consult with the HRPP Director or IRB Manager, to determine if use of an external IRB is acceptable.

Additional information is available in FDA guidance: [Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers](#).

14.7.2 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 may be circumstances under which a health care provider may wish to use an unapproved device when a 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
- Planned Emergency Research (See Section 12.12.2.1)
- Compassionate Use (or Single Patient/Small Group Access)
- Treatment Use
- Continued Access

Investigators, when 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 Allina Health HRPP, to ensure that proper regulatory procedures are followed.

Unless the conditions that permit an emergency use exemption are satisfied (see Section 14.8), Prospective IRB review and approval is required. This requires, among other things, that the IRB review the proposed use at a convened meeting at which a majority of IRB members are present. There are two exceptions when prospective review and approval of the convened IRB for expanded access use of a medical device are not required:

- The conditions that permit an emergency use exemption (see Section 14.8) are satisfied, or
- A physician is requesting a compassionate use (or Single Patient/Small Group Access) for a medical device. The physician must obtain concurrence by the IRB Chair or another designated IRB member before treatment use begins. The physician should notify the Allina IRB Office about the compassionate use request and create a package in IRBNet. The IRB Office or IRB Chair may determine that prospective review of the convened IRB is required for the compassionate use.

When an expanded access protocol is already opened through a central IRB, or the expanded access use is time-sensitive but does not satisfy the emergency use exemption criteria, and the Allina Health IRB may not be able to convene within sufficient time to meet the needs of the patient(s), the investigator should consult with the HRPP Director or IRB Manager, to determine if use of an external IRB is acceptable.

14.8 Emergency Use

If an appropriately trained and licensed health care provider in an emergency situation determines that IRB approval for the use of an investigational drug/device at the facility cannot be obtained in time to prevent serious harm or death to a patient, the drug or device may be used without prior IRB approval. The health care provider must, within 5 days after the emergency use of the drug or device, provide written notification of the use to the IRB including the identification of the patient involved, the date of the use, and the reason for the use.

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.

14.8.1 Emergency 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 (e.g., in another patient or a subsequent course of treatment with the original patient) 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 be 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 14.8.2), informed consent must be obtained in accordance with [21 CFR 50](#) and documented in writing in accordance with [21 CFR 50.27](#).

At Allina Health, providers must seek approval from the Vice President for Medical Affairs (VPMA), designee, or administrator on call for emergency uses, or, if prior approval is not possible, provide notification as soon as possible after the use.

Certification from an independent physician (i.e., a physician not otherwise involved in the decision to treat with the investigational product) that the criteria for an emergency use are satisfied is required for **all** emergency uses at Allina Health. If immediate use of the test article is required to preserve the life of the subject, and time is not sufficient to obtain the

independent physician certification in advance of using the test article, the clinical investigator (provider) shall document his or her determinations that the criteria for emergency use are satisfied and, within 5 working days after the use of the article, have these determinations reviewed and evaluated in writing by an independent physician.

The Allina Health IRB must be notified within **5 working days** when an emergency exemption is used via the submission of the Emergency Use Report and Independent Physician Certification via the IRB electronic system. The necessary forms are available in the electronic system's Forms and Templates Library or by contacting the IRB office. The IRB Chair or designee will review the report to verify that circumstances of the emergency use conformed to FDA regulations. This must not be construed as an approval for the emergency use by the IRB, 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, the IRB will 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 article. Any research using an investigational device or drug within Allina Health requires prior notification and review by the Office of Sponsored Programs (OSP). Investigators may contact OSP with any questions about the process for review.

Charging for investigational products is discussed in Section 14.8.4.

14.8.2 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 or unapproved test article without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific 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 legally authorized representative; 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 Allina Health IRB must be notified within 5 working days when an emergency consent exception is invoked via the submission of the Emergency Use Report and Independent Physician Certification via the IRB electronic system. The necessary forms are available in the electronic system's Forms and Templates Library or by contacting the IRB office. The IRB Chair or designee will review the report to verify that circumstances of the emergency consent exception conformed to FDA regulations.

14.8.3 Waiver of Informed Consent for Planned Emergency Research

The Allina Health IRB follows FDA regulations, [21 CFR 50.24](#), and any applicable state requirements which permit waiver of informed consent requirements for emergency research when human subjects in need of emergency medical intervention cannot provide legally effective informed consent and their legally authorized representatives (LARs) are also unable or unavailable to give informed consent on their behalf.

See Section 12.12 for additional detail on Planned Emergency Research.

14.8.4 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 use of an investigational product within Allina Health requires prior notification and review by the Office of Sponsored Programs (OSP). Investigators may contact OSP with any questions about the process for review.

14.8.4.1 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\(b\)\(8\)](#)].

14.8.4.2 Charging for Investigational Drugs and Biologics

In 2009, FDA updated its rules at 21 CFR 312 regarding charging for Investigational Drugs Under an IDE. 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 an IND — Questions and Answers](#).

15 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” (also referred to as UPs, UAPs, and UPIRTSOs).

This section provides definitions and procedures for the reporting of UPIRTSOs to the Allina Health 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 8.1.1.

15.1 Definitions

Unanticipated problems involving risk to participants or others. Unanticipated problems involving risks to subjects or others (UPIRTSO) refer to any incident, experience, outcome, or new information that:

1. Is unexpected
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

UPIRTSOs also encompass all 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\(s\)](#)].

15.2 Procedures

15.2.1 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, the Allina Health IRB does not accept reports of adverse events that are not UPIRTSOs.

Investigators must report the following events or issues to the IRB as soon as possible but within **7 working days** after the investigator first learns of the event using the “Event Report” form in the IRB electronic system.

If investigators are uncertain but believe that the event might represent an UPIRTSO, a report should be submitted.

Examples of UPIRTSOs 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 not 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. Adverse events involving direct harm to subjects enrolled by the investigator (i.e., local adverse events), which in the opinion of the investigator or sponsor, may represent an unanticipated problem involving risk to subjects or others.
7. An unanticipated event related to the research that exposes subjects to potential risk but that does not involve direct harm to subjects (e.g. lost laptop).
8. An unanticipated event related to the research that results in actual harm or exposes individuals other than the research participants (e.g., investigators, research assistants, students, the public, etc.) to potential risk.
9. IND Safety Reports from sponsors that meet the criteria for an unanticipated problem involving risk to subjects.
10. Unanticipated adverse device effects (UADEs).
11. Any other adverse event 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.

15.2.2 Review Procedures

1. Upon receipt of the Event Report, the IRB staff pre-reviews the submission and, if needed, contacts the investigator for corrections or additional information.
2. The IRB Chair or designated reviewer receives and reviews the report and makes an initial determination as to whether the event represents an UPIRTSO. If needed, the Chair or designee may request additional information from the investigator, sponsor, or DSMB.
3. If the reviewer determines that the problem does not meet the definition of an UPIRTSO, they will determine whether any additional actions are necessary to ensure the protection of human subjects. As warranted, the reviewer may refer the matter to the convened IRB for review. The results of the review will be recorded in the electronic system and communicated to the investigator.
4. If the reviewer determines that the event may be an UPIRTSO, the report will be referred for review by the convened IRB. The convened IRB will determine whether the event is a UPIRTSO and whether any additional actions, such as those outlined below, are necessary to ensure the protection of human subjects. If needed, the IRB may request additional information from the investigator, sponsor, or others (including study committees, such as data monitoring committees, data safety monitoring boards, or steering committees). 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 an UPIRTSO, the IRB may take any of the following actions, or others, to ensure the protection of human subjects:
 - a. Requiring modifications to the protocol/research plan
 - 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, Compliance, Risk Management, Privacy)
 - 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 an UPIRTSO, the IRB staff 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.

16 Noncompliance

This section provides definitions and procedures for the reporting of noncompliance to the Allina Health 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 8.1.1.

16.1 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 policies and/or federal 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 Non-Compliance. Allegation of Non-Compliance is defined as an unproved assertion of non-compliance.

16.2 Reporting

Investigators and their study staff are required to report instances of possible noncompliance to the IRB within **7 working days** of discovery using the Event Report form in the IRB electronic system. Additionally, anyone may report concerns of possible noncompliance to the HRPP or IRB verbally, by email, or other means. In such cases, the reporting party is responsible for making these reports in good faith, maintaining confidentiality and, unless reporting anonymously, cooperating with any subsequent fact-finding in relation to the report.

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 Director, IRB Manager, or Chair directly to discuss the situation informally.

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.

Investigators who have concerns regarding the conduct of research at Allina Health, Allina Health's HRPP or IRB, or the IRBs Allina relies upon, should report such concerns as outlined in Section 21.2.

16.3 Review Procedures

1. Upon receipt of the Event Report, the IRB staff 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 Director, IRB Manager, or assigned staff will develop a written report summarizing the available information and will upload the report into the IRB electronic system. 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 Director, IRB Chair, and, when appropriate, the Research Compliance Director or IO, 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 or designated reviewer 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 reviewer may request additional information from the investigator or others. When circumstances warrant, the HRPP Director or IRB Manager may bypass this step and assign the report for convened board review.
3. If the reviewer 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 reviewer may refer the matter to the convened IRB for review. The results of the review will be recorded in the electronic system 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/research plan
 - 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, Compliance, Risk Management, Privacy)
 - 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 IRB staff 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 9.12.

17 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 investigator and his or her staff are responsible for the safety and welfare of all subjects enrolled in their studies. When an investigator hears complaints or concerns from subjects, he or she will try to resolve them.

Investigators conducting research under the auspices of Allina Health must report complaints to the Allina Health 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 8.1.1. Investigators conducting research under the oversight of the internal IRB report complaints using the Event Report form in the IRB electronic system. Investigators are encouraged to contact the HRPP Director, Medical Director, or IRB Manager 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 staff will do the following:

- Document the complaint or allegation. When appropriate, the staff may request that the subject submit the complaint in writing.
- Reassure the subject that the HRPP/IRB will take all necessary measures to inquire into the circumstances and to address the issue.
- Provide written confirmation of receipt of the complaint to the subject, if the subject is willing to provide contact information.
- Convey the information to the IRB of record in a timely manner.
- When appropriate, contact the investigator for additional information or to assist with resolution.
- When appropriate, contact other resources (e.g., Research Compliance, Risk Management) within Allina to assist with information-gathering or resolution.

For research under the oversight of the internal 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 convened IRB or designated expedited reviewer. A report will be provided to the IRB at the next available meeting if the research is subject to convened IRB review or provided to the designated expedited reviewer. 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, Allina Health's IO and or Director of Research Compliance will be immediately notified.

18 Other Reportable Events

In addition to UPIRTSOs, noncompliance, and complaints, any change to the research implemented without IRB approval, and any issue or event that may impact the rights, safety, or welfare of subjects, must be reported to the internal IRB within **7 working days** of discovery using the Event Report or Protocol Deviation Report, as applicable. Investigators may also need to submit non-local reportable events when requested by the IRB Office. 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 8.1.1.

Other reportable events include, but are 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. 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.
4. New information (e.g., an interim analysis, report, publication, or finding) that indicates increased risk, new risk(s), or decrease in benefit from what was previously understood.
5. Audit or inspection reports that indicate noncompliance or other potential issues with the research.
6. Breaches of confidentiality (unapproved access, use, or disclosure of confidential information).
7. Incarceration of a subject in a study not approved to include prisoners.
8. Pregnancy of a subject not approved to include pregnant women.
9. Holds, suspensions, or terminations of a study, in part or in full, by an investigator, sponsor, or others.
10. New information that may impact the willingness of participants to continue in the research.
11. Audit or inspection reports that indicate problems with the research or noncompliance with the regulations or the requirements of the IRB.

18.1 Review Procedures

1. Upon receipt of the report, the IRB staff pre-reviews the submission and, if needed, contacts 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 Director, IRB Chair, and, when appropriate, the Research Compliance Director or IO, 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 or designated reviewer receives and reviews the report and if the report may represent an UPITRSO or noncompliance, reviews the report as described in Section 15 or 16. When circumstances warrant, the HRPP Director or IRB Manager may bypass this step and assign the report for convened board review.
3. If the reviewer determines that the event or issue is not noncompliance or an UPIRTSO, 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 reviewer may refer the matter to the convened IRB for review. The results of the review will be recorded in the electronic system and communicated to the investigator.

19 Miscellaneous Reports

Routine reports that do not indicate any issues or problems with the research are submitted using the Miscellaneous Report. Miscellaneous reports may include, but are not limited to, routine monitoring reports, DMSB reports or interim analyses that don't indicate any issues or problems with the research, audit or inspection reports that don't indicate any problems or noncompliance, sponsor or coordinating center notices or letters that don't indicate any issues or problems with the research.

The internal IRB requires the submission of monitoring, audit, inspection, and DSMB reports. These reviews serve as "*sources . . . that no material changes have occurred since [the] previous IRB review*" [[45 CFR 46.103 \(b\)\(4\)](#)]. 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 8.1.1.

20 Reporting to Regulatory Agencies, Sponsors, and Organizational Officials

Federal regulations require prompt reporting to appropriate organizational officials and, as applicable, the federal department or agency head or the FDA, of (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing non-compliance with this policy or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval. Allina Health IRB complies with this requirement as follows. When research is under the oversight of an external IRB, the terms of the agreement with that IRB will guide reporting.

20.1 Procedures

1. IRB staff will initiate these procedures as soon as the internal IRB takes any of the following actions:
 - a. Determines that an event may be considered an unanticipated problem involving risks to participants or others
 - b. Determines that non-compliance was serious or continuing
 - c. Suspends or terminates approval of research
2. The HRPP Director or designee, in collaboration with Research Compliance, Legal, and others as appropriate, is responsible for preparing reports or letters which include the following information:
 - a. Reason for the report (Unanticipated problem involving risks to participants or others, serious or continuing non-compliance, suspension or termination of IRB approval of research)
 - b. Name of the involved institution(s)
 - c. Title of the research project and/or grant proposal in which the problem occurred
 - d. Name of the investigator on the project
 - e. Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement)
 - f. A detailed description of the problem including the findings of the organization and the reasons for the IRB's decision
 - g. Actions the institution is taking or plans to take to address the problem (e.g., revise the protocol/research plan, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.)
 - h. Plans, if any, to send a follow-up or final report by the earlier of:
 - i. A specific date

- ii. When an investigation has been completed or a corrective action plan has been implemented
3. The IRB Chair and the IO or designee review the letter and recommend modifications as needed.
4. The IO is the signatory.
5. The HRPP Director or designee sends a copy of the report to:
 - a. The IRB Chair
 - b. The IO
 - c. Federal agencies, as follows:
 - i. OHRP, if the study is subject to DHHS regulations or subject to a DHHS FWA.
 - ii. If the study is conducted or supported by any federal agency other than DHHS that is subject to the Common Rule, the report is sent to OHRP or the head of the federal agency as required by the agency.
 - iii. If the study is conducted or supported by any federal agency that has not adopted the Common Rule, and reporting is required, the report is sent to the party identified by the agency.
 - iv. FDA, if the study is subject to FDA regulations.

Note: Reporting to a regulatory agency is not required if the event occurred at a site that was not subject to the direct oversight of the organization, and the agency has been notified of the event by another party (e.g., sponsor).
 - d. Investigator
 - e. Director of Research Compliance
 - f. Sponsor, if the study is sponsored
 - g. Others as deemed appropriate by the IO

The HRPP Director ensures that all steps of this policy are completed within 30 working days of the determination. For more serious actions, the Director will expedite reporting. When additional time is needed to gather facts, or determine corrective actions, a preliminary report will be submitted within 30 days, to be followed by a final report as described above.

21 Investigator Responsibilities

Principal Investigators (PIs) are ultimately responsible for the conduct of research. Investigators 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 the research.

Within the regulations, the term ‘investigator’ refers to individuals involved in the design, conduct, or reporting of the research. Such involvement could include one or more of the following:

- Substantive involvement in designing the research
- Obtaining information about living individuals by intervening or interacting with them for research purposes;
- Obtaining identifiable private information about living individuals for research purposes;
- Obtaining the voluntary informed consent of individuals to be subjects in research; and
- Studying, interpreting, or analyzing identifiable private information or data for research purposes.

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 that minimizes risk to the subjects;
3. Incorporate into the research a plan to ensure the just, fair, and equitable recruitment and selection of subjects;
4. When some or all 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 coverage for periods of absence or decreased availability.
 - 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. Assure 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 Minnesota and the policies of Allina Health;
 10. Assure that all study personnel are educated in the regulatory requirements regarding the conduct of research and the ethical principles upon which they are based;
 11. Assure that all persons assisting with the research are adequately trained and informed about the protocol/research 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 private health information 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 and any applicable grant or contract;
 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 legally authorized representative, 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 required 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, non-compliance, 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 or benefits of the research;
25. Obtain IRB review and approval before changes are made to the research unless a change is necessary eliminate apparent immediate hazards to the subject(s);
26. Seek HRPP or IRB assistance when in doubt about whether proposed research requires IRB review; and
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 elsewhere in this document.

21.2 Investigator Concerns

Investigators who have concerns regarding the conduct of research at Allina Health, Allina Health's HRPP or IRB, or the IRBs Allina relies upon, should convey them to the HRPP Director or Medical Director, the Director of Research Compliance, the Chief Compliance Officer, or the IO, as 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 IRB Manager will be available to address investigators' questions, concerns and suggestions.

Anyone with concerns may also report via the Allina Integrity Line by calling the 24-hour toll-free hotline (1-800-472-9301). Information obtained from the Integrity Line will be treated confidentially and reported to the Integrity and Compliance Department for follow-up.

Consistent with Allina Health policies, there will be no retaliation against employees who report concerns in good faith. See *System-wide Policy: Compliance Program (SYS-CC-ECOC-402.01.01)* and *Human Resources Non-Retaliation Policy (MyAllina.com)* for further information.

22 Sponsored Research

It is Allina Health policy that any sponsored research conducted under the auspices of the Organization 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

All sponsored research must be governed by a written agreement (including grants and contracts). All financial support, including payments and provision of Study Supplies, must be set forth in the written agreement. Written agreements will be reviewed for the following by the Office of Sponsored Programs (OSP), with consultation with the IRB, as necessary:

1. A provision that addresses medical care for research participants with a research-related injury, when appropriate.
2. In studies where Sponsors conduct research site monitoring activities, a provision requiring that the Sponsor promptly reports to Allina Health findings that could affect the safety of participants or influence the conduct of the study.
3. When the Sponsor has the responsibility to conduct data and safety monitoring provisions for monitoring the data to ensure the safety of participants and for providing data and safety monitoring reports to Allina Health.
4. 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, a provision that the investigator or Allina Health 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. See Section 23.3 for additional detail.

23 Conflict of Interest in Research

It is Allina Health policy to preserve public trust in the integrity and quality of research by reducing actual or perceived conflict of interest in the conduct of research.

Conflicts of interest (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. Conflicts of interest 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, conflicts of interest should be eliminated when possible and effectively managed and disclosed when they cannot be eliminated.

23.1 Researcher Conflicts of Interest

Pursuant to the Conflict of Interest policy "*Outside Interests and Conflicts Management (SYS-COMPLIANCE-909)*", Allina Health maintains a Research Conflict of Interest Committee (RCOI Committee). The HRP and IRB will collaborate with the COI Administrator and Research Compliance, as appropriate, to ensure that COIs of researchers and research staff (researchers) are identified and managed before the IRB, whether internal or external, completes its review of any new research application.

23.1.1 Procedures

23.1.1.1 Disclosure of Researcher COI

For IRB purposes, researcher conflict review occurs at the time of new study submission, continuing review, with the addition of a new researcher, and whenever a researcher updates their COI disclosure indicating a new or changed interest. IRB staff notify the COI Administrator whenever a submission requiring conflict review is received. The COI Administrator reviews the researchers' disclosures and either notifies the IRB staff that no researcher COI was identified or that one or more researchers has an interest that requires evaluation by the RCOI Committee. In the event a conflict that requires disclosure or management is identified, the COI Administrator will provide a written summary describing the conflict and the conflict management plan (CMP).

23.1.1.2 Evaluation of COI

The IRB will review COIs and CMPs to determine:

- Whether the COI affects the rights or welfare of research subjects
- Whether the COI might adversely affect the integrity or credibility of the research or the research program, and

- Whether the CMP effectively protects research subjects and the integrity and credibility of the research and the research program

In evaluating COIs and CMPs, among other factors the IRB may consider:

- How the research is supported or financed
- The nature and extent of the conflict
- The role and responsibilities of the conflicted individual in the design, conduct, and reporting of the research, and
- 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 CMP, if any, allow the research to be approved. With regard to the CMP issued by the RCOI Committee, the IRB shall either affirm or request changes to strengthen it. The IRB can require additional measures to manage a COI so that the research may be approved. However, the IRB cannot weaken a CMP approved by the RCOI Committee.

For example, in addition to the CMP, the IRB may require:

- Disclosure of the COI to subjects through the consent process
- Modification of the research plan or safety monitoring plan
- Monitoring of research by a third party
- Disqualification of the conflicted party from participation in all or a portion of the research
- Appointment of a non-conflicted PI
- Divestiture of significant financial interests
- 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

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 him/herself from the deliberations and vote by leaving the room.

All members and alternate members of the IRB complete a conflict disclosure when first appointed and annually thereafter or sooner if their circumstances change. These forms are submitted through the COI Smart system where the COI Administrator reviews the disclosures and determines if a COI exists. The details of the management plans will be provided to staff who may share with the IRB Chair or other members as appropriate. The IRB staff, in turn,

ensures that IRB members and alternates are not assigned to conduct reviews of studies for which the member has a conflict and reminds members of conflicts at convened meetings as needed to ensure recusal. IRB staff may consult with the Research Compliance team 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 (See *Outside Interests and Conflicts Management Policy* for a definition of significant financial interests) related to the research being reviewed,
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 a 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, videoconference or web meeting, the member's participation (connection) is terminated for 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 conflict of interest 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, bonus payments, unrelated to actual items or services, designed to accelerate recruitment ("bonus payments") are also not permitted. Bonus payments do not include payments for bona fide items or services.

24 Research Privacy

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 Privacy Rule defines individually identifiable health information transmitted or maintained by a covered entity in any form (electronic, written or oral) as “protected health information” (PHI) and establishes the conditions under which investigators may access and use this information in the conduct of research.

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 under the Common Rule and FDA regulations.

24.1 Definitions (per [HIPAA Privacy Booklet for Research](#), or Allina Health’s policy on *Use and Disclosure of Protected Health Information for Research, SYS-ADMIN-RA-005*)

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. However, PHI disclosures made before the compliance date for a covered entity are not part of the accounting requirement.

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.

Covered entity. A health plan, a health care clearinghouse, or a health care provider who 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 how it will be protected.

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 of information in any other manner outside Allina Health (i.e., to an External Researcher).

Health Information. Health Information means any 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; 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 PHI that excludes 16 categories of direct identifiers and 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, with a data use agreement.

Minimum Necessary. The standard that uses the least information 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 protected health information 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 plan 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 conflict of interest.

Protected Health Information. PHI means health information, including demographic information, that is individually identifiable (i.e., contains patient-specific information) and that

is created, maintained, received, used or disclosed by or for an Allina Business Unit or other covered entity. More specifically, the term refers to information that:

- (i) identifies or could reasonably be used to identify the individual; and
- (ii) related to:
 - a. the past, present or future physical or mental health or condition of an individual;
 - b. the provision of health care to an individual; or
 - c. the past, present, or future payment for health care provided to an individual

PHI excludes information in education records, 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.

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 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 an investigator 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 DHHS and FDA Protection of Human Subjects Regulations include protections to help ensure the privacy of subjects and the confidentiality of information, the Privacy Rule supplements these protections 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.

Allina Health's designated IRBs will 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 DHHS Protection of Human Subjects regulations and, if applicable, FDA regulations,

including using either the normal review procedures (review by the convened IRB) or 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. DHHS and FDA have established categories of research that may be reviewed by an IRB through an expedited review procedure. Expedited review of a request for a waiver or an alteration of the Authorization requirement is permitted where the research activity is on the DHHS or FDA list of approved categories and involves no more than minimal risks. In addition, 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 plan, 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 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 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:

- The identity of the approving IRB
- The date on which the waiver or alteration was approved
- A statement that the IRB has determined that all the specified criteria for a waiver or an alteration were met
- A brief description of the PHI for which use or access has been determined by the IRB to be necessary in connection with the specific research activity
- A statement that the waiver or alteration was reviewed and approved under either normal or expedited review procedures
- The required signature of the IRB Chair or the Chair's designee.

Allina Health will not release PHI to investigators 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 under the Common Rule and FDA regulations. Just as a valid consent under Common Rule and FDA regulations must meet certain requirements, a valid authorization must contain certain statements and core elements [[45 CFR 164.508.6\(c\)](#)]. At Allina Health, the HIPAA authorization is incorporated into the consent document (i.e., a compound authorization), with limited exceptions at the discretion of the HRPP Director in consultation with Legal and/or the Chief Privacy Officer. Template HIPAA authorization language for insertion into consent documents is available in the electronic system’s Forms and Templates Library. A single set of signature lines is present to document both informed consent and HIPAA authorization. When the HIPAA authorization is incorporated into the consent document, the Allina Health IRB or Allina-designated external IRB reviews the content of the authorization to ensure 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. Investigators are not required to retrieve information that was disclosed under the authorization before learning of the revocation. Additionally, investigators may continue to use and disclosure PHI already obtained for the research under an authorization to the extent necessary to protect the integrity of the research.

When an authorization is obtained for research purposes, the Privacy Rule requires that it pertain only to a specific research study, not to nonspecific research or to future, unspecified projects. The Privacy Rule considers the creation and maintenance of a research repository or database as one specific research activity, the subsequent use or disclosure by a covered entity of information from the database for a specific research study requires separate authorization unless a waiver of the requirement is granted.

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 DHHS Protection of Human Subjects regulations or the FDA Protection of Human Subjects 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 (“end of the research study” or “none” are permissible for research, including for the creation and maintenance of a research database or repository).
6. 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, including research-related treatment and consequences of refusing to sign the Authorization, if applicable.
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 of 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 authorization must be retained for 6 years from the date of its creation or the date it was last in effect, whichever is later.

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 PHI for a 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 research purposes, such as accessing PHI for research recruitment purposes. An IRB or Privacy Board may also approve a request that removes some PHI, but not all, or alters the requirements for 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 (absent a healthcare or research justification for retaining them or a legal requirement to do so).
 - 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.
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 Privacy Board to be used to obtain or release PHI in connection with a multi-site project.

24.5 Activities Preparatory to Research

Under the preparatory to research provision of the Privacy Rule, a covered entity may permit an investigator who works for that covered entity to use PHI for purposes preparatory to research such as assessing the feasibility of conducting a research project, developing a grant application, or identifying potential subjects. A covered entity may also permit, as a disclosure of PHI, a researcher who is not a workforce member of that covered entity to review PHI (within that covered entity) for purposes preparatory to research.

The covered entity must obtain from an investigator representations that (1) the use or disclosure is requested solely to review PHI as necessary to prepare a research plan or for similar purposes preparatory to research, (2) the PHI will not be removed from the covered entity in the course of review, and (3) the PHI for which use or access is requested is necessary for the research.

At Allina Health, this is accomplished by the investigator submitting either a Preparatory to Research Attestation to Allina Health Information Management (for projects in development) or a request for a partial waiver authorization for screening purposes to the IRB of record.

24.6 Research Using Decedent's Information

The investigator submits:

(A) Representation that the use or disclosure sought is solely for research on the protected health information of decedents; (B) Documentation, at the request of the covered entity, of the death of such individuals; and (C) Representation that the protected health information for which use or disclosure is sought is necessary for the research purposes.

At Allina Health, this is accomplished by the investigator submitting a Research Use of Decedents' PHI Attestation to Allina's Health Information Management.

24.7 Future Uses: Databases and Repositories

The Privacy Rule recognizes the creation of a research database or a specimen repository to be a research activity if the data/specimens to be stored contain PHI. There are two separate activities that the covered entity must consider: (1) the use or disclosure of PHI for creating a research database or repository and (2) the subsequent use or disclosure of PHI in the database for a particular research plan.

Individual authorization for the storage of PHI for future research must be sought unless the IRB has determined that the criteria for a waiver of the authorization requirement are satisfied. See Section 24.4 of this policy manual for a discussion of waivers of authorization.

At Allina Health, consent for research and authorization for use and/or disclosure of PHI are separate. Both the consent and authorization for future research must describe the future research uses in sufficient detail to allow the potential subject to make an informed decision. The investigator and IRB should be cognizant of uses of information/specimens that the target community may consider particularly sensitive, such as genetics, mental health, studies of origin, and use of tissues that may have cultural significance.

The authorization for future research can be a stand-alone document or may be incorporated into another authorization if the information/specimens will originate from another research activity, such as a clinical trial, unless the research involves the use or disclosure of psychotherapy notes. Authorizations for the use or disclosure of psychotherapy notes can only be combined with another authorization for a use or disclosure of psychotherapy notes.

If the authorization for future research is combined with another authorization, the authorization must clearly differentiate between the research activities and allow the individual to opt-in to the future research. Opt-outs for future research are not permitted under the Privacy Rule because an opt-out process does not provide individuals with a clear ability to authorize the use of their information/specimens for future research, and may be viewed as coercive.

24.8 Corollary and Sub-studies

Subject participation in corollary or sub-studies not essential to the primary aims of the research should be on a voluntary basis. This is particularly important when the primary

research offers a potential benefit, such as treatment, that might compel the potential subject to agree to something that they otherwise would not.

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, it is acceptable to combine in a single document the authorization for a conditioned activity, such as a clinical trial, with authorization for an unconditioned activity 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 each 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.

24.9 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. The “Safe Harbor” method permits a covered entity to de-identify data by removing all 18 data elements that could be used to identify the individual or the individual’s relatives, employers, or household members. 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 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.
 - 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 health information could be used, alone or in combination with other 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 is considered de-identified under HIPAA may still be considered human subject data under the Common Rule and may require IRB review and approval, particularly when working with a small data set that can be further divided into smaller subsets. For example, while coded information may be de-identified under HIPAA, if the investigator holds or has the ability to access both the code and the data, the information is considered identifiable private information under the Common Rule and would require IRB approval.

24.10 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, protected health information 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;
- 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, even when the recipient is a member of its workforce. The data use

agreement 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 will be made of the data, 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 and that the recipient will report any uses or disclosures of the PHI that they become aware of that not in keeping with the terms of the DUA. Data Use Agreements for the purposes of research are available through Research Administration.

24.11 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 Allina Health authorization template.

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 communicating that information within the covered entity. A disclosure of PHI means communicating that information to a person or entity outside the covered entity. 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
 - 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.
- 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.

See Allina Health Policy *SYS-ADMIN-RA-005 (Use and Disclosure of Protected Health Information for Research)* for a detailed discussion on Accounting for Disclosures.

24.13 Minnesota Health Records Act; Minnesota Research Authorization

In addition to federal laws (including HIPAA), researchers conducting research in Minnesota must also comply with Minnesota law (the Minnesota Health Records Act) and Allina Health's privacy policies. To comply with Minnesota law and Allina Health's commitment to protect patient privacy while conducting research, researchers using health records generated on or after January 1, 1997 must adhere to the research authorization processes detailed in Allina Health policy *SYS-ADMIN-RA-005 (Use and Disclosure of Protected Health Information for Research)*.

24.14 Substance Use Disorder

Information about patients who receive treatment from substance use disorder treatment programs at Allina Health, including identified units and medical personnel or other staff in a general medical care facility whose primary function is the provision of alcohol or drug use disorder diagnosis, treatment, or referral for treatment, is subject to special federal requirements and restrictions to protect the confidentiality and re-use of that information, which may include "Break the Glass" functionality in the electronic medical record. See the treatment program policies and procedures for use and disclosure of substance use disorder treatment program records. Other uses and disclosures of patient information that may be affected by the substance use disorder treatment program requirements are noted in the *Use and Disclosure of Protected Health Information (PHI) Policy, SYS-PSC-703*. Specifically, see Appendix D Confidentiality of Substance Abuse Patient Records and Appendix E Substance Abuse Patient Records Authorization Form Checklist.

If you have questions about the disclosure of information about a patient who either is currently receiving or has received substance use disorder treatment services at an Allina facility, including a request to acknowledge the person's presence at the facility, you should consult, the following, as necessary, before making the disclosure:

- The privacy and security policies and procedures
- Your Manager

- The Chief Privacy Officer
- Risk Management

25 Responsible Data Management in Research

25.1 Data Protection

In order to maintain the integrity of stored data, project data should be protected from physical damage as well as from tampering, loss or theft. This is best done by limiting access to it. PIs should decide which project members are authorized to access and manage the stored data. Study data should be kept together in a safe secure location away from public access, e.g., a locked file cabinet.

Electronic data storage requires additional consideration and safeguards. Privacy and confidentiality should be assured by replacing PHI with encoded identifiers, with the encoding key kept in a different secure location. The following can be directly linked to individuals and must NOT be used as a code number: Social Security numbers, Medical record numbers, Employee numbers, School Identification numbers.

26 Information Security

Allina Health has established policies and safeguards to protect patient information and to ensure compliance with federal and state privacy and information security laws and regulations. It is the responsibility of investigators to familiarize themselves with and comply with these policies and safeguards. Individuals must immediately report any known or suspected privacy or security concerns to both the IRB and Allina Health Corporate Compliance so that appropriate steps can be taken to assess the situation, protect the information, and comply with regulations. Additionally, investigators are required to immediately report the theft or loss of a device to the IS Service Desk.

While all policies and standards should be reviewed, it is important to note that under the Mobile Computing Device and Portable Media Security policy, all mobile computing devices used to connect with Allina's network and applications, regardless of ownership, must be properly authorized and configured before they are used to store, transmit, receive, or, in any way, interact with Allina's electronic systems or data. The authorized user of any mobile computer used to store, transmit, or process any data is responsible for any transaction initiated by, or transferred through, that mobile device. Proper authorization and configuration includes, but is not limited to, the download and continued use of device configurations that require use of a device password and timed lockout.

Provisions for data security must be described in applications to the IRB and updated as necessary. When information containing direct identifiers such as Social Security Numbers or PHI, including data considered sensitive, is to be sent outside of the institution, the provisions for data security may be subject to further review and approval.

See the Allina Health Privacy and Information Security policies for further information. (e.g. *Safeguarding Protected Health Information (“PHI”) and Personally Identifiable Information (“PII”) SYS-PSC-704; Mobile Computing Device and Portable Media Security Reference SYS-IS-ISLG-4600*).

27 Special Topics

27.1 Mandatory Reporting

[Minnesota Statute 626.556](#) addresses reporting requirements for the maltreatment of minors. Under the statute, health care professionals, social workers, hospital administrators and others are mandated to report known or suspected child neglect or physical or sexual abuse. When research is likely to reveal this type of information, investigators must disclose their obligation to report during the consent process. When parental permission and/or child assent are documented using written permission/assent forms, the forms should clearly indicate that the investigator is required to report known or suspected abuse or neglect of a child.

Additional information and procedures for reporting are available in *SYS-PC-RMC-003 “Maltreatment of Minors”*.

[Minnesota Statute 626.557](#) addresses reporting requirements for the maltreatment of vulnerable adults. Vulnerable adults are described as *“adults who, because of physical or mental disability or dependency on institutional services, are particularly vulnerable to maltreatment.”* Under the statute, health care professionals, social workers, educators and others are mandated to report when a vulnerable adult has sustained a physical injury which is not reasonably explained and the suspected abuse, neglect or financial exploitation of a vulnerable adult. When research is likely to reveal this type of information, investigators must disclose their obligation to report during the consent process. When consent and/or assent are documented using written consent/assent forms, the forms should clearly indicate that the investigator is required to report unexplained physical injuries and suspected abuse, neglect, or financial exploitation.

Additional information and procedures for reporting are available in *SYS-PC-RMC-002 “Vulnerable Adult Maltreatment: Assessment and Reporting”*.

27.2 Certificate of Confidentiality

Certificates of Confidentiality (CoC) protect identifiable research information from forced disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. A CoC does not protect against voluntary disclosures by the investigator, but those disclosures must be specified in the informed consent form. An investigator may not use the CoC to withhold data if the participant consents in writing to the disclosure.

Generally, any research project that collects personally identifiable, sensitive information and that has been approved by an IRB operating under either an approved FWA issued by OHRP or the approval of the FDA is eligible for a CoC. All ongoing or new research funded by NIH as of December 13, 2016 that is collecting or using identifiable, sensitive information is automatically issued a CoC through a term and condition of award.

Investigators conducting research covered by a CoC, even if the research is not federally funded, must ensure that if identifiable, sensitive information is provided to other investigators or organizations, the other investigator or organization must comply with applicable requirements when research is covered by a CoC even if they are not funded by NIH. When the research is supported by NIH, written materials for the research must stipulate this requirement.

Allina Health does not conduct research involving DoD personnel, or research under contract for a DoD component where data was collected under a pledge of confidentiality or research involving large scale genomic data collection.

27.2.1 Statutory Basis for Protection

Protection against compelled disclosure of identifying information about subjects of biomedical, behavioral, clinical, and other research is provided by the Public Health Service Act §301(d), [42 U.S.C. §241\(d\)](#):

"The Secretary may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, including research on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals."

27.2.2 Usage

CoC may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. By protecting investigators and institutions from being compelled to disclose information that would identify research subjects, CoCs help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to subjects.

Any investigator engaged in research in which sensitive information is gathered from human subjects (or any person who intends to engage in such research) may apply for a CoC.

In the consent process and form, investigators must tell research subjects that a CoC is in effect. Subjects should be given a fair and clear explanation of the protection that it affords, including the limitations and exceptions noted above. Every research project that includes human research subjects should explain how identifiable information will be used or disclosed, regardless of whether a CoC is in effect.

When following DHHS requirements for NIH-supported research covered by a certificate of confidentiality, written materials ensure that if identifiable, sensitive information is provided to other researchers or organizations, regardless of whether or not the research is federally

funded, the other research or organization must comply with applicable requirements when research is covered by a certificate of confidentiality.

27.2.3 Limitations

The protection offered by a CoC is not absolute. A CoC protects research subjects only from legally compelled disclosure of their identity. It does **not** restrict voluntary disclosures by subjects or investigators.

For example, a CoC does not prevent investigators from voluntarily disclosing to appropriate authorities such matters as child abuse, a subject's threatened violence to self or others, or from reporting a communicable disease. However, if investigators intend to make such disclosures, this must be clearly stated in the consent process and form.

In addition, a CoC does **not** authorize the person to whom it is issued to refuse to reveal the name or other identifying characteristics of a research subject if

1. The subject (or, if he or she is legally incompetent, his or her legal guardian) consents, in writing, to the disclosure of such information;
4. Authorized personnel of the Department of Health and Human Services (DHHS) request such information for audit or program evaluation, or for investigation of DHHS grantees or contractors and their employees; or
5. Release of such information is required by the federal Food, Drug, and Cosmetic Act or regulations implementing that Act.

27.2.4 Application Procedures

Any person engaged in research collecting sensitive information from human research subjects may apply for a CoC. For most research, CoCs are obtained from NIH. If NIH funds the research project, the investigator may apply through the funding Institute. However, even if the research is not supported with NIH funding, the investigator may apply for a CoC through the NIH Institute or Center funding research in a scientific area similar to the project.

If the research is conducting a sensitive research project that is covered by the Agency for Healthcare Research and Quality (AHRQ) confidentiality statute (42 US. section 299a-1(c) entitled "Limitation on Use of Certain Information") or the Department of Justice (DoJ) confidentiality statute (42 USC section 3789g), then a CoC is not required.

If there is an Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE), the sponsor can request a CoC from the FDA. For more information, see the [NIH CoC Kiosk](#).

27.3 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 Allina Health 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. The Allina Health IRB regards such limited case report preparation as an educational activity, not research, and thus it is permissible under the Privacy Rule (HIPAA) as a part of health care operations ([45 CFR 164.501](#)). When a larger series of patients is being evaluated for presentation or publication, 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 seems arbitrary, it serves as a guide to those who would prepare case reports for presentation or publication. 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 consult on the question of whether the case report constitutes research. As always, anyone who is unsure whether a project requires IRB review should contact irb@allina.com for assistance.

Regardless of the number of cases, providers must comply with all applicable laws and Allina Health policies related to the release of health information. Please see “Procedures” below regarding consultation with the Compliance Department.

27.3.1 Procedures

27.3.1.1 Retrospective Single Case Reports or Series of up to 3 Retrospective Cases

Although IRB review is not required, providers seeking to publish or present single case reports or case series must comply with all applicable federal and state laws, as well as Allina Health policies, including those related to the release of health information. Providers should consult with the Compliance Department for guidance on patient privacy and HIPAA.

A copy of this policy can be provided to journal editors or others who request confirmation of IRB review or waiver. If needed, the IRB office can provide a letter confirming that submission of single case reports or series of up to 3 cases is not required.

27.3.1.2 Case Reports/Series Not Covered by 26.3.1.1

Investigators seeking initial IRB approval for case series not covered by 26.3.1.1 submit the following materials to the IRB via the IRB electronic system:

- IRB Application 1
- IRB Application 2 – Retrospective/Prospective Chart Review*
- Protocol
- Consent Form and HIPAA Authorization, when waivers of such are not being requested

- Other relevant materials (e.g., training certificates) as identified in the Application Form

*Note: If information for the series will be obtained directly from subjects (e.g., interviews) or other sources in addition to or instead of from records, contact the IRB office at irb@allina.com for guidance on which type of application should be submitted.

27.4 Databases, Registries, & Repositories

Databases, registries, and biospecimen repositories (referred to as repositories throughout this section) are used to store data and/or biospecimens for future use.

There are two type of repositories:

- 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.

27.4.1.1 Non-research Repositories

Even though repositories 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 repositories 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 repositories, and, regardless of identifiability, when specimens will be used to evaluate the safety or effectiveness of a medical device. Research under the auspices of Allina Health that includes the use of coded private information or specimens, must either be submitted for IRB review or for a “Human Subjects Research Determination” (See Section 6).

Researchers submitting an application for research using data or specimens from non-research repositories must describe the source of the data/specimens and any terms, conditions, or restrictions on use. Data/specimens cannot be used for research if the person from whom the data/specimens originated objected to its use for research (See Section 24.13). Informed consent and HIPAA authorization must be obtained unless the IRB determines that the criteria for a waiver are satisfied.

27.4.1.2 Research Repositories

Research repositories involve three distinct activities:

- Collection of data/specimens;

- Storage and management of data/specimens; and
- Distribution of data/specimens.

Collection

Informed consent and HIPAA authorization must be obtained unless the IRB determines that the criteria for a waiver are satisfied.

Informed Consent information should include:

- A clear description of
 - What data/specimens will be collected;
 - Where the data/specimens will be stored, who will have access, and how the data/specimens will be secured;
 - Whether the data/specimens will be identifiable, coded, or deidentified;
 - The types of research to be conducted and any limitations or restrictions on such; and
 - The conditions under which data/specimens will be released to recipient-investigators.
- A statement regarding future withdrawal of the data from the study (i.e., state whether subjects may, in the future, request that their data be destroyed or that all personal identifiers be removed from data and how to make such a request).
- When appropriate, the plan for management of incidental findings and sharing of results.

Storage and Management

Repositories should have written policies on:

- Conditions under which data/specimens will be accepted
 - Informed consent
 - IRB review
 - Sources
- Whether data/specimens will be identifiable, coded, or de-identified, and, if coded, management of the linkage key
- Physical and procedural mechanisms for the secure receipt, storage, and distribution of data/specimens

Distribution

- How data/specimens may be requested and by whom
- Any requirements associated with a request for data/specimens (e.g., verification of IRB approval or that approval is not required)

- Any limitations or restrictions on how data/specimens may be used
- Whether released data/specimens will be identifiable, coded, or de-identified, and, if coded, any circumstances under which recipient investigators will access to or be provided with the key or other means to re-identify
- Agreements with recipient investigators specifying the terms of use.

27.4.1.3 IRB Oversight

IRB approval is required for the establishment and operation of a research repository when the data/specimens that are accessed, received, stored, or distributed are identifiable. In general, private information or specimens are considered individually identifiable when the identities of the subjects are known to investigators/repository operators or when the data/specimens can be linked to specific individuals either directly or indirectly through coding systems.

Separate IRB approval is required for the use of data/specimens from a repository when the recipient investigator(s) know or may readily ascertain the identity of individual subjects, and, regardless of identifiability, when specimens will be used to evaluate the safety or effectiveness of a medical device. Research under the auspices of Allina Health that includes the use of coded private information or specimens, must either be submitted for IRB review or for a “Human Subjects Research Determination” (See Section 6). The only exception to this policy is when the coded private information or specimens are to be obtained from an IRB-approved repository and the rules of that repository 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.

27.5 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.

Allina Health’s Community Benefit and Engagement department conducts a Community Needs Assessment for each of our hospitals every three years that evaluates, identifies, analyzes health priorities in the community and creates a plan on how to address these priorities.

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?

27.6 Research Conducted or Supported by the Department of Defense (DoD)

Research conducted or supported by the Department of Defense (DoD Research) is reviewed and conducted in compliance with part 219 of title 32 CFR, part 980 of title 10 USC, applicable parts of title 21 CFR (50, 56, 312, 600, 812), DoD Instruction 3216.02, DoD Directive 3210.07, and applicable additional requirements from respective DoD component(s). Support of a study generally means the provision of funding, personnel (both military and civilian DoD employees), facilities, and any other resources.

DoD components (e.g., Army, Navy) may have additional requirements. The PI and a representative of the HRPP or IRB should contact the Human Research Protection Official (HRPO) for the DoD Component conducting or supporting the research. The HRPO provides administrative review and approval to confirm the research is compliant with federal and DoD requirements.

It is the responsibility of the PI to ensure compliance with DoD requirements for human subject protection. The IRB will use the DoD Reviewer Checklist to assess research proposals for compliance with DoD requirements.

27.6.1 Application and Scope

The following additional requirements apply to all research involving human subjects conducted under the jurisdiction of Allina Health when it:

- Conducts, reviews, approves, oversees, supports manages otherwise is contractually subject to regulation by the DoD; and/or
- Uses DoD property, facilities, or assets.

In most cases, protocols covered by these requirements also will have review, approval and oversight by the DoD component HRPP. DoD review must be conducted before research involving human subjects can begin.

Allina Health assures that DoD supported research complies with all relevant DoD human subjects protection requirements, including but not limited to:

- The Belmont Report
- Title 32 Code of Federal Regulations Part 219 ([32 CFR 219](#)), Department of Defense Regulations, “Protection of Human Subjects” (DoD adoption of the “Common Rule”)
- Title 45 Code of Federal Regulations Part 46, ([45 CFR 46](#)) Department of Health and Human Services Regulations, “Protection of Human Subjects,” Subparts B, C, and D as made applicable by [DoD Instruction \(DoDI\) 3216.02](#)
- Title [21 Code of Federal Regulations 50, 56, 312, and 812](#), Food and Drug Administration (FDA) Regulations
- [DoDI 3216.02](#), “Protection of Human Subjects and Adherence to Ethical Standards in DoD-supported Research”
- Title 10 United States Code Section 980 ([10 USC 980](#)), “Limitation on Use of Humans as Experimental Subjects”
- [DoDI 3210.7](#), “Research Integrity and Misconduct”
- [DoDI 6200.2](#), “Use of Investigational New Drugs in Force Health Protection”

27.6.2 Key Additional Requirements Not Covered by Title 45 CFR 46, Subparts B, C and D; 21 CFR 50, 56, 312, and 812

27.6.2.1 Minimal Risk [DoDI 3216.02, enclosure 3, para 6b]

The definition of minimal risk based on the phrase “*ordinarily encountered in daily life or during the performance of routine physical or physiological examination or tests*” shall not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a

special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain.)

27.6.2.2 Education and Training *[DoDI 3216.02, enclosure 3, para 5]*

All personnel involved in the conduct of DoD research must complete initial and continuing education in the protection of human subjects as described in this manual. Personnel must also familiarize themselves with DoD's specific requirements by reviewing these SOPs, DoDI 3216.02, and any relevant materials specific to the DoD component. The DoD component may require additional education and/or certification to ensure that personnel are qualified to perform the research. The DoD component may evaluate the education policies to ensure the personnel are qualified to perform the research, based on the complexity and risk of the research.

IRB staff, chairs and members will use these SOPs, DoDI 3216.02, the DoD Reviewer Checklist, and any relevant component-specific instructions or materials to guide the IRB review and oversight of DoD research.

27.6.2.3 Appointment of a Research Monitor *[DoDI 3216.02, enclosure 3, para 8]*

27.6.2.4 The appointment of a research monitor is not required for DoD-funded or supported research. Additional protections for vulnerable subjects *[DoDI 3216.02, enclosure 3 para 7]*

Non-exempt research involving **pregnant women, fetuses, or neonates** as subjects must meet the requirements of Subpart B of the Common Rule, with the following modifications:

- For purposes of applying Subpart B, the phrase “biomedical knowledge” shall be replaced with “generalizable knowledge.”
- The applicability of Subpart B is limited to non-exempt research involving:
 - Pregnant women as human subjects involved in research that is more than minimal risk and that includes interventions or invasive procedures to the woman or the fetus; or
 - Involving fetuses or neonates as subjects.
- Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g.

Research involving **prisoners** as subjects must meet the requirements of Subpart C of the Common Rule, with the following modifications:

- Research involving prisoners cannot be reviewed by the expedited procedure.
- When the IRB reviews research involving prisoners, at least one prisoner representative must be present for quorum. The prisoner representative may be a prisoner, an employee of the prison, or an individual not affiliated with the prison.

- In addition to the four allowable categories of research involving prisoners in Subpart C, two additional categories are allowable:
 - Epidemiological research that meets the following criteria:
 - The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor association for a disease.
 - The research presents no more than minimal risk
 - The research presents no more than an inconvenience to the participant.
 - Prisoners are not a particular focus of the research
 - Research that would meet the criteria for exemption described at 32 CFR 219.101(b), can be conducted but must be approved by a convened IRB and meet the requirements of subpart C, DoDI 3216.02, and other applicable requirements.
- When a previously enrolled human subject becomes a prisoner and the research was not previously approved for the inclusion of prisoners:
 - The PI must promptly notify the IRB.
 - If the PI asserts to the IRB that it is in the best interest of the prisoner to continue to participate in the research while a prisoner, the IRB Chair may determine that the prisoner may continue to participate until the convened IRB can review the request to approve a change in the research protocol and until the IO and DoD Component office review the IRB's approval to change the research protocol. Otherwise, the IRB Chair shall require that all research interactions and interventions with the prisoner (including obtaining identifiable private information) cease until the convened IRB can review the request to approve a change in the research protocol.
 - The convened IRB, upon receipt of notification that a previously enrolled human subject has become a prisoner, shall promptly re-review the research protocol to ensure that the rights and wellbeing of the human subject, now a prisoner, are not in jeopardy. The IRB should consult with a subject matter expert having the expertise of a prisoner representative if the IRB reviewing the research protocol does not have a prisoner representative. If the prisoner can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner's confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research from continuing as approved, the convened IRB may approve a change in the study to allow the prisoner to continue to participate in the research. This approval is limited to the individual prisoner-subject and does not allow recruitment of prisoners as participants.

- This type of request for change in the research protocol cannot be reviewed and approved by expedited review. The research does not have to meet one of the six allowable DoD categories for research involving prisoners.
- Allina Health shall promptly report all decisions in this matter to the component HRPO. The HRPO must concur with the IRB decisions before the human subject can continue to participate while a prisoner.

Research involving **Children** as subjects must meet the requirements of Subpart D of the Common Rule, including that:

- The exemption for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

Research involving any **DoD personnel** (Military or Civilian) as subjects:

- Surveys performed on DoD personnel must be submitted, reviewed, and approved by the Information Management Control Officer (IMCO) after the research protocol is reviewed and approved by the IRB. When a survey crosses DoD components (e.g., Army, Navy), additional review is required.
- Allina Health does not conduct DoD funded or supported research involving DoD personnel's genomic data or data that was collected under a pledge of confidentiality.

Research involving **Military Personnel** as subjects must meet the following requirements:

- Service members shall follow their command policies regarding the requirement to obtain command permission to participate in research involving human subjects while on-duty and for approving off-duty employment or activities.
- Superiors (e.g., military and civilian supervisors, unit officers, and noncommissioned officers (NCOs)) are prohibited from influencing the decisions of their subordinates (e.g., junior enlisted personnel and equivalent civilians) regarding participation as subjects in research.
- Superiors of Service members (e.g., unit officers, senior NCOs, and equivalent civilians) in the chain of command shall not be present at any human subject recruitment sessions or during the consent process in which members of units under their command are afforded the opportunity to participate as research subjects. When applicable, the superiors so excluded shall be afforded the opportunity to participate as research subjects in a separate recruitment session.
- When research involving Service members is greater than minimal risk and recruitment occurs in a group setting, the IRB shall appoint an ombudsman. The ombudsman shall not be associated in any way to the research and shall be present during the recruitment to monitor that the voluntary involvement or recruitment of the Service members is clearly and adequately stressed and that the information

provided about the research is clear, adequate, and accurate. The ombudsman may also be the research monitor.

Research involving **DoD Civilians** as subjects must meet the following requirements:

- DoD Civilians shall follow their organization’s policies regarding the requirement to obtain permission to participate in research
- Supervisors (e.g., military and civilian supervisors or anyone in the supervisory structure) are prohibited from influencing the decisions of their subordinates regarding participation as subjects in research
- Supervisors (e.g., military and civilian supervisors or anyone in the supervisory structure) shall not be present at any human subject recruitment sessions or during the consent process in which DoD civilians under their supervision are afforded the opportunity to participate as human subjects. When applicable, supervisors so excluded shall be afforded the opportunity to participate as human subjects in a separate recruitment session.
- For research involving civilians as human subjects when recruitment occurs in a group setting, the IRB shall discuss appointing an ombudsman. The decision to require the appointment of an ombudsman should be based in part on the human subject population, the consent process, and the recruitment strategy.

Research involving **other vulnerable populations** must meet the following requirements:

- Investigators, IRBs, and IOs shall consider the need for appropriate similar safeguards for other vulnerable populations, such as: research involving human subjects and investigators in supervisor-subordinate relationships, human subjects with decisional or mental impairments, human subjects with a physical disability, or any other kind of human subjects in circumstances that may warrant provision of additional protections. As appropriate, qualified individuals (e.g., research monitors, ombudsmen, advocates) may be appointed to perform oversight functions or assist the human subjects.

27.6.2.5 Limitation of Waivers and Exceptions from Informed Consent [DoDI 3216.02, enclosure 3 para 9 and 13; 10 U.S.C. 980]

If the research participant meets the definition of “Experimental Subject,” waiver of consent is prohibited unless a waiver is obtained from the DoD Office for Human Research Protections (DOHRP). If the research participant does not meet the definition of Experimental Subject, the IRB may waive consent. The requirement to obtain consent cannot be waived for any research involving the DoD, except under one of the following conditions:

- The research is intended to be beneficial to the subject, the subject lacks the capacity to provide consent, and a legally-authorized representation will provide consent. (Examples: young minors, cognitively impaired individuals.)
- The Head of the DoD component involved in the research may waive the requirement for consent with respect to a specific project in order to advance the development of a

medical product necessary to the Armed Forces, but only if the research may directly benefit the subject and the research is carried out in accord with all other applicable laws and regulations (e.g., 21 CFR 50.24).

- This prohibition does not apply to screening (sometimes called “pre” screening) of records to identify possible subjects. The IRB can grant a waiver of consent for such activities (see IRB Department of Defense Requirements policy)
- DoD regulations prohibit an exception from informed consent in emergency medicine unless the PI obtains a waiver from the DOHRP.

When following Department of Defense regulations, the DOHRP may waive the requirements for consent when the following is met:

- The research is conducted in compliance with all other applicable laws and regulations.

Please note that for classified research, waivers of consent are prohibited.

27.6.2.6 Limitations on Compensation for Human Subjects in Research *[Dual Compensation Act, 24 U.S.C. 30, and DoDI 3216.02, enclosure 3 para 11]*

DoDI 3216.02 describes allowable and prohibited compensation for human subjects participating in DoD research and for Federal personnel such as civil servants and Service members. These provisions are intended to ensure compliance with the Dual Compensation Act and 24 U.S.C. 30. Summarized:

- Federal personnel while on duty and non-Federal personnel may be compensated for blood collections for research up to \$50 for each blood collection.
- Federal personnel are prohibited from receiving pay or compensation for research during duty hours (except for blood collection as noted above).
- Non-Federal personnel may be compensated for research participation other than blood collections in a reasonable amount, as approved by the IRB according to local prevailing rates and the nature of the research.
- Federal personnel may be compensated for research if the participant is involved in the research when not on duty in the same way as human subjects who are not Federal personnel (i.e., compensated for participation in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research). However, payment to off-duty Federal personnel for research participation other than blood draws must not be directly from a Federal source (payment from a Federal contractor or other non-Federal source is permissible).

Additional detail is available in DoDI 3216.02 or by consulting the component HRPO.

27.6.2.7 Reporting Requirements [DoDI 3216.02, enclosure 3 para 4(b)(4)]

The Institution shall promptly (no longer than within 30 days) notify the HRPO of the following:

- when significant changes to the research protocol are approved by the IRB;
- the results of the IRB continuing review;
- if the IRB used to review and approve the research changes to a different IRB;
- when the institution is notified by any Federal body, state agency, official governing body of a Native American or Alaskan Native tribe, other entity, or foreign government that any part of its HRPP is under investigation for cause involving a DoD-supported research protocol;
- all UPIRTSOs, suspensions, terminations, and serious or continuing noncompliance regarding DoD-supported research involving human subjects;
- change in status when a previously enrolled participant becomes pregnant, or when the researcher learns that previously enrolled participant is pregnant, and the protocol was not reviewed and approved by the IRB in accordance with 45 CFR 46, Subpart B;
- change in status when a previously enrolled participant becomes a prisoner, and the protocol was not reviewed and approved by the IRB in accordance with 45 CFR 46, Subpart C; and
- closure of a DoD-supported study.

27.6.2.8 Recordkeeping Requirements [DoDI 3216.02, para. 5.3.2; SECNAVINST 3900.39D, para 8c (18)]

Recordkeeping requirements for DOD-supported research with human subjects are longer than the Common Rule's requirement. DOD may require submitting records to DOD for archiving.

Records maintained that document compliance or non-compliance with DoD requirements shall be made accessible for inspection and copying by representatives of the DoD at reasonable times and in a reasonable manner as determined by the supporting DoD component.

27.6.2.9 Addressing and Reporting Allegations of Non-Compliance with Human Research Protections [DoDI 3216.02, para. 4.b.4; SECNAVINST 3900.39D, para 8d(2) and 6k]

Report the initiation of all investigations and report results regardless of the findings to the HRPO.

The following must be promptly reported to the Component Office of Human Research Protections (COHRP):

- Reports of audits of DoD-conducted or DoD-supported human participant research by another federal or state agency, official governing body of a Native American or Alaskan native tribe, other official entity, or foreign government, within five business days of discovering that such audit reports exist.

- Allegations of serious or continuing noncompliance related to HSR that are substantiated by investigation, and subsequent actions taken based on the findings, within five business days of completion of the report. Unanticipated problems involving risks to participants or others and any subsequent actions taken based on the findings, within five days of completion of the report.
- Suspensions or terminations of IRB approval, within five days of the IRB action.

27.6.2.10 Addressing and Reporting Allegations of Research Misconduct [DODI 3210.7; SECNAVINST 3900.39D, 8d(2) para 6l]

Organizations must adhere to the requirements of DODI 3210.7 and the terms of any DoD award.

At Allina Health allegations of research misconduct must be reported to the Allina Health Chief Compliance Officer at ResearchIntegrityOffice@allina.com.

27.6.2.11 Prohibition of Research with Detainees [DoDI 3216.02, enclosure 3 para 7c; SECNAVINST 3900.39D, para. 6a(8)]

Involvement of detainees (e.g. civilian internees, retained persons, lawful and unlawful enemy combatants) as human subjects of research is prohibited. Research involving any person captured, detained, held or otherwise under the control of DoD personnel (military and civilian, or contractor employee) is prohibited. There is an exception for treatment of detainees with an investigational drug or device described below.

A detainee is defined as any individual captured by, or transferred to the custody or control of, DoD personnel pursuant to the law of war. This does not include persons being held solely for law enforcement purposes, except where the United States is the occupying power.

The prohibition of research involving a detainee does not apply to the use of FDA-regulated investigational new drugs or investigational devices for the purpose of diagnosis or treatment of a medical condition in a patient. Such treatment (e.g., an investigational new drug) may be offered to detainees with the detainees' informed consent when the medical products are subject to FDA regulations as investigational new drugs or investigational medical devices, and only when the same product would be offered to members of the U.S. Military Services in the same location for the same medical condition and only when consistent with established medical practice involving investigational drugs and devices. Such permitted treatment involving detainees as subjects shall comply with all sections of DoDI 3216.02.

27.6.2.12 Classified research [DoDI 3216.02, enclosure 3 para 13]

Allina Health does not allow the conduct of Research involving human subjects where classified material is necessary to adequately perform IRB review and oversight, required to obtain effective informed consent of participants, or, by design, communicated by or to research participants.

27.6.2.13 Additional Requirements for DoD Research

- a) IRB review must consider the scientific merit of the research. The IRB may rely on outside experts to provide an evaluation of scientific merit.
- b) When conducting research with international populations, additional safeguards for research conducted with international populations include: The Organization or Researcher has permission to conduct research in that country by certification or local ethics review and the Researcher follows all local laws, regulations, customs, and practices.
- c) Disclosure regarding the provisions for research-related injury follow the requirements of the DoD component.
- d) When any institution relies upon another institution's IRB for DoD research, there must be a written agreement defining the responsibilities and authorities of each organization in complying with the terms of each institution's Federal assurance and DoDI 3216.02.
- e) When conducting multi-site or collaborative research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.